Ann. Anim. Sci., Vol. 23, No. 2 (2023) 353–362 *DOI: 10.2478/aoas-2022-0072*

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THE POTENTIAL THERAPEUTIC ROLE OF CAMEL MILK EXOSOMES – A REVIEW

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Abstract

Exosomes (EXOs) are naturally occurring nano-sized vesicles released into the extracellular environment by exocytosis. EXOs contribute to intercellular communications by regulating DNA, mRNA, and protein levels. EXOs are considered good vehicles for delivering therapeutic agents in multiple diseases. Camel milk (CM) is a valuable food with a rich source of EXOs. Camel milk exosomes (CMEXOs) have unique ingredients compared to other animal milks. It is reported that CMEXOs reduce the growth of cancer cells by inducing apoptosis, and inhibiting oxidative stress and inflammation. CMEXOs can block stress signaling pathways including inflammation and apoptosis which could be resulted in adverse effects if medication levels exceed the therapeutic range. Moreover, CMEXOs improve the antioxidant capability in both *in vitro* and *in vivo* experiments. On the other hand, the anti-angiogenesis property of CMEXOs has been reported via decrease in expression of the angiogenesis-related gene of vascular endothelial growth factor (*VEGF*). It is predicted that exosomal lactoferrin (LF) and kappa casein (KC) mRNAs are crucial parts of CMEXOs mediating their anticancer effects. The immunomodulatory effect of CMEXOs may be attributed to their high contents of LF and KC. According to previous works, CMEXOs are promising alternatives in developing new therapeutic models for multipile diseases. This review aims to provide an overview of the isolation, characterization and biological activities of the exosomes derived from camel milk for addressing their possible use in therapeutics.

Key words: camel milk exosomes, anticancer activity, anti-inflammatory activity, immuno-modulatory activity, antioxidant activity

In the Middle East, the daily drinking of camel milk (CM) is usually supposed to improve immune capacity and decrease the risk of many diseases. Several beneficial properties of CM were reported including immunostimulatory, anti-microbial, anti-viral, anti-parasitic, anti-inflammatory, antioxidant, and anti-allergic effects (Badawy et al., 2018; El-Kattawy et al., 2021; Khan et al., 2021). The main health-encouraging bioactive components in CM are lactoferrin (LF), kappa casein (KC), and some other molecules having the mentioned properties (Iigo et al., 2009; Shariatikia et al., 2017)**.** Exosomes (EXOs) are common extracellular nanovesicles that contribute to intercellular communications by transporting, supporting and chaperoning biologically kinetic elements such as DNA, mRNA, microRNA, proteins, etc. (Colombo et al., 2014; Cintio et al., 2020). Because of their nano size (40–100 nm diameter), EXOs are auspicious delivery elements in individual therapy (Bunggulawa et al., 2018). EXOs that are isolated from milk, have superior significance impacts due to their capability in transferring genetic material from mother to infants (Mincheva-Nilsson and Baranov, 2010).

The EXOs are located in different tissues and biological fluids including blood plasma, milk, saliva, oviductal, urine, cerebrospinal fluid, ascites, amniotic fluid and others (Colombo et al., 2014). Among them milk is the only biological fluid comprising high amounts of EXOs (Adriano et al., 2021). Camel milk (CM) is one of the wealthy sources of beta-caseins and whey proteins, comprising lactoperoxidase, lysozyme, alpha-lactalbumin, lactoferrin, and immunoglobulins. The antioxidant, antibacterial, anti-diabetic, anti-viral, anti-cancer, and anti-inflammatory properties of CM might be attributed to the high contents of those biological components (Khan et al., 2021; Swelum et al., 2020; Mostafa et al., 2022).

Among all types of exosomes in different milk sources, camel milk exosomes (CMEXOs) have received much awareness in the last few years, owing to their diagnostic, theranostic, and therapeutic uses.

Several authors reported that EXOs of CM have more stability in low pH and high and low temperature (Yassin et al., 2016) and it can be easily absorbed through the gastrointestinal barrier to circulation (Baier et al., 2014).

Furthermore, EXOs of cow or human milks also have anti-cancer properties and improve immune response against different tumor cells (Anand, 2010; Abels and Breakefield, 2016).

The anti-cancer properties of CMEXOs have been described via suppression of inflammation, metastasis, oxidative stress (OS), and augmentation of tumor cell apoptosis (Abels and Breakefield, 2016). Generally, CMEXOs have greater biocompatibility, low adverse immune effects and no systemic toxicity, and inflammatory responses (Badawy et al., 2018; Bunggulawa et al., 2018). In the last years, it was reported that EXOs are promising candidates as anti-cancer drugs by induction of apoptosis and suppression of angiogenesis and inflammation pathways (El-Kattawy et al., 2021). The immunomodulatory and antioxidant effects of CMEXOs are due to the high contents of caseins and lactoferrin (Ibrahim et al., 2019). However, the use of milk EXOs in therapeutic sciences still needs to be further explored. Therefore, there is an indispensable necessity to discover more operative, secure, and selective additives to produce anti-cancer treatments to enhance their therapeutic plausibility and reduce their secondary impacts. In this paper, we overviewed the isolation of CMEXOs and their possible therapeutic use as anti-cancer, anti-inflammatory, anti-angiogenesis, and antioxidant intermediates.

Milk exosomes

According to the procedures of the International Society for Extracellular Vesicles, various immunological, physical, and physicochemical methods are used to isolate milk EXOs (Lötvall et al., 2014). EXOs are often produced by multivesicular bodies which are released via the fusion process with the plasmatic membrane of a cell (Adriano et al., 2021). Based on the size of secretion factors, these released vesicles were named as "exosomes", which have a size range between 40 and 100 nm, while the other secretions called microvesicles have a 1 μm range size (Adriano et al., 2021).

The literature supported that the EXOs contain several fragments from the parent cells, comprising different types of RNAs (microRNA, long non-coding RNA, and tRNA), DNA nucleotides, proteins and lipids (Ngu et al., 2022). For quantification and characterization of EXOs in milk or other fluids, the most common method for visualization is via the transmission electron microscopic images (Lázaro-Ibáñez et al., 2014; El-Kattawy et al., 2021). A further full clarification of the biogenesis and structure of exosomes, and other types of extracellular vesicles (components) are mentioned in recent papers (Akers et al., 2013).

Exosomes in milk of different mammalian species

Many publications have revealed that the goat milk exosomes had the highest loading capacity compared to other milk exosomes derived from cow and buffaloes (Ahmed et al., 2022; Yan et al., 2020). Moreover, the use of doxorubicin-encapsulated goat milk exosomes caused significant inhibition of cell viability in several types of cancer cells including A549, HCT-116, and HepG2 cells (Ahmed et al., 2022). Santos-Coquillat et al. (2022) reported that the concentration of pure goat's milk exosomes was 2.29±0.25 mg/mL as quantified by Coomassie-Bradford test. While Yassin et al. (2016) found that the levels of phosphatidylserine, and phosphatidylcholine ranged between ~10–15 μg/mL and ~20–25 μg/mL, respectively, in dromedary milk exosomes which were steady throughout various lactation stages. Several scientific papers suggested that the beneficial health effects of CM might be attributed to its high contents of phospholipids, such as those reported in CMEXOs (Ali et al., 2017; Zheng et al., 2022). After extensive investigations of milk exosomes, it should be clear that no standard amounts of EXOs have been recorded. From this point of view, extensive clarification should be done in this scientific point to develop the method of characterization and identification of milk EXOs.

Isolation of milk exosomes

Different centrifugation techniques are adopted to isolate milk EXOs as a result of variability in milk content of animals (Yassin et al., 2016; Cintio et al., 2020; El-Kattawy et al., 2021). Successive centrifugations are applied to detach the EXOs. First, a low speed centrifugation (600–1000× *g*) is operated to defat the milk and precipitate the cells, then 10×10^3 – 16×10^3 g is used to precipitate milk proteins, and finally, one or numerous multi-ultracentrifugations at 100×10^3 – 200×10^3g are utilized to separate the EXOs (Yassin et al., 2016; Badawy et al., 2018; El-Kattawy et al., 2021). Commercially, several supply materials are used, including volume-excluding polymers for isolation of milk EXOs such as ExoQuick (System Biosciences, Palo Alto, CA, USA), containing PEG 8000 kDa; Total Exosome Isolation (Thermo Fisher Scientific, Waltham, MA, USA), comprising polyvinyl, polyethylene glycol, and dextrans with a molecular weight above 1000 kDa, and their mixtures with other approaches (Jiao et al., 2020). Additionally, the immunomagnetic approach is applied to separate EXOs through a semipermeable membrane (Bunggulawa et al., 2018). EXOs of high quality could be obtained by ultracentrifugation from different body fluids (milk, seminal plasma, oviductal, uterine, blood plasma, urine, lacrymal). In addition, cell culture fluid generally has "nonvesicles" with 20–100 nm in diameter. These "nonvesicles" are morphologically accredited to intermediate and very-low-density (40–100 nm) and low-density lipoproteins (20–40 nm) (Grigor'eva et al., 2017). Transmission electron microscopy can detect the ultrastructure of the cell discriminate EXOs, therefore EXOs were categorized by transmission electron microscopy (Badawy et al., 2018; El-Kattawy et al., 2021). The previously method detected specific protein markers such as TSG101 (a truncated 35 KDa protein), which was discovered explicitly for CMEXOs rather than the previously described 43 KDa mammalian

one (Yassin et al., 2016). This may be attributed to the specific protein in each species and the unique properties of CMEXOs. Decisively, several commercial kits are also offered for rapid isolation of EXOs. Among them, ThermoFisher, Sigma, FUJIFILM Wako Pure Chemical Corporation, Nano View Biosciences, Qiagen, Takara Bio, Biocompare, System Biosciences, IZON, BioCat GmbH, Miltenyi Biotec, BioVision Inc., etc are well-known companies. Nonetheless, such kits are used for the isolation of EXOs from the cell culture medium and/or human biological fluid. Consequently, in this part, the generally applied isolation approaches are discussed for milk EXOs (Yassin et al., 2016; Badawy et al., 2018; El-Kattawy et al., 2021). There is no one standard technique for the isolation of EXOs from milk and other biological fluids. Successful isolation of milk-derived EXOs is under investigation and there is an unmet need to develop a reliable and reproducible EXOs separation technique.

Bioactive compounds of milk exosomes

CM comprises the important nutrients as well as potentially health-beneficial compounds with antihypertensive, anti-viral, anti-inflammatory, antidiabetic, anticarcinogenic, and antioxidant properties (Al-Majali et al., 2007; Izadi et al., 2019; Ghazzawi, 2020). It has been used for preventing or treating some diseases such as allergies, diabetes, and autism. Also, CM could decrease blood cholesterol levels and improve metabolism because CM is a rich source of the unique combination of biological compounds such as protein, nucleic acids, and EXOs (Jilo and Tegegne, 2016). Additionally, CM is full of beta-caseins and many of whey proteins, comprising lactoperoxidase, immunoglobulin, lactoferrin, alpha-lactalbumin, and lysozymes (Jilo and Tegegne, 2016). Lactoferrin is the second main protein after casein, it has numerous biological roles, regulating the iron metabolism in the body, boosting the immune response, and has a critical role in the cellular defense against pathogenic bacteria through its bactericidal and/or bacteriostatic activities (Al-Majali et al., 2007; Jilo and Tegegne, 2016). CMEXOs have received more attention in the last years due to their health-promoting properties. The biological compounds of milk EXOs can meaningfully affect biomolecules delivery. Therefore, a comprehensive scrutiny of the content of milk EXOs that are also termed "exosomics" (by analogy with genomics, transcriptome, proteomics, and other -omics technologies), is compulsory (Yassin et al., 2016). Al-Majali et al. (2007) suggested that camel milk EXOs proteins such as TSG101 (a 35 KDa of molecular weight) could be accredited with various biological roles in cell development and regulation pattern. To date, the biological function of TSG101 is ambiguous and needs further explorations to demonstrate the molecular purpose.

Studies revealed that the biological properties of CM proteins might be attributed to their high content of exosomes (extracellular nanovesicles) (Gu et al., 2012; Khan et al., 2021). Generally, the milk exosomes have many proteins that contribute to various biological functions in cellular development.

Furthermore, CMEXOs have many specific types of proteins that regulate their biological roles, specifically, conveyance of microRNA and adhesion to the target cells including tetraspanins, CD81, CD63, and CD9 as previously reviewed by Khan et al. (2021). More specifically, both lactoferrins and kappa casein mRNAs were noticed in camel milk exosomes (Ibrahim et al., 2019). El-Kattawy et al. (2021) found a significantly higher transcript of kappa casein and lactoferrins genes in colostrum-derived EXOs than in other lactation stage-derivative EXOs. The higher contents of EXOs in colostrum show a greater immune-stimulatory function, which can be a part of the innate immunity of infants (Gu et al., 2012). On the other hand, no substantial alteration was detected in expression amounts of both kappa casein and lactoferrins in late- and mid-lactation milk of camel. The recognition of kappa casein and lactoferrins mRNAs in CMEXOs suggests that their mRNAs are protected from degradation by milk RNase (Keller et al., 2011; Yassin et al., 2016; Khan et al., 2021). The antioxidant capacity of CM has also been credited to the structural configuration of high amount of beta-caseins content. Upon hydrolysis, the CM beta-caseins are converted to some bioactive peptides showing helpful antioxidant actions. The caseins and whey proteins of CM have antioxidant and cytotoxic activities alongside the MCF7 cells. Moreover, casein of CM presented plausible apoptotic and anti-HCV activity in HeLa cell lines and human hepatoma (Almahdy et al., 2011). EXO RNAs are one of the most common components in camel milk, however, there is no published data regarding the characterization and global transcriptomic microRNA in this species. Therefore, CM can be a good environment to explore the profile of EXO microRNAs for using in different biomedical and scientific components. In the other species, various microRNA of milk and its EXOs generally have various targets and have a significant role in cell proliferation, pregnancy, fetal development, immune system improvement, insulin resistance, sugar metabolism and inflammation (Sedykh et al., 2020). In addition, natural lipid compounds of milk EXOs are more well-matched and less toxic than synthetic liposomes for uses as drug delivery vehicles (Elsharkasy et al., 2020). According to the literature, proteins of milk EXOs have significant roles in formation of cytoskeleton protein, homeostasis, cell development, cellular defense, and signal transduction etc., but this kind of roles for CM proteins have been not illustrated and need further exploration.

In a recent study, He et al. (2021) performed the proteomic analysis on Bactrian camel milk and found higher contents of lactoferrin, lactoperoxidase isoform 1 preproprotein, and FABP domain-containing protein as well as κ-casein, alpha-1-acid glycoprotein and peptidoglycan-recognition protein. It has been reported that EXOs depending on their source can be divided into virtuous and malicious exosomes. Exosomes derived from CMEXOs

are an example of virtuous EXOs which exhibited a superior anticancer effect (inhibition of the growth and metastatic potential of MCF7 cells) to that of CM (Badawy et al., 2018).

The phospholipid membrane encircling EXOs defends exosomal substances (DNA, RNA, protein) from degradation by digestive enzymes and acidic conditions (Record et al., 2014). This gastric constancy may elucidate anti-cancer property for EXOs when it is administered orally compared to CM used alone. Besides, the absorbed EXOs will take a few hours to arrive at the cellular target and may undergo dilution, by circulation all over the body, before contacting the tissue tumors. This shows that local injection of EXOs in tumor tissues has better consequences than oral administration. However, regarding the biological properties of EXO, it is urgent to do more explorations, especially in CMEXOs to detect different EXOs of this species which could be used in several biomedical fields.

Camel milk exosomes as:

Anti-cancer agent

The potential therapeutic role of CMRXOs in cancer remains an emerging scope of research. A huge number of reports have illustrated that CMEXOs have capability to prevent the progression of tumor cancer in several *in vivo* or *in vitro* experiments (Badawy et al., 2018; El-Kattawy et al., 2021). Studies have indicated that cancer cells survive via different molecular mechanisms such as restraining of apoptosis, immunosuppression, and stimulation of inflammation (Wong, 2011; Diakos et al., 2014; Badawy et al., 2018; El-Kattawy et al., 2021). It is identified that a conceivable part of CMEXOs inhibits the growth and proliferation of MCF7 cells and diminishes breast tumor development. The cancer therapy might be associated with higher apoptosis pathways; eminent attenuation in angiogenesis, inflammation, and metastasis; as well as notable reduction of oxidative stress synthesis, and greater immune response (Badawy et al., 2018). Furthermore**,** Almahdy et al. (2011) and Korashy et al. (2012) showed that the administration of whole CM led to high cytotoxic influence on MCF7 tumor cells in a dose-dependent manner. Earlier investigations showed that CM triggered apoptosis of tumor cell line (type MCF7) (Korashy et al., 2012) and other cell lines comprising BT-474, Hela, and HepG2, via the same molecular pathway (Almahdy et al., 2011; Hasson et al., 2015). This stimulatory machinery of CM could be connected to high contents of immunoproteins such as lactoferrin, α-lactalbumin, and other bioactive compounds (for example exosomes) which have been unclarified (Almahdy et al., 2011). Badawy et al. (2018) reported that the apoptosis indices such as both caspase 3, and *Bax* transcripts were significantly increased and decreased *Bcl2* gene expression, as well as high DNA fragmentation was recorded in EXOs treatment compared to CM treatment, indicating that CM could induce apoptosis, at least in part, interceded by exosomes. Totally, the inhibitory upshot of CM and its EXOs on tumor cells is owing to the antioxidative properties and induction of the apoptosis process. And the anti-cancer activity of CMEXOs is related to the attendance of defensive proteins such as lysozyme, lactoferrin and lactoperoxidase and other immunological indices such as IgG, and IgA (Jilo and Tegegne, 2016). As previously clarified, the high levels of lactoferrin in CM could prevent the propagation of colorectal cancer cells and have antioxidant and DNA injury-repressing characteristics in cancerous cells (Habib et al., 2013).

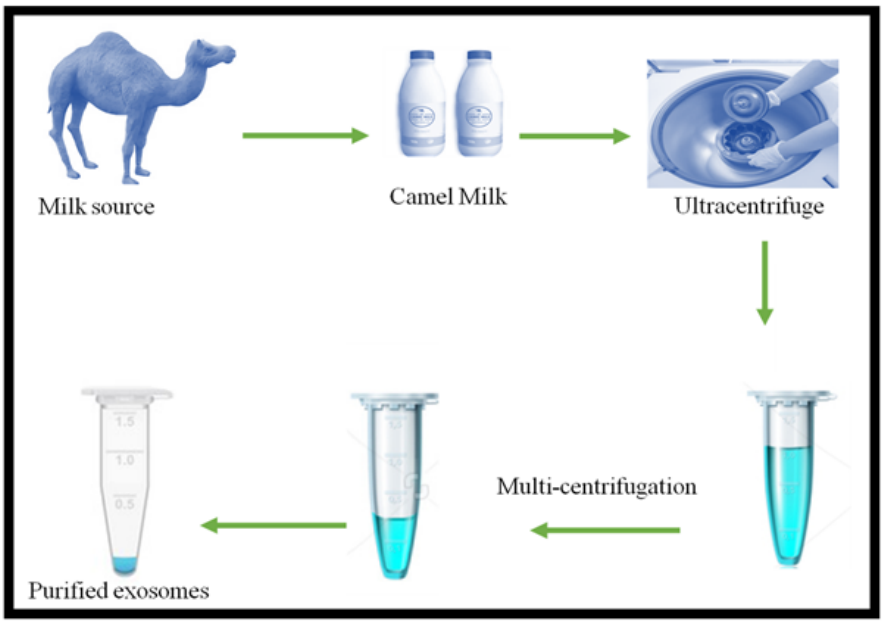


Figure 1. The method for isolation and purification of camel milk-derived exosomes using ultra-centrifugation method

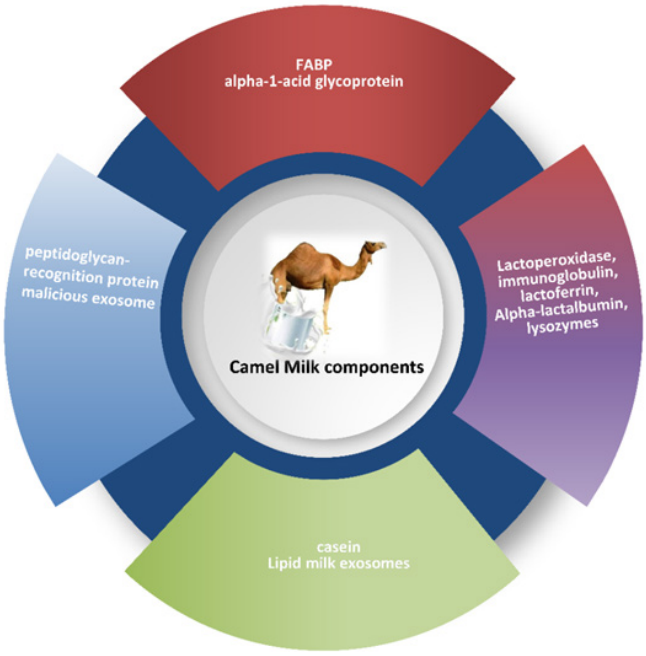


Figure 2. The biological components of camel milk documented in the present article

Lately, Badawy et al. (2021) showed a significantly superior DNA impairment catalogue in tumor tissues such as HepaRG cells after treating with CMEXOs. In this case, CMEXOs triggered HepaRG cells dispersion via apoptosis pathways that can be associated with the potentiality of exosomes-treated cells to exhibit a significant increment in the expression of caspase 3 and Bax and a significantly lower expression of Bcl2 than the control group (Badawy et al., 2021). The apoptosis induction approach is one of the main innovative tools for cancer therapy. Tumor cells sustain their viability via induction of inflammation, and suppression of apoptosis and angiogenesis in the tumor microenvironment (Diakos et al., 2014). Likewise, CMEXOs showed a potent apoptotic property on HepaRG as discovered by a substantial upregulation of *Bax* and caspase3 and a noteworthy downregulation of *Bcl2*, with noteworthy fluctuations in colostrum-treated cells. Parallel apoptotic alterations were observed in the subsequent treatment of HepG2 and MCF7 (Korashy et al., 2012; Badawy et al., 2018). In *in vivo* and *in vitro* studies, TR35, which was separated from Xinjiang Bactrian camel milk, could meaningfully constrain Eca109 cell propagation and persuade its apoptosis (showed by caspase-3 activity, MTT assessment, and Annexin V-FITC) (Yang et al., 2019). Moreover, TR35 could constrain the development and progression of xenografted tumors in nude mice without loss in body weight (Yang et al., 2019**).** The tiny proteins isolated from CM could be used as a potential therapeutic ingredient according to its historical anti-cancer activity. Although several investigations have explored the use of the whole CM in different types of cancer therapies, further explorations are needed to discover the effect of nano biomolecules isolated from CM that can be used in modern therapy.

Anti-inflammatory activity

In addition to anti-cancer property, CMEXOs also exhibited high capability of anti-inflammatory activity. Augmented amounts of pro-inflammatory cytokines like TNFα, TGFβ1, IL1β, and NFkB, are indispensable for tumor initiation, metastasis and attack (Han et al., 2014; Elgazar et al., 2018**).** In a study on rats, Arab et al. (2018) reported that CM could restore the inflammatory environments connected with diabetes and 5-fluorouracil-incited renal impairment in rats via restraining the pro-inflammatory cytokines statement. Additionally, Badawy et al. (2018) described that the anti-inflammatory property of CMEXOs exhibited superior impact to CM, as documented by downregulation of the inflammation-related genes, interleukin 1 beta (*IL1*β), and nuclear factor-kappa B (*NF*κ*B)* in cancer tissues. In parallel with the previous results, the anti-inflammatory effect of camel urine was evidenced on the tumor cell such MCF7 cells in rats (Romli et al., 2017). Linking with the biomolecules of camel urine and milk, it is conceivable that EXOs are the main players in this achievement as they are formed by almost all cell subgroups and plentifully isolated or derived from the urine or/and milk (Romli et al., 2017). Ibrahim et al. (2019) clarified that the CMEXOs display anti-inflammatory activities against tumors through a substantial augment in the expression of TNF-α and IL-6 as well as a noteworthy reduction in the expression abundance of IFN-γ after administration with cyclophosphamide as related to the control rats (Ibrahim et al., 2019). NF-κB is one of the vital transcription features that helps the expression of various genes of immune and inflammatory responses such as IL-6 and TNF-α (Mauriz et al., 2013). A previous description documented the anti-inflammatory property for CMEXOs via the downregulation of NF-κB and IL-1β in rat's mammary tumor tissues

(Badawy et al., 2018). Certain *in vivo* studies revealed that camel undenatured whey proteins restricted the extended inflammation in diabetic rats via the decrease in the concentrations of serum IL-1β, IL-6 and TNF-α (Ebaid et al., 2013). Moreover, CM repressed renal inflammation persuaded by 5-fluorouracil via suppression of IL-1β, and TNF-α as well as repressed NF-κB stimulation in Wistar rats (Arab et al., 2018). Numerous bioactive peptides are showing various health-promoting purposeful properties in milk proteins. Consequently, camel undenatured whey protein can boost the immune response via the augmentation of mRNA expression of both IFN-γ and IL-2 in rats after four months of streptozotocin-induced diabetes (Ebaid, 2014). Among the chronic hepatitis B patients, it was reported that the levels of serum IFN-γ in camel milk-drinking patients were meaningfully greater than those in patients who did not receive CM (Saltanat et al., 2009). This might be showing the potential antiviral activity of CM or its bioactive peptides. Moreover, lactoferrin supports the development of dendritic cells by augmenting their capability to induce propagation and synthesis of IFN-γ in the attendance of allogeneic human T-lymphocytes (Actor et al., 2009), and it can trigger the synthesis of IL-12 by antigen offering cells, which in turn improves IFN-γ synthesis and initiates Th1 cell growth (Actor et al., 2009; Daneshmandi et al., 2017).

Casein-loaded dendritic cells could somewhat provoke the Th1 cell response via the improvement of lymphocyte propagation and inducement of IFN-γ synthesis (Daneshmandi et al., 2017). Recently, CMEXOs showed a significant modulation in the inflammation process of cancer cells through significant downregulation of inflammatory-related genes such as *TNFα*, *NFkB*, *TGFβ1*, and *Cox2* in HepaRG cells (Badawy et al., 2021). In rats bearing breast cancer, it has been reported that the CMEXOs have a potential role in repressing the pro-inflammatory cytokines (Badawy et al., 2018). Collectively, previous evidence clarified the pulsative role of CMEXOs in reduction of the pro-inflammatory cytokines response in different *in vitro* and *in vivo* models, however, further explorations are essential to elucidate more molecular mechanisms behind their effects.

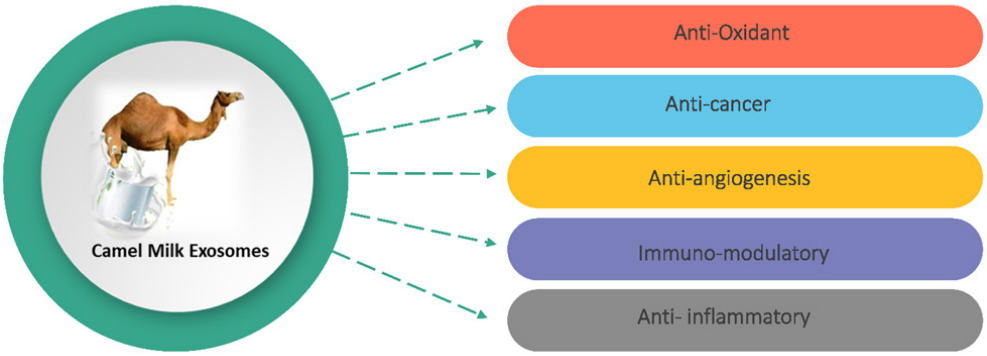


Figure 3. Therapeutic potential of camel milk exosomes with potent anticancer, antioxidant, anti-inflammatory, and anti-angiogenesis effects

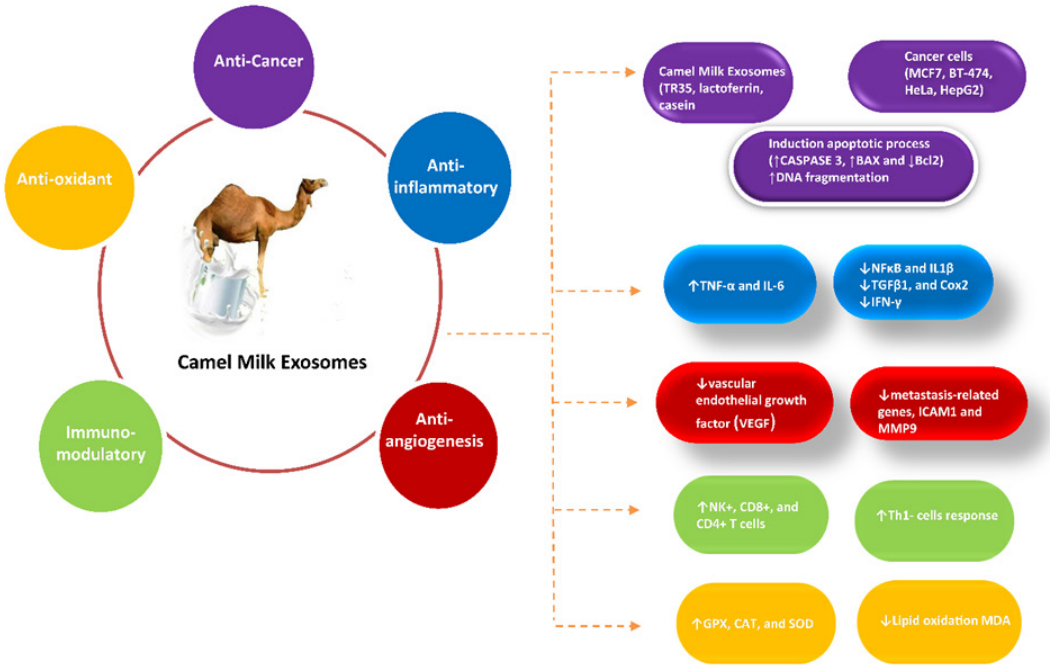


Figure 4. The mechanistic roles of exosomes isolated from camel milk

Anti-angiogenesis activity

Generation of new development of the vascular network is vital since the metastatic spread, proliferation of cancer cells be contingent on a satisfactory supply of nutrients and oxygen and the elimination of waste products (Nishida et al., 2006). Angiogenesis is controlled by both inhibitor and activator molecules. The detection of angiogenic inhibitors or anti-angiogenesis can support a decrease in both mortality and morbidity from carcinomas. Milk EXOs are hopeful candidates in emerging new therapeutic tactics to exhibit different anti-angiogenesis activities**.** Various diseases have been reported to have higher activity of vascular endothelial growth factor (VEGF) (Nishida et al., 2006). A substantial correlation between the expression of VEGF and prognosis has been described in several types of cancers and other diseases (Badawy et al., 2018, 2021). Administration of CMEXOs led to substantial downregulation of angiogenesis-related gene (VEGF) expression in tumor tissues as compared to the tumor group (Badawy et al., 2018, 2021). This feature could suggest the inhibitory property of CMEXOs on tumor environment angiogenesis. Besides, CMEXOs also exhibited an antimetastatic activity on MCF7 cells as shown by an *in vitro* wound healing test, which discovered inferior cell migration percentage with superior effect when EXOs were employed (Badawy et al., 2021). To further authenticate the antimetastatic probability of CM and its EXOs, the metastasis-related genes (*ICAM1* and *MMP9*) were examined. As predicted, the application of CM and its EXOs meaningfully downregulated the transcript of *MMP9* and *ICAM1* in tumor tissues with the greatest enhancement by EXOs administration (Badawy et al., 2021).

Similarly, studies have indicated that the inferior expression of the metastasis-related gene such as *ICAM1* was observed in tumor tissues of mice subsequently treated with camel urine (Romli et al., 2017) or CM or its EXOs (Badawy et al., 2021)**.** Furthermore, the upregulation of *ICAM1* was related to the invasive and metastatic capability of several cancer cells (breast cancer and other carcinoma cells). As previously indicated, chemokine in the tumor microenvironment shows a significant function in the invasion and migration of carcinoma cells (Fernandis et al., 2004). Badawy et al. (2018) confirmed that CM and its EXOs are new disruptors for chemotaxis-based migration of MCF7 cells (Badawy et al., 2018). HepaRG cells treated with EXOs displayed significant downregulation of *VEGF*, which indicates the aptitude of EXOs to constrain the angiogenesis process in the tumor tissues. A comparable anti-angiogenesis property was described for EXOs derived from mesenchymal stem cells in the HCC microenvironment, unlike those originating from cancer stem cells which presented angiogenic activity (Alzahrani et al., 2018). Mice co-administered with CMEXOs and some phytochemical displayed inferior expression of both *VEGF* and *Bcl2* and superior expression of *Cas3* and *Bax* genes in MCF7 xenograft compared to those administered with each alone (Badawy et al., 2021)**.** This reveals a potent anti-angiogenetic activity of EXOs for the incorporated therapy compared to a single treatment.

Immuno-modulatory activity

The immune system plays an essential function in different cellular development and growth in living organisms as well as is responsible for induction of different diseases. This feature is primarily intermediated by several immune cells: T cells, including CD4+ helper, CD8+ cytotoxic, and natural killer (NK) cells (Grivennikov et al., 2010). CM proteins exhibited better immune responses connected with the enhancement of infectious diseases. In this regard**,** Badawy et al. (2018) clarified that administration of CM and its EXOs significantly enhanced the immune criteria such as NK+, CD8+, and CD4+ T cells in the spleen of rats. Higher T cell differential detected in animals could reflect better immunity and lesser tumor sizes. Likewise, various articles documented that cancer patients with high levels of T cells such as NK+, CD8+, and CD4+ cells have superior prognosis and survival rates (Malmberg et al., 2008; Laghi et al., 2009)**.** Improving the levels of the CD4+ cell could constrain the development and progress of tumors via suppression of inflammation interrelated cytokines (Chen et al., 2021; Lei et al., 2022; Hou et al., 2022). On the other hand, CD8+ cells can reduce cancer cells directly or indirectly by augmenting the synthesis of other cytotoxic cytokines (Grivennikov et al., 2010).

Surprisingly, administration of CM caused superior percentages of NK1, CD8+, and CD4+ compared to co-administration of EXOs. This might be explained by the fact that the CM has other immune-stimulant compounds than those existing in their EXOs. The immune-stimulatory activity of CM could be attributed to its content of immunoglobulins, casein, lysozyme, lactoferrin, and lactoperoxidase (El Agamy et al., 1992). Furthermore, CM comprises unique nanobodies with variable heavy chain, and has no typical light chains like normal antibodies. These very tiny nanobodies presented in CM IgGs can easily penetrate the cell membrane of any cells (including cancer cells) and localize intracellularly to achieve different immune-stimulatory activities (Korashy et al., 2012; Sedykh et al., 2020; Khan et al., 2021). Consequently, it was supposed that CMEXOs can transport or be a ligand for these immune-stimulant components. This mechanistic insight needs further explorations to be clarified. Ibrahim et al. (2019) reported that CM and its EXOs moderately enhanced lymphocyte profile of rats treated with cyclophosphamide. The same authors indicated that the rats co-treated with CMEXOs and cyclophosphamide exhibited significant increases in both CD8+, CD4+ cells and T-lymphocyte relative to the cyclophosphamide group. Authors suggested that the immunomodulatory effects of CM and its EXO may be accredited to their contents of caseins and lactoferrin. In addition, they confirmed fruitful delivery of CMEXO kappa casein and lactoferrin mRNAs into the rat tissues via separation and sequencing of camel kappa casein and

lactoferrin from the spleen of the treated rats. Daneshmandi et al. (2017) showed that casein-loaded dendritic cells could improve the Th1 immune status in mice. The activation of NF-κB, lactoferrin and MAP kinase can stimulate the proliferation, maturation, differentiation, activation of different immune cells (Actor et al., 2009). It has been revealed that lactoferrin shows a beneficial role in the reconstitution of the cellular immune response as it promotes cellularity and enhancement of CD4+, CD3+ lymphocytes in the spleen and reinstates the host T cell compartment (Artym et al., 2003; Bhattacharyya et al., 2014) Besides, lactoferrin infusion produced a strong Th1- response and encouraged the activation of T-lymphocytes such as CD8+ and CD4+ in tumor-bearing models.

Antioxidant activity

Oxidative stress (OS) can be defined as a disparity between the free radical production and the body's capability to combat against the destructive impacts of antioxidants. The subsequent difference in homeostasis on the explanation of excessive reactive oxygen species (ROS) induces cell impairment and is one of the leading reasons for emerging ailments such as gastric/colorectal cancer, inflammatory bowel disease, and gastroduodenal ulcers (Bhattacharyya et al., 2014). Badawy et al. (2018) indicated that CM and its EXO significantly enhanced the synthesis of antioxidant enzymes (catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPX)), and reduced the content of lipid peroxidation indicator malondialdehyde (MDA), and the transcript of the OS indicator *iNOS* in tumor matters as relative to the tumor group. This suggests that OS/antioxidant pathway may be complicated with the repressive role of CM and its EXOs on tumor development. It was revealed that co-treatments of cyclophosphamide with CM or CMEXOs meaningfully decreased the lipid peroxidation signal MDA amount and increased the antioxidant enzymes GPX, CAT, and SOD levels as relative to the cyclophosphamide -treated rats (Ibrahim et al., 2019). CM enhanced the antioxidant response in renal tissues and repressed the OS triggered via 5-fluorouracil induction in Wistar rats (Arab et al., 2018). Furthermore, a prior investigation verified the antioxidant capabilities of various peptides primarily attained from caseins of the CM (Ibrahim et al., 2019). Synergistic effect of EXOs and some phytochemical showed significantly lower MDA, and higher CAT and GPx activities in hepatic tissues than in control mice (Badawy et al., 2021). This potential ability of EXOs to bring the apoptosis to avoid angiogenesis and invasion in MCF7 cells could be a beneficial approach in treating some diseases. Remarkably, the combined therapy using phytochemical (tamoxifen, and hesperidin) and EXOs also restored the disrupted OS/antioxidant status to normal levels related to that of the standard control. Inclusively, tamoxifen, hesperidin and EXOs mixture treatment can not only potentiate tamoxifen anti-cancer activity but also boost antioxidant status that decreases OS impairment triggered by tamoxifen and/or cancer problem (Badawy et al., 2021).

Conclusions and future perspective

An increasing body of evidence has discovered the potential role of CMEXOs in anti-cancer, anti-inflammatory, antioxidant and anti-microbial properties which could be used in treating several ailments, enhancing health, as well as contributing as a new therapeutic window. Investigations exhibited that EXOs derived from CM have more stable form under adverse environments, such as freezing-thawing, low pH, and heating, and can be easily absorbed through the intestinal barriers to the circulation system. In this paper, the potential roles of CMEXOs including anti-cancer, anti-inflammatory, antioxidant were reviewed. Moreover, the CMEXOs can also serve as oral delivery vehicles for chemotherapeutic mediators and further amendment of the EXOs with a tumor-targeting ligand allows the targeted delivery of drugs to the tumor sites. Furthermore, the significance of these novel achievements of CMEXOs is constructed through their advantages over prevailing therapeutic opportunities. Developments in technical isolation of EXOs and a greater understanding of the mechanistic details will support the medical community to extend us a safe and effective tool for resolving public health problems on a broader scale. In addition, it would be significant to create a standardized and cost-effective technique to isolate, purify, and employ EXOs from CM to safeguard the quality of the EXOs for industrial and clinical uses. Future reports are essential to validate how individual bioactive compounds within EXOs employ biological roles, including antitumor, antidiabetic, anti-obesity, and antihypertensive properties to elucidate any plausible undesirable effects upon EXO remediation.

Funding

This work was funded by the National Key Research and Development Program of China (No. 2018YFD0501700), National Modern Agricultural Industry Special Program (No. CARS-37), the National Natural Science Foundation of China (31972994), the Agricultural Science and Technology Innovation and Transformation Project of Shaanxi Province (NYKJ-2018-LY09) and the Key Research and Development Program of Ningxia (Grant No. 2019BEF02004).

Acknowledgments

We thank Shaqra University and the Scientific Research Deanship of Shaqra University, KSA for their kind support to Althobaiti N.A., BinMowyna M.N., and Aldawsari R.D.

Competing Interests

The authors declare that they have no competing interests.

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Received: 26 I 2022
Accepted: 16 IX 2022