



Health-promoting Effects of Camel Milk and its Exosomes

Mohammed Abu El-Magd

Anatomy Department, Faculty of Veterinary Medicine, Kafrelsheikh University, Post Box 33516, El-Geish Street, Kafrelsheikh, Egypt.

*Corresponding Author: E-mail: mohamed.abouelmagd@vet.kfs.edu.eg; ORCID ID: <https://orcid.org/0000-0002-3314-9202>.

Camels (*Camelus dromedaries*) produce milk that is lower in cholesterol and lactose, but higher in minerals, vitamins, and insulin-like substances than that produced by cows and could be safely consumed by people suffering from lactose intolerance and immune deficiency (Shariatikia et al., 2017). Regular drinking of camel milk was thought to boost immunity and decrease susceptibility to many diseases and cancer in the Middle East. Camel milk has many beneficial health-promoting effects on some diseases and health disorders such as dropsy, jaundice, anemia, autism, multiple sclerosis, psoriasis, lupus, and Crohn's disease (Homayouni-Tabrizi et al., 2017). In vitro studies revealed an anticancer impact of this milk against HepG2, HepaRG, Hepa 1c1c7, MDA-MB-231, and MCF7 cancer cells, and apoptosis induction is the mechanism responsible for this impact (Badawy et al., 2018a; Badawy et al., 2018b; El-Kattawy et al., 2021; Homayouni-Tabrizi et al., 2017; Korashy et al., 2012a; Korashy et al., 2012b; Shariatikia et al., 2017). In vivo studies also revealed potent immunostimulatory and anti-inflammatory properties of camel milk on liver diseases (El Miniawy et al., 2014; Mohamed et al., 2015). These health-promoting effects could be due to the unique contents of camel milk especially kappa casein (KC), lactoperoxidase (LP), and lactoferrin (LF) which possess anti-tumor, and anti-inflammatory properties (Dong et al., 2020; Habib et al., 2013; Iigo et al., 2009; Rodrigues et al., 2009; Shariatikia et al., 2017; Tellez et al., 2010). Camels' milk was shown to contain more of these proteins than cow's milk (Habib et al., 2013).

Camel milk, like that of other mammals and humans, includes exosomes, which have been isolated from the milk and then characterized morphologically using a transmission electron microscope (TEM) and molecularly by exosomal specific proteins (Ali et al., 2020; Alzahrani et al., 2018; Alzahrani et al., 2021; Badawy et al., 2018a; Badawy et al., 2021a; El-Kattawy et al., 2021; Ibrahim et al., 2019; Othman et al., 2021; Yassin et al., 2016). Most of these studies reported potent anticancer, anti-inflammatory, antioxidant, and immunostimulant effects for camel milk exosomes. The latter exert potent apoptotic effects on liver cancer (HepaRG, HepG2), colorectal cancer (CaCo2), breast cancer (MCF7), and leukemia (HL60) cells through overexpression of apoptotic markers (Bax and caspase3) and reduction of Bcl2 mRNA levels (Badawy et al., 2018b; Badawy et al., 2021b; El-

Kattawy et al., 2021; Othman et al., 2021). Camel milk exosomes also inhibit MCF7 migration, as revealed by downregulated expression of *MMP9* and upregulation of *TIMP1*, and angiogenesis as indicated by downregulation of *VEGF* (Badawy et al., 2018b). Moreover, the anti-tumor activity against MCF7 xenografts in mice was considerably increased when camel milk exosomes were coupled with hesperidin and tamoxifen (Badawy et al., 2021b). HepaRG cell growth was inhibited by camel milk exosomes, although normal THLE-2 cells were unharmed and possible mechanisms of this impact include apoptosis induction, inflammation suppression, and angiogenesis inhibition (El-Kattawy et al., 2021). Moreover, camel milk exosomes have been shown to also have selective anticancer capability against HepG2, PANC1, CaCo2 cancer cells, with a greater margin of safety on normal Vero and H6c7 cells (Ali et al., 2022; Shaban et al., 2023). Camel milk exosomes also showed immunostimulatory effects in cyclophosphamide-immunocompromised rats (Ibrahim et al., 2019). Recently, it was reported that camel milk exosomes could relieve diabetic nephropathy (DN) in rats through activation of antioxidant endogenous enzymes and inhibition of ROS and associated renal damage with subsequent repression of DN-related genes (*TGFβ1*, *ICAM1*, and *ETS1*, *ITGβ2*, *TIMP2*, and *KIM1*) (Shaban et al., 2022). Regarding the in vitro effect of camel milk exosomes on microorganisms, it has been recently documented that camel milk exosomes had bacteriostatic, rather than bactericidal, effects against Gram-negative bacteria (Shaban et al., 2023).

The method used for raising camels and the type of food they feed on can affect the components of camel milk. Interestingly, all the above-mentioned studies of camel milk exosomes were performed on camels grazing and feeding on wild plants in the desert. It is well known that desert plants can grow in harsh environments due to the presence of plenty of phytochemicals. Thus, milk obtained from camel grazing on these plants could have unique health-promoting components. However, it is also worth comparing milk contents including exosomal proteins and miRNAs between these camels and other camels raised on the farms. Another factor that may affect milk exosomal contents is the lactation period. Accordingly, colostrum-derived exosomes had higher contents of miRNAs related to immune response such as (miR-15b, miR-27b, miR-106b, miR-155, and miR-223) compared to mature cow milk (Izumi et al., 2012; Izumi et al.,

2015). Similarly, camel colostrum exosomes had a more potent anticancer effect against HepaRG cells than exosomes extracted from the other lactation periods (El-Kattawy et al., 2021). Based on this previous study, camel colostrum-derived exosomes had higher levels of LF and KC mRNAs than exosomes derived from other lactation periods. This is compatible with the potent immunostimulatory potential of colostrum, particularly at young ages (Gu et al., 2012). Moreover, the presence of LF and KC genes implies the capability of exosomes to safeguard their mRNAs from destruction by milk nucleases (Keller et al., 2011). The camel milk exosomes' capacity to take diverse paths in the microenvironment of cancerous and healthy cells was also noted. Indeed, camel milk exosomes can kill cancer cells through the elevation of intracellular ROS and inhibition of antioxidant enzymes and associated genes (*Nrf2* and *HO-1*) but they exert the opposite effect on the normal cells (Badawy et al., 2018b; El-Kattawy et al., 2021; Shaban et al., 2023). There is still much to learn about camel milk exosomes and their function in facilitating cross-talk between healthy cells and cancer cells in the tumor microenvironment.

Conflict of interest

The author declares that he has no conflict of interest.

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