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Potential Anti-Cancer Qualities of Camel Milk and Urine - Review

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Abstract

Traditionally, camel milk (CM) and camel urine (CU) have been used in the treatment of various pathologies, such as tuberculosis, hemorrhoids, ascites, abdominal problems, anemia, and abdominal tumors. The therapeutic qualities of CM and CU are due to a number of potent biomolecules with promising medicinal qualities including apoptic capacity to modulate, slow and/or inhibit growth or kill cancer cells. These biomolecules include but not limited to: lactoferrin, alpha-lactalbumin (α-LA) protein, Milk-derived peptides, especially whey proteins and lactoperoxidase, that contribute to the non-immune host defense system, exerting anti-cancer, anti-viral, and anti-bacterial activity, on Gram-negative bacteria and promoting growth activity. In addition, CM contains enzymes that exert antibacterial and immunological properties, viz.: lysozyme, unique immunoglobulins, complements components, and Peptidoglycan Recognition Protein (PGRP). The PGRP has a broad antimicrobial activity but has also been reported to control cancer metastasis. On the other hand, thirty different compounds have been isolated from CU and it is believed that the latter has a therapeutic effect for a wide range of diseases. The in vitro and in vivo studies in animals and humans of the anticarcinogeneic effects of the CM and CU biomolecules are mainly attributed to: inhibition of carcinogenesis and mutagenesis, proliferation of cancer cells, and induction of cancer apoptosis and the improvement on the life span and the survival of animals due to clearance of malignant tumors in various organs and the inhibition of progression to metastasis. Prospects of isolating promising therapeutic nanoparticles/nano-bodies/nano-rods from camels are now being explored for cancer therapy. However, there is still a wide gap with regard to advanced research geared towards identifying and designing suitable therapeutic nano-materials from CM and CU for clinical use. Therefore, this review examines the claims attributed to camel milk and urine, and proposes a deeper understanding of the therapeutic clinical potential of CM and CU biomolecules in the management of human and animal cancers.

Keywords: Camel Milk; Urine; Anti-Cancer Properties

Abbreviations

CM: Camel Milk; CU: Camel Urine; PGRP: Peptidoglycan Recognition Protein; MPBUH: May Peace Be Upon Him; ROS: Reactive Oxygen Species; PCE: polychromatic erythrocyte; NCE: Normochromic Erythrocyte; GSH: Glutathione; MDA: Malondialdehyde; CP: Cyclophosphamide; FAOSTAT: FAO Statistics.

Introduction

Camels have been domesticated for about 3000 years and provide food such as milk and meat and also fiber and wool for textiles, transport, sports and tourism. The one-humped camels, most famous of the 3 species (Camelus bactrianus, Camelus dromedarius and Camelius ferus) comprise about 94% of the world's camel population. This

species is the most famous of three species of the camels, whereas the two-humped camels form about 6%. The total world camel population was estimated to be 35,525,270 [1]. Over 80% of the world camels are found in Africa. The main camel rearincountries in Africa are: Somalia (7,100,000), Chad (6,400,000), Ethiopia (1,200,000), Kenya (2,986,057), Mali (1,028,700), Mauritania (1,379,417), Niger (1,698,110), Sudan (4,830,000) [2]. In the Arab world where the camel was first domesticated 3000 years ago, the total dromedary population is about 1.5 million camels, of which about 53% are found in Saudi Arabia [3]. People living in camel rearing regions of the world, have for long recognized the health benefits of Camel milk (CM) and Camel urine (CU). The use of CM has been observed in the treatment of various infections and conditions such as: jaundice, asthma and hypertension and diabetes. Both CM and CU have potent antibacterial and antifungal effects. C M exosomes (CM-EXO), nano vesicles 40–120 nm in diameter secreted by almost all cell types and providing humoral intercellular interactions, has been shown to inhibit the proliferation of a large variety of cancer cells including HepaRG, MCF7, Hl60, and PANC1.

Camel Urine (CU) As an Anti-Cancer Agent

In the camel rearing communities of Middle East, Asia and Africa CU is used as prophylactic and therapeutic agent for treatment of diseases, including cancer. A study conducted in 2018 showed that 15.7% of patients with cancer in Saudi Arabia consumed CU, either alone or mixed with CM, as alternative remedy [4-6]. An in vivo study in mice further showed that treatment with CU had significant anti-metastatic effects on breast cancer cells [7]. Chemical analysis of CU using gas chromatography and mass spectrometry revealed the presence of 20 metabolites in CU compared to only 14 metabolites in bovine urine, which included but not limited to: canavanine, erythritol, benzenepropanoic acid and melibiose [8]. Reports of earlier studies had confirmed that canavanine has potent anti-neoplastic activity and that 2% of this metabolite is excreted in CU [9-11].

In an earlier study it was observed that CU at 50% concentration produced a significant cytotoxic effect in mouse bone marrow cells [12]. The reduction in the ratio of polychromatic erythrocyte (PCE) to normochromic erythrocyte (NCE) that was observed indicated that CU had a cytotoxic potential. This was further corroborated by the decreased nucleic acids and glutathione (GSH) levels and increased malondialdehyde (MDA) in the same study. The cytotoxic effect of camel urine was comparable to that of cyclophosphamide (CP), a standard drug for chemotherapeutic treatment of cancer patients. That notwithstanding, CU-treated mice did not show any clastogenic activities, in contrast to CP, which has high clastogenic activity. A similar finding was also noted where CU was found to be mitodepressive but not clastogenic [13,14]. Furthermore, CU showed no clastogenic effect on the bone marrow cells of mice, and 25 and 50 ml/kg of CU treatment significantly improved the cyclophosphamide-induced clastogenic effect in mice. Thus, the presence of antioxidative and antimutagenic components, such as creatinine and uric acid, in CU may contribute to the non-clastogenic nature of CU [15,16]. It was observed that uric acid is a potent scavenger of peroxyl and hydroxyl radicals and singlet oxygen [16] and can chelate metal ions by converting them to poorly reactive forms that cannot catalyse free-radical reactions [17-20].

In vitro studies by Yousef N, et al. [21] using ten types of cancer cell lines showed that CU exhibits varying anticancer properties on the ten cancer cell types. Significantly, CU killed more than 80% of MDA-MB-231 (breast cancer cells) but not the MCF 10A cells (kin of non-tumourigenic breast epithelial cells) which were used as control. These findings provide evidence that shows that CU has varying cytotoxic and inhibitory effect to cancer cells. The effect on breast cancer cells is quite significant. CU was also shown to induced apoptosis (90%) in the group of CU-sensitive cells, which also manifested a slight degree of necrosis. High levels of caspase-3 and PARP, 18.6- and 3.4-folds higher than normal, respectively, were believed to trigger apoptosis via the mitochondrial pathway and also showed potent inhibitory effects on two major apoptosis inhibitor proteins, Bcl-2 and survivin, which are involved in breast cancer pathology [22-24]. CU is believed to possess a significant anti-proliferative effect on breast cancer cells, as evidenced by the proliferative inhibitory effect on MDA- MB-231 cells immediately following treatment and this could be due to the mediatiation by the cyclin-dependent kinase inhibitor p21, associated with the acquisition of senescence phenotypes in breast cancer cells as observed earlier [25]. This finding also corroborated the findings of other workers Lacroix M, et al. [26] who found an up-regulation of p21 in the p53-defective MDA-MB-231 cells, indicating a p53-dependent effect. It is well known that p53 transcriptionally activates genes which induce cell cycle arrest or apoptosis and in turn eliminates and inhibits the proliferation of abnormal cells, thus peveventing the development of cancerous cells or their proliferation and metastasis [27].

Camel Urine may also act as an anticancer agent by enhancing the production of IFN-ɣ and inhibiting IL-4, IL-6 and IL-10. IL-4 lis inked to tumor cell growth, whilst IL-6 is a potent growth factor for breast cancer [28,29]. Both IL-4 and IL-10 levels were almost undetectable after treatment with CU. A high level of IL-10 correlates well with poor survival of cancer patients [30]. Thus, inhibition of these cytokines holds a promising therapeutic strategy for breast cancer treatment. Other workers used Hepa 1c1c7 cells, a hepatoma cell line, to evaluate the ability of CU to inhibit cytochrome

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P450 1a1 (CYP1A1) gene expression. The CYP1A1 is a known cancer-activating gene and strongly correlates with an increased incidence of colon, rectal and lung cancers [31-33]. Figure 1 shows the modulation of CYP1A1 catalytic activity by camel urine. The most potent inducer of CYP1A1 is 2,3,7,8-Tetra chlorodibenzo-p-dioxin (TCDD) [34]. CYP1A1 is believed to stimulate the bioactivity of pro-carcinogens to regenerate reactive metabolites Rendic S, et al. [35] which form DNA adducts and contribute to mutagenesis, eventually leading to the development of various types of cancer [36]. Correlations between DNA-adduct formation and exposure, hepatocyte initiation and hepatocellular carcinoma were adequately demonstrated [37]. It was observed that a concentration of up to 25 mg/ml of CU was not toxic to Hepa 1c1c7 cells for virgin, pregnant and lactating rats in an in vivo cytotoxic study.

However, a recent clinical study ever carried out using CU on 20 humans cancer patients in Saudi Arabia in 2023, demonstrated that a combination of CM and CU had no clinical benefits for any of the cancer patients. Furtermore, drinking CM/CU was suspected to have even caused zoonotic infections (MARS COV and Brucellosis) in some of the patients [38]. The study recommended that the promotion of camel urine as a traditional medicine should be stopped because there was no scientific evidence to support it. That notwithstanding, this study had a few limitations, namely: the type of cancer the patients were suffering from is not mentioned (CU may not treat all cancers); how CU was prepared and the dosage could have affected the outcome of the experiment. Therefore more clinical studies must be carried out with better CU formulations and dosages to enable credible and informed opinion. Recently it was shown that CU has anticancer and antiviral effect up to 8-fold of dilution in an in vitro study [39]. The main components defined in fractionated urine were the anticancer chemicals: dimethylamine and formamide. The study showed that CU had cytotoxic effect for different cancer cell lines and antiviral effect of up to 8 folds of dilution. Dimethylamine and formamide are major components of current cancer chemotherapy.

Anti-Cancer Properties of Camel Milk (CM)

CM has been reported to have a number of potent biomolecules with promising apoptic capacity to modulate, slow and/ or inhibit growth or kill cancer cells. These include but not limited to: lactoferrin, alpha-lactalbumin (α-LA) protein, milk-derived peptides, especially whey proteins, lactoperoxidase that contribute to the non-immune host defense system, exerting bactericidal activity, mainly on Gram-negative bacteria [40,41]. CM also contains a number of other protective proteins, mainly enzymes that exert antibacterial and immunological properties, viz: lysozyme, immunoglobulins, complement components, and Peptidoglycan Recognition Protein (PGRP) [42-48]. PGRP has broad antimicrobial activity but has also been reported to have the ability to control cancer metastasis. The reported bioactive molecules regulate many pathways including the apoptotic pathways, thereby stopping the cancer cells' proliferation and spread [49-51].

The influence of CM on human cancer cells' proliferation in an in vitro model of the human hepatoma (HepG2) and human breast (MCF7) cancer cells was examined by Korashy HM, et al. [52] and observed to inhibit the proliferation of HepG2 and MCF7 cancer cells by activating the caspase-3 mRNA and inducing the death receptors in HepG2 and MCF7 cell lines. Consequently, the expression of oxidative stress markers, heme oxygenase-1 and ROS production was enhanced by camel milk in HepG2 and MCF7 cell lines [53]. It appears CM induces the cell surface death receptor-4 (DR4) mRNA, which is involved in the activation of caspase-3, in mice HepG2 and MCF7 cells and also associated with apoptotic induction, which in addition activates the caspases [54,55]. The levels of ROS production and oxidative stress biomarkers were also enhanced in the HepG2 and MCF7 cell lines treated with CM [53]. Camel Peptidoglycan Recognition Protein (PGRP) has broad antimicrobial activity and has the ability to control cancer metastasis.

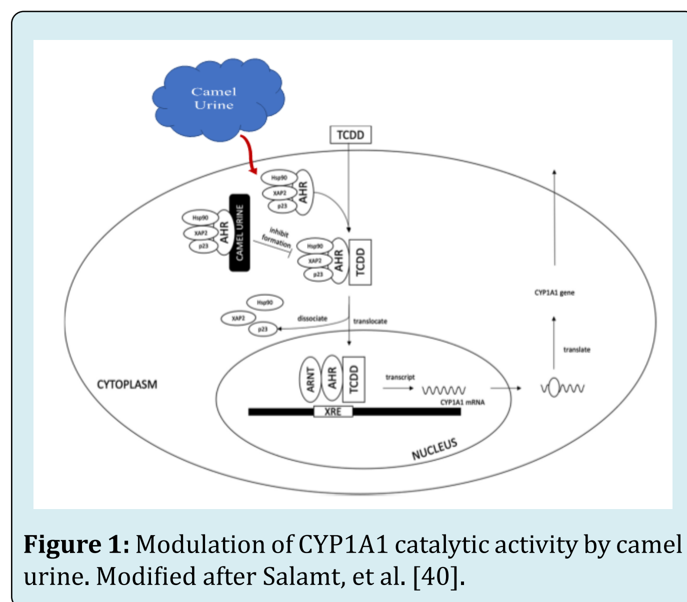

Figure 1: Modulation of CYP1A1 catalytic activity by camel urine. Modified after Salamt, et al. [40].

CM lactoferrin is a potent biomolecule and is reported to prevent the proliferation of colorectal cancer cells and exerts antioxidant and DNA damage-inhibitory properties in cancerous cells [56]. The caseins in CM and whey proteins have been shown to have cytotoxic and antioxidant activities against the MCF7 cells [57]. CM has been reported to regulate

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the antioxidants and cell apoptosis and also to inhibit the survival and proliferation of HepG2 and MCF7 cells through the intrinsic and extrinsic metabolic pathways as shown in Figure 2 below.

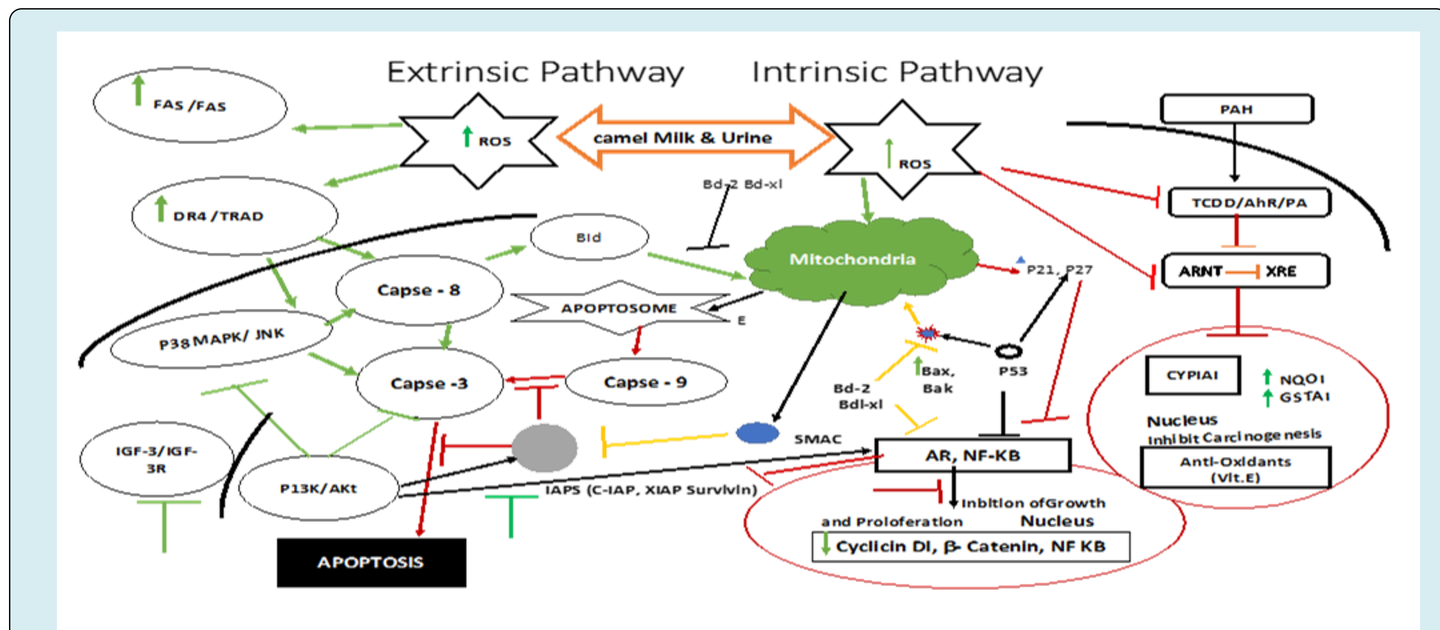

Figure 2: Possible pathways (Extrinsic and Intrinsic) and targets of anti-cancer properties of camel milk (CM). Camel Milk induce apoptosis in various cancer cells through extrinsic pathway by enhancing DR4 expression and ROS production, causing activation of c-Jun N-terminal kinases (JNK) and Caspases and in the intrinsic pathways mainly by enhancing ROS production that leads to activation of Caspases. Inhibition of carcinogenesis by down-regulating the induction of Cyp1a1, a cancer activating gene, and inducing Nqo1 and Gsta1, cancer protecting genes. Furthermore, activation of these pathways leads to the Inhibition of Cell cycle progression, proliferation and survival of cancer cells by interfering with the binding of insulin-like growth factor receptor, a known regulator of the phosphatidylinositol 3-kinase/Akt pathway as well as activation of Caspases, causing increase in Cyclin-dependent Kinase (CDK) inhibitor p21 and p27 protein levels. Activation by CM (green), CU (yellow), CM & CU (red); inhibition by CM (green), CU (yellow), CM & CU (red); ↑ increase, decrease. Adopted from Alebie g, et al. [58] and Khan MZ, et al. [59].

Some of the anti-cancer properties of CM are associated with its strong antimicrobial and anti-oxidative activities that help in reducing liver inflammation. CM has many nutrients that are required for a healthy liver function [52]. The molecular mechanisms that govern the effect of CM on human cancer cells and the functional properties of CM lactoferrin (Figure 2; Table 1) were examined and found that the main iron-binding protein of the latter could induce a 56% reduction of cancer growth [56]. These studies clearly demonstrated that CM induces apoptosis in human hepatoma (HepG2) and human breast (MCF7) cancer cells through apoptotic and oxidative-stress-mediated mechanisms. In addition, it was demonstrated that CM also has antigenotoxic and anticytotoxic effects through the inhibition of micronucleated polychromatic erythrocytes (MnPCEs) and that this may improve the mitotic index of bone marrow cells [60]. The proliferation viability and migration of human colorectal HCT 116 cells and breast MCF-7 cancer cells was inhibited in response to CM [61]. They observed that CM was able to significantly regulate the cytotoxicity in HCT 116 and MCF-7 cells [61]. A decrease in viability, migration and proliferation of HCT 116 and MCF-7 cells was especially observed in response to higher concentrations (100 and 250 µL/mL after 48 h) of CM. The HCT 116 and MCF-7 cells treated with the commercial CM were observed to have significant morphological changes characterized, mainly by the loss of cell membrane integrity along with extensive vacuolization. Moreover, Krishnankutty R, et al. [61], further observed that CM induced autophagy in HCT 116 and MCF-7 cells, similar to many other anti-cancer agents that facilitate autophagic fluxes in cancerous cells Mathew R, et al. [62] as shown in (Figure 3) below.

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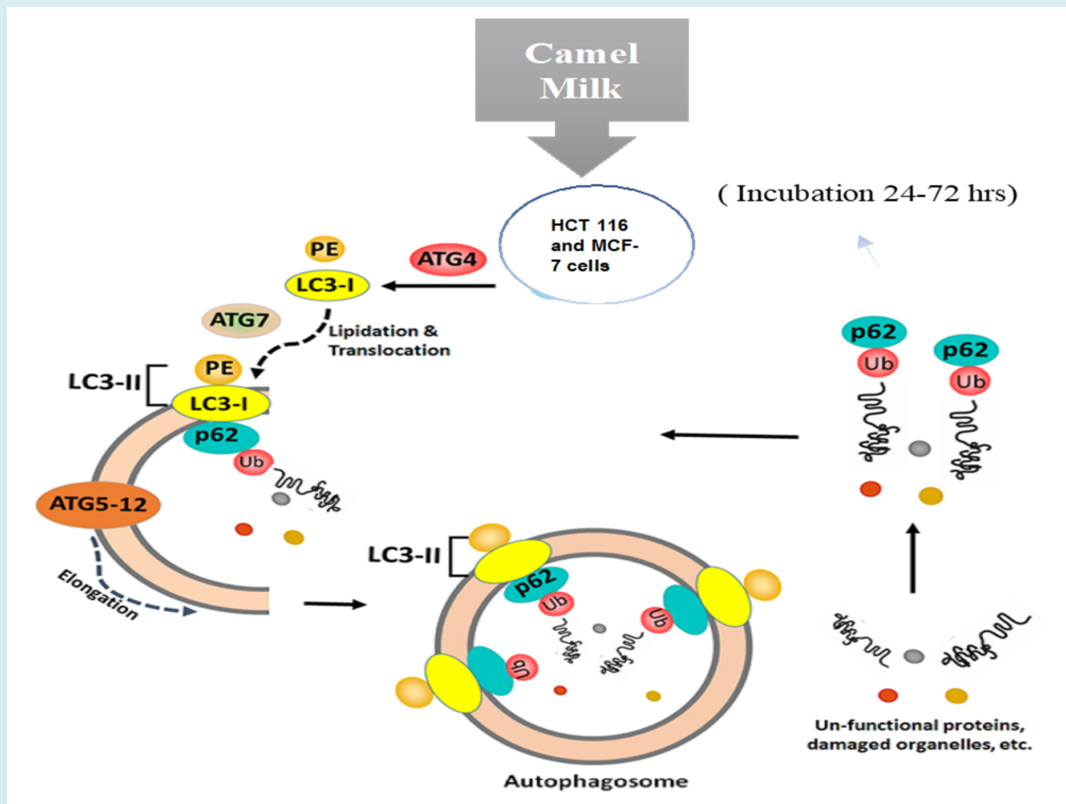

Figure 3: Autophagic Flux and formation of Autophagosomes after treatment of cancer cells with camel milk, emphasizes the role of various proteins involved. Microtubule-associated protein 1 light chain 3 (LC3) precursors are form LC3-I and further lipidated by phosphatidyl ethanolamine (PE) to form active LC3-II, which is then localizes onto the double membrane vesicles that form the nascent autophagosomes. The autophagy proteins such as ATG5 and ATG12 form a complex ATG5-12), which then gets attached onto the double membrane vesicles. These further mediate and elongation process leading to the autophagosome formation. The p1protein p62 (sequestosome 1) co-localizes with the ubiquitinated proteins (Ub, fated to be degraded) gets sequestered into the double membrane vesicles and subsequently gets engulfed into the autophagosomes destined for degradation. Adopted from Krishnankutty R, et al. [61].

The notion that whey protein in CM may influence acute myeloid leukaemia cells by interrupting the connection between PI3 Kinase (PI3K) and B-cell lymphoma 2 (BCL-2) signals and thus down-rgulate their expression to initiate the process of apoptosis in primary acute myeloid leukaemia (AML) cells Badr G, et al. [63] was backed up by the observation of higher expression of PI3K and BCL-2 (anti-apoptotic genes) noticed in AML patients, which increased the survival of AML cells. Higher expression of PI3K and BCL-2 was linked to chemoresistance and tumorigenesis [64]. Previous reports had shown that camel whey proteins significantly enhanced antioxidative stress and enhanced the recovery of damaged immune organs by lowering the expression of the anti-apoptotic BCL-2 gene [65,66] and the whey proteins mediated the migration of B and T cells towards the site of antigen recognition in lymphoid organs, thus enhancing the immunological mechanisms that may be involved in fighting cancer.

The alpha-lactalbumin (α-LA) protein isolated from CU has also been explored for its important role as a human anti-cancer agent, which is due to its ability to bind oleic acid (OA), observed to be due to the latter's ability to enhance apoptotosis, suppressed cyclinD1 and BCL-2, enhance the expression of p53 and cleaved caspase-3 [67,68]. In addition, the anti-cancer activity of the OA–α-cLA complex has been studied in four human cancer cell lines {Caco-2 colon cancer cells, PC-3 prostate cancer cells, HepG-2 hepatoma cells and Michigan Cancer Foundation-7 (MCF7)}. OA–α-cLA complex causes cancer cell death through the induction of apoptosis and cell-cycle arrest, which inhibits the tyrosine kinase (TK) activity of human cancer cells [67,69]. It was further observed that after binding to α-lactalbumin and lactoferrin, OA forms complexes and selectively targets the malignant cells without causing toxicity in normal cells [69,70]. The anti-cancer effect of camel milk and its exosome onto in vitro and in vivo MCF7 cells were also observed to significantly improve the

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activities of antioxidant enzymes (SOD, CA, and GPx) in MCF7 cells [70]. The inhibitory effect of camel milk and its exosome on cancerous cells is believed to be due to the induction of apoptosis and antioxidative effects. The supplementation of CM and its exosomes per os or parentally, was reported to significantly decrease the progression of breast cancer cells, thereby enhancing apoptosis by increasing the expression of caspase-3 activity and BCL2-associated X protein (Bax) and lowering the expression of the BCL-2 gene and to further inhibit the oxidative stress (MDA, inducible nitric oxide synthase (iNOS), inflammation-cytokines (interleukin 1B, NF-κB), angiogenesis- (VEGF) and metastasis (intercellular adhesion molecule 1 (ICAM-1) and matrix metalloproteinase 9 (MMP-9)-associated genes [70]. Cisplatin in combination with CM inhibited hepatocarcinogenesis in rats after initiating cancer-inducing diethylnitrosamine, which is again due to the antioxidant effect of CM [71]. Exploitation of CM, its exosome and peptides could be further undertaken, as this is already yielding promising results in the field of oncology for the therapeutic management of cancers Boohaker RJ, et al. [72] and to inhibit breast cancer cell line (MDA-MB-231) and nasopharyngeal carcinoma cells. Furthermore, it was observed Kamal H, et al. [73] that the three was Antiproliferative, anti-cancer (cytotoxicity), antidiabetic and anti- inflammatory effect in liver cancer cells treated with hydrolysates of CM whey proteins. Similarly, TR35 (whey protein) isolated from CM has an anti-cancer ability and inhibited the progression of human carcinoma cells of the esophagus (Eca109) [74]. Moreover Yang J, et al. [74] showed that TR35 inhibited the development of a xenografted tumor and cell proliferation and induced apoptotic activity in mice and Eca109 cells. Transcriptomic and proteomic studies with TR35-treated cells have also been reported. Among the genes studied, those related to apoptosis and necrosis and other pathways in cancer inhibition were identified in TR35-treated cells. CM has also been found to be effective against fibrosarcoma in a murine model. The anti-cancer drug etoposide (ETP), which was embedded in liposomes isolated from CM phospholipids, slowed down tumor growth and increased survival [52]. Similarly, the anti-cancer agent doxorubicin (Dox) or ETP loaded with CM phospholipid showed stronger anti-cancer activity in a murine model suggesting that CM can be a useful ajuvant to anti-cancer drugs and enhance the efficacy of anti-cancer therapy. The phosphatase and tensin homolog (PTEN) gene with anti-cancer efficacy was lower in tumor-induced cells, however, the PTEN gene was found to be higher in phospholipid-embedded doxorubicin-treated cancer cells [75,76].

Subjects of the Study	*In vitro/ In vivo*	Camel product used in the study	Dose and duration	Major clinical observations	Ref.
Healthy human voluteers	*In vivo*	CU (PM701 capsule)	3 capsules (300mg) daily for 4 months	Safe in healthy volunteers; no adverse effect observed in vital organs	[77]
Mice Leukaemia (L1210)	*In Vitro*	CU (PM701	16mg/ml for 0 -72hrs	Controlled tumour progression, metastasis and prevented metastasis	[78]
Lung Cancer cells(A539)	*In Vitro*	CU (PM701	-	Inhibition of cell proliferation	[79]
Murine Hepatoma -Hepa 1c1c7 Cell line	*In Vitro*	CU Virgin, lactating and pregnant mice)	-	Inhibition of the TCDD-Mediated toxicity and depression of the Cyp1a1,at the mRNA and protein expression levels	[80]
Murine Hepatoma -Hepa 1c1c7 Cell line	*In Vitro*	CU Virgin, lactating and pregnant mice)	-	Inhibition of carcinogenesis and mutagenesis/modulation of AhR-regulated genes- Ho-1, Nq1 and Gesta1 at the transcription and pos-transcriptional levels; TCDD-mediated induction of Cypt 1a1 activity and Cypt 1a1 mRNA protein	[81]
Healthy mice	*In Vitro*	CU (PMF)	2-20 x of thetherapeutic dose (0.75)	Safe in mice; has no any hepatotoxicity, no nephrotoxicity	[82]
Healthy mice	*In Vitro*	CU (PMF)	2-20 x of thetherapeutic dose (0.75)	Safe in mice; no any hepatotoxicity and nephrotoxicity observed	[83]

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Healthy mice	*In Vitro*	CM	5 and 10 ml/ml	Safe in mice; has no any hepatotoxicity, nephrotoxicity and haematological toxicity observed	[84]
Hepatocellular carcinoma	*In vivo*	CM	5ml 7 10ml	Hepatocellular carcinoma	[85]
Colon cancer cell line (HCT-116) cell lines	*In vitro*	CM	-	Anti-proliferation effect; Inhibit DNA Damage and exert antioxidant activity	[56]
Human lung cancer cells (A549)	*In vitro*	CU(PM 701)	-3(10-3) PM701 for 24 hrs	Selectively killed cancer cells	[86]
Human lung cancer cells (A549), Mice's leukemia cells (L1210)	*In vitro*	CU(PM 701)	-5 to -2PM701; 24-96 hrs	Selective anti-cancer activity- Apoptotic effect/damage of the cell nuclei, limiting the vision of cells, causing degradation in apoptotic manner	[87]
Mice's leukemia cells (L1210)	*In vitro &In vivo*	CU(PM 701)	-3(103)PM701 for 24 hrs -3(103) PM701 after 7 days of treatment	Apoptotic effect/damage the cell nuclei acids Antimitotic effect/inhibit tumor progression	[88]
Human hepatocellular carcinoma (HEPG2), colon carcinoma (HCT 116) and glioma (U251) cell lines	*In vitro*	CU (PMFand its subfractions (M2-M8)	-1, 2.5, 5, 10 µg/ml	Cytotoxic effects	[89]
Lung cancer cells (A549)	*In vitro*	CU(PM701,PMF, PMFK)	2-20 µg/ml for 24, 48, 72 hrs	Cytotoxic activity and inhibition of proliferation	[90]
Lung cancer cells (A549)	*In vitro*	CU (PMF)	-	Induction of apoptosis/caused biochemical changes such as protein, lipid and nucleic acid structures	[91]
Lung cancer cells (A549)	*In vivo*	CU (PMF)	-	Induction of apoptosis/PH, caused biochemical changes associated with disruption of lipid, protein and nucleic acid structures	[92]
Breast cancer cell (MCF-7)	*In vitro*	CU(PM701,PMF, PMFK)	2-20 µg/ml for 24, 48, 72; 96 hrs	Inhibition of proliferation ; Induction of apoptosis	[93]
Breast carcinoma; colorectal cancer cells, liver carcinoma, Leucemia cells; lung cancer cells	*In vitro*	CU (PMF)	0.5mg/ml for 4 and 8 days	Anti- cancer effect by increasing capoptosis and altering cellular metabolic activity	[94]
Rodent's Lung Cancer	*In vivo*	CU (PMF)	120 mg PM/kg/day; 4-6 months	Anti-neoplastic effect but with long time treatment	[95]

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Human hepatoma HepG2 and breast cancer MCF7 cells	*In vitro*	CM	20 and 76 mg/mL	Inhibition of proliferation and growth Induction of apoptosis/through apoptotic- and Oxidative stress-mediated mechanisms DR4, [mRNA, intracellular ROS, JNK activation of caspase -3 mRNA and¯ ERK	[52]
Breast cancer (MDA-MB-231; MCF-7); breast epithelial cells (MCF 10A), Medulloblastoma IScells (DAOY, MED-4, MED-13 and MED-8), osteosarcoma (U2OS), and the colon cancer (LoVo and HCT-116) cells	*In vitro*	CU	20 and 76 mg/mL	Selective cytotoxic effect; inhibition of proliferation; Cyclin-dependent Kinase Inhibitor p21; ¯b-Catenin and Cyclin D1; Induction of apoptosis / Bd-2; Bax, Active cleaved Caspase 3; Immunemodulatory effect/ inflammatory cytokines	[95,96]
Human cancer cells (A549, HCT116, HepG2, MCF-7, U251 and Hela)	*In vitro*	CU (new PMF with large and small molecule)	1-10 μg/ml 48 and 72 hrs	Effective and selective anti-cancer properties	[97]
Human breast cancer cell (BT-474)	*In vitro*	Lyophilized CM	2.5-30 mg/mL for 24 hrs	Repressed cells growth and proliferation/initiation of the intrinsic and extrinsic apoptotic pathways	[98]
HepG2 and HeLa cell lines	*In vitro*	CM (Casein)	0.5- 2.0 mg/mL for 4 and 8 days	Casein with a-Lactalbumin initiate cellular apoptotic cascade	[99]
Hepatotoxicity induced by intraperitoneal injection of MTX	*In vivo*	CU and CM	20mg/kg into rats for 4 weeks	Treatment with CM and CU for four weeks decreased the liver enzymes FBG, DFF-40 and CK-18 levels and increased total proteins, albumin, fibrinogen and TAC. However, the changes in AT,PT, and APTT persisted. CM and CU showed promising abilities to counteract MTX hepatotoxicity and they exerted cytoprotective, antihyperglycemic antithrombinic and antiapoptotic effects	[100]
MCF- 7 human breast cancer cells.	*In vitro*	CM	52.82 μg/mL	Results of this study showed that camel milk-derived Treatment with lactoferrin peptides, particularly PEP66, exhibited strong anticancer activity against MCF- 7 breast cancer cells, with the lowest IC50 value compared to other peptides.	[101]

Table 1: Reports of evidence of anti-cancer properties of CM, CU and their extracted biologicals.

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Active copound	Dose	Cancer Cell/ Cell line	Effects/ Mechanism of action	Status	Reference
α–Λαχταλβυμιν	0.5 and 2.0 mg/ mL	Liver and blood cancer (HepG2 and HeLa cells)	Induced Apoptosis	*In vitro*	[102]
PMF nanoparticles; Zn, Ag, Y, Cs, Rb and hippuric and benzoic Acids. Mainly a nanoshell of Glycine	PMF added to the ordinary media in the ratio of 2.5 mg : 1ml of medium	lung cancer cells (A549)	induction of apoptosis/attack the nuclear membrane and the other cell organelles resulting completely paralyzing the cells	*In vitro*	[103]
PMF701nanoparticles Tyrosine, Glycine, Cyctine, arginine, hippuric and benzoic acids and ZnO nanoparticles	-	Lung cancer (A549)	Apoptosis/Glycine-attack nuclear membrane and other organelles after being engulfed by cancer cells- which are addicted to it hence provide heavy nanoparticles to enter and degenerate the mitochondria of cancer cell through apoptosis	*In Vitro*	[104]
Chlorine and Bromine elements in PMF-G and amino acids such astheronine, cysteine, tyrosine and ethionine which are very important for damage the proliferated cancer cells.	-	lung cancer cells (A549)	Anti-proliferate effect and apoptotic effect/bind OGF (opiod growth factor) and repress cell replication	*In vitro*	[105]
PMF (Cesium (Cs) and Rubidium (Rb) nanoparticles)	2.5mg/ml up to 30mg/ml	human lung cancer cells (A549)	Induction of apoptosis/caused biochemical changes such as protein, lipid and nucleic acid structures	*In vitro*	[106]
Phosphatidylcholine (PC), Phosphatidylethanolamine (PE), Lysophosphatidylcholine (LPC) and phosphatidylinositol (PI) as major Phospholipids	5mg/kg of encapsulated etoposide into liposomes composed of camel milk phospholipids.	Fibrosarcoma (TopisomeraseII)	Increasing the anti-cancer effect of etoposide, encapsulated with PE-containing liposomes	*In vitro*	[53]
Phospholipids	5 mg/kg of each formulation: CML-Lip- Dox; CML-Lip-ETP; CML-Lip-(Dox+ETP)	Fibrosarcoma	Antitumor activity/Dox and ETP loaded into CML-Lip showed increased survival and reduced tumor growth	*In Vivo*	[53]
Phosphatidylethanolamine (PE)	30-50 μl/μg PE liposomes encapsulating cisplatin	Melanoma	Cytotoxic effects/PE Liposomes were efficient delivery for cisplatin targeting melanomas and it maintained concentration of cisplatin in tumour for 72 h	*In vitro & in vivo*	[107]
α– Λαχταλβυμιν (α–Λα)	2-40 mM a-La with oleic acid or linoleic acid	human prostate cancer cells (DU145)	Cytotoxic effect Inhibition of proliferation		[108]

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Camel lactoferrin (cLf), N- and C-lobes lactoferrin	0.5 and 1.0 mg/ml	Huh 7.5 cells	cLf and C-lobe but not N-lobe have cytotoxic effects	*In vitro*	[109]
Camel antibody's single domain fragments (cAb-Lys2 & cAb-Lys3) univalent or bivalent format	10 mg/ml	BW-Li & 3LL-R variants derived from BW5147 T-cell lymphoma &Lewis Lung carcinoma respectively	Non-immunogenic, rapid pharmacokinetic clearance and specifically target solid tumors and metastatic lesions	*In vitro*	[110]
CAR-TCells expressed Camelid single Dormain Antibody	107 cells/mouse	CEACAM6-expressing pancreatic cell line BxPC	Reduced cell viability growth inhibition	*In vitro*	[111]
Antibodies	EC50 of 10 pmol/L 100 µg of human PBMCs and bsFab C21	human ovarian carcinoma (SKOV3-CEA), colon carcinoma (LS174T), pancreatic (BxPC3, HT29) cancers	Antibody-dependent NK cell-mediated cytotoxicity	*In Vitro*	[112]
ZnO NP		Leukemia and lymphoma (T-cell cancer lines) leukemic and Hut-78 lymphoma T cell lines)	Induction of apoptosis Inhibition of proliferation	*In Vitro*	[113]
Intercalation of Hippuric acid nanocomposite (hippuric acid with ZLH/HAN) with doxorubicin and Oxaliplatin		Breast cancer and colon cancer (MCF-7, MDA MB231, Caco2)	Cytotoxicity/suppression of cell proliferation	*In Vitro*	[114]

Table 2: In vitro and In vivo experimental studies on therapeutic properties of CM and CU nanoparticles against various human cancer cells and cell lines.

Discussion and Conclusion

It can be concluded that biomolecules in CM and CU affect cancer cell physiology via mechanisms, including: apoptosis, antiangiogenesis, cytotoxicity and antioxidant effects on breast and liver cells , leukaemia, nasopharyngeal carcinoma and colorectal cancer. Both CM and CU show anti-cancer effects by inhibiting angiogenesis [75]. These observations have promising clinical therapeutic implications for both products in the management of human cancers. However, there are a number of issues to be addressed, namely: 1) The protocols and dosages used; 2) No sufficient evidence for their use in modern medicine; 3) Most studies were still in their early stages, using in vivo and in vitro studies on animal cell lines, and not involving actual human patients or credible animal models that simulate the human system; 4) Toxicity studies were not conducted and information on side effects is largely lacking; and 5) There are also major concerns about the correlation between preclinical and clinical data as clearly demonstrated by the Saudi Arabian clinical study. There is a need therefore, to show evidence of a strong correlation between anticancer agents applied in preclinical studies and the clinical benefits in humans and The standardize the protocols with respect to: dosages, routes of administration and to determine the safety and potential side effects of CM and CU before they can be recommended for alternative treatment for cancer in humans. Contaminants of CM and CU with pathogens such as the Middle East Respiratory Syndrome virus, Brucella spp, T.B bacteria, E.coli, Staphylococcus spp and Salmonella spp microrganisms, other zoonotic pathogenic microrganisms, and even toxins like mycotoxins (aflatoxins), veterinary drug residues and agrochemicals which could contaminate raw CM and CU, should be addressed to safeguard the latters' public health concerns. Exploitation, of CM's exosome and whey derived peptides could further be attempted as adjuvants to the current cancer chemotherapy as this is already yielding promising results in the field of oncology for the therapeutic management of cancers [72].

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