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Therapeutic Applications of Camel's Milk and Urine against Cancer: Current Development Efforts and Future Perspectives

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Abstract

The management of cancer in human yet remains a major challenge in contemporary medicine. Natural products have been identified as one of the sources of numerous therapeutic agents. Camel's milk and urine are among such natural products enriched with molecules that are safe to humans and endowed with profound anti-cancer properties. *In vitro* studies of the anticancer effects of these products are mainly attributed to inhibition of carcinogenesis and mutagenesis, proliferation, and induction of apoptosis. Camel products also showed an improvement in the life span and the survival of animals among the *in vivo* studies recorded, an effect caused mainly *via* clearance of malignant tumors in various organs and inhibition of progression to metastasis. Furthermore, prospects of harvesting promising therapeutic nanoparticles/nano-bodies/nano-rods are now being explored from such natural products for cancer therapy. Yet, prominent gap is evident in regard to advanced research geared towards identifying and designing suitable nano-materials. Therefore, a multi-pronged approach entailing a deeper understanding of cancer biology, nanomaterial's molecular characteristics on tumor environment, and further formulation of nano-clones is underscored to position them as clinically useful pharmaceuticals.

Keywords: Camel milk; Camel urine; Cancer; Cancer therapy

Introduction

Cancer, a disease characterized by uncontrolled cellular proliferation and differentiation, remains a worldwide public health concern, with an estimated 14.1 million new cases and 8.2 million deaths having occurred worldwide in 2012, wherein more than 70% of deaths occurred in low- and middle-income countries (LMIC) [1]. Typical hallmarks of the acquired capabilities of tumor cells during tumorigenesis include: sustained proliferation, evasion of growth suppressors, resisting cell death, replicative immortality, activating invasion, metastasis, evading the immune system, and reprogramming energy metabolism, as well as other features including epigenetic alterations [2-4].

Cancer is caused by exogenous factors, including tobacco, infectious organisms, & unhealthy diets, as well as endogenous factors such as inherited genetic mutations, hormones, and immune conditions. Such factors may act in concert or in sequence to orchestrate this multifactorial ailment, and due to this complexity of this interaction; ten or more years often pass between exposure to external factors and detection of cancer [5,6].

The management of cancer in humans still constitutes a major challenge for contemporary medicine [7,8]. Albeit the significant amount of progress made thus far with regards to expounding the etiology of cancer to develop a cancer biology framework, the standard antineoplastic therapies available rely primarily on surgery, chemotherapy, radiotherapy, hormone therapy, and immunotherapeutic approaches [9]. As any golden standard treatment regime are those which could selectively kill the malignant cells whilst sparing healthy tissues and vital organ function unlike the available treatment schemes, this shows that they are still far from being ideal [10,11]. Chemotherapy is, in particular, the primary treatment mode at different stages for a wide range of cancer types albeit being characterized by high toxicity, long lasting side effects, morbidities, and even potential lethality [12,13].

Such drawbacks underscore on the dire need to intensify the strides to develop alternative treatment and/or management regimes that are less evasive and with minimal side-effects. One of the best known paths to be followed therein to in pursuit of better cures relates to research on natural products. Natural products have long been recognized as important sources of therapeutically effective substances, with the majority of the world's population relying almost entirely on natural products for medication. Their use has been reborn following a diminished utility these past few decades, with advanced technologies as high-throughput screening & combinatorial chemistry having taken the center stage in drug discovery.

A notable point regarding natural products in cancer treatment, of the 121 FDA approved prescription drugs in use its treatment, 90 are derived from plant species, and more striking are the fact that 74% of such drugs were discovered by investigations following a folklore claim [14,15]. Further, as the currently available therapeutic approaches lack specificity for the particular cancer cells, a strict necessity of searching for novel anticancer therapeutics with desired characters from the popular realm of natural remedies in ethno-medicine has been underscored. One such source of promising organic substances with profound health benefits & therapeutic values refers to products and byproducts of the dromedary camel, namely camel milk and camel urine [16].

Anticancer Effects of Camel's Milk and Urine

Management of cancer is one of the major challenges in medical practice as there are no available medical modalities that can selectively

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kill cancer cells without any adverse effect on normal living cells or the functions of vital organs. Chemoprevention by dietary constituents in the form of functional food has a well-established beneficial role in health promotion and emerged as a novel approach to control disease like cancer [17].

Camel milk is among such dietary supplement with profound nutraceutical values. From medicinal value point of view, it has a rich content of protective minerals and proteins that could have vital role for enhancing immune defense mechanism [18]. It contains higher amount of zinc which offer significant role in the development and maintenance of a normally functioning immune system [19]. Camel milk has insulin like activity, regulatory and immunomodulatory functions on βcell. It contains good amount of protective proteins, including lysozme, lactoferrin, lactoperoxidase, peptidoglycan recognition protein (PGRP) enzyme, immunoglobulin G, and secretory immunoglobulin A. These immune factors are present at greater concentrations in camel milk [20].

Despite waste product, camel urine has been also used as a source for many therapeutic agents [21]. It contains various complex bioactive compounds that could act against carcinogenic agents [22]. Drinking camel urine is shown to be effective in treating numerous cancers in human (Figure 1) [23].

Safety Profile

The safety assessment of drug compounds is the primary step to be done for its therapeutic use in humans. Several drugs have been withdrawn from the market due to the severe adverse effects in patients [24-26]. Most of these drugs have shown potential to cause toxicity in healthy organs such as hepatotoxicity and nephrotoxicity [27-29]. On the other hand, camel's milk (CM) is an excellent source of well-balanced nutrients and serves as the main source of food. It exhibits a range of biological activities that influence digestion, metabolic responses to absorbed nutrients, growth and development of specific organs and resistance to diseases [30,31].

Camel urine is a rich source of natural by-product with no harmful health effect in human. Compounds, such as ammonia and urea known to offer bad smell and toxicity of urine in human and all other animals are lacking or minimal in camel urine. Other distinguishing features of camel urine include; it contains about ten folds more mineral salts than human urine, it is basic with a pH value of 7.8 while human urine is acidic [32].

Numerous preclinical and clinical-based investigations have been done thus far on the safety profile of camel's urine components (PM701, bioactive fraction (PMF) and its sub-fraction (PMFK)). As a result, it has found to be safe to human use as no change in the architectures and hepatotoxic, nephrotoxic effects and any hematological toxicity were observed under all experimental conditions used [9,33-35]. Notably, these components are found to activate the immune system through enlarging the germinal centers of the white pulp lymph nodules in the spleen [9].

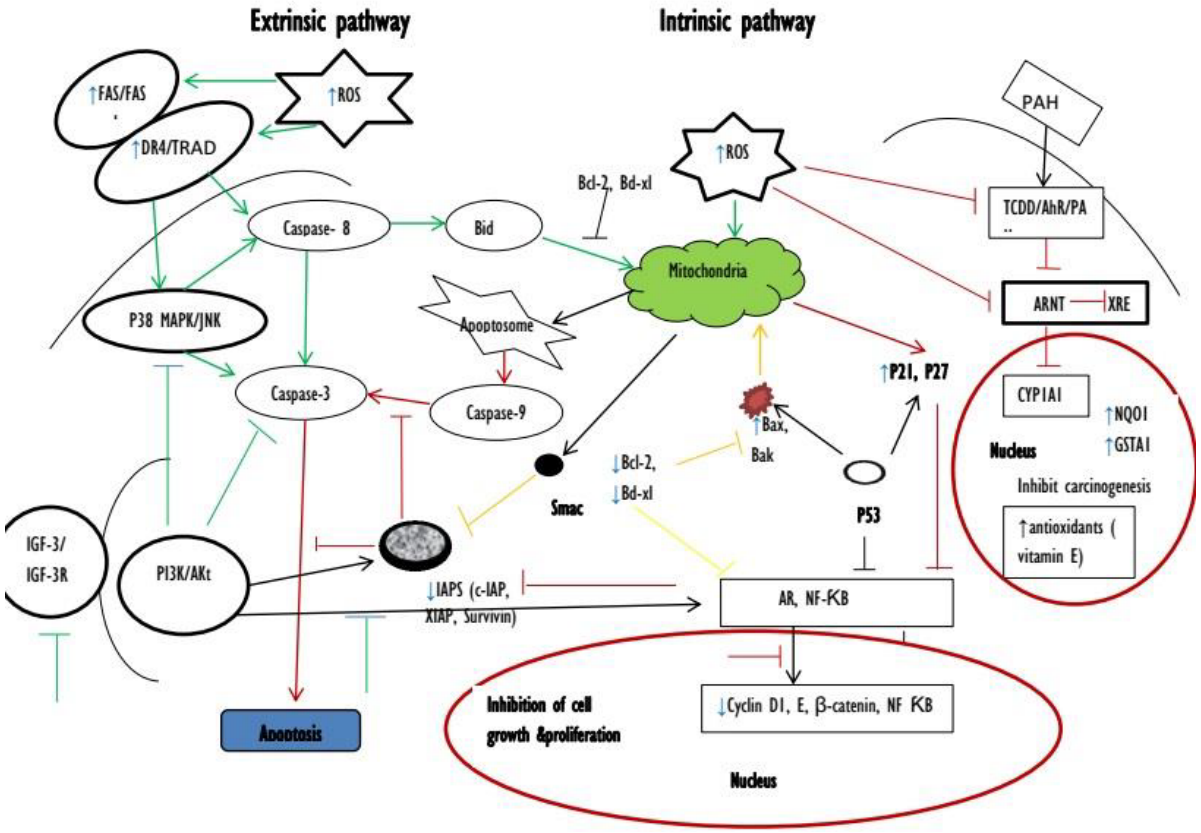

Figure 1: Anticancer effect of camel's milk and urine (CM & CU). CM & CU induce apoptosis in various cancer cells through extrinsic pathway by enhancing DR4 expression and ROS production, causing activation of JNK and caspases and intrinsic pathways mainly by enhancing ROS production that lead to activation of caspases. Inhibit carcinogenesis by down-regulating the induction of *Cyp1a1*, a cancer activating gene, and inducing *Nqo1* and *Gsta1*, cancer protecting genes. Inhibit Cell cycle progression, proliferation and survival of cancer cells by interfering on 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.

Cytotoxic Effect

It is of primary importance to find an anticancer agent that kills cancer cells without un-acceptable toxicity to patient's own tissues and overall functions. Both camel milk and urine are among natural products endowed in agents with such desirable characteristics. These products possess supreme cytotoxic effect against various cancer cells and cell lines (Table 1) [9-11,16, 23, 36-51].

Camel products could exert cytotoxic activity against cancer cells through different mechanisms while inhibition of carcinogen-activating genes signaling pathways is well understood in this regards. Camel's milk and urine are recognized to significantly inhibit the induction of a cancer-activating gene (*Cyp1a1*), and to induce cancer protecting genes (*Nqo1*and *Gsta1*) in several lines of cancer cells at the mRNA, protein and activity levels. These products mediate CYP1A1 inhibition at

Experimental Model	Stage of validation	Camel product/ byproduct (compounds)	Dose and time	Major effects/mechanisms of action	References
Healthy humans	Clinical trial (healthy volunteers)	CU (PM 701 capsule)	3-10 capsules (300 mg capsule^{-1}) daily for 4 months	Safe in healthy volunteers/no adverse effect in vital organs	[9]
Mice leukemia (L1210) cell	*In vitro*	CU (PM-701)	16 mg/ml for 0-72 h	Control tumor progression, metastasis and prevent recurrence	[11]
Lung cancer cells (A549)	*In vitro*	CU (PM-701)	-	Inhibition of cell proliferation (Magateer breed>Majaheem with respect to age and sex)	[16]
Murine hepatoma Hepa 1c1c7 cell line	*In vitro*	CU (Virgin, lactating and pregnant)	-	Inhibition of the TCDD-mediated toxic effect/↓expression of *Cyp1a1*, at the mRNA and protein expression levels	[23]
Healthy mice	*In vivo*	CU (PMF)	2-20 × of therapeutic dose (0.75 µl)	Safe in mice/has not any hepatotoxicity and nephrotoxicity	[33]
Healthy mice	*In vivo*	CU (PMF)	2-20 × of therapeutic dose (0.75µl)	safe in mice/has not any hepatotoxicity and nephrotoxicity	[34]
Healthy mice	*in vitro*	CU (PM 701)	10 g kg^{-1} for 4 weeks	safe in mice/has not any hepatotoxicity, nephrotoxicity and hematological toxicity	[35]
Murine hepatoma Hepa 1c1c7 cell line	*In vitro*	CM	5 and 100 µL/mL	Inhibition of carcinogenesis and mutagenesis/ modulation of AhR-regulated genes; ↑ *Ho-1*, *Nqo1* and *Gsta1* at the transcriptional and posttranscriptional levels; ↓TCDD-mediated induction of *Cyp1a1* activity, Cyp1a1 mRNA, protein	[36]
Hepatocellular carcinoma	*In vivo*	CM	5 ml up to 38 weeks	Inhibit hepatic carcinogenesis	[37]
Colon cancer cell line (HCT-116) cell lines	*In vitro*	CM (lactoferrin)	-	Anti-proliferation effect Inhibit DNA Damage and exert antioxidant activity	[38]
Human lung cancer cells (A549)	*In vitro*	CU (PM 701)	-3(10-3) PM701 for 24 h	Selectively kill cancer cells	[39]
Human lung cancer cells (A549), Mice's leukemia cells *(L1210)*	*In vitro*	CU (PM 701)	-5 to -2PM701; 24-96 h	Selective anti-cancer activity Apoptotic effect/damage the cell nuclei, limiting the division of cells, causing degradation in apoptotic manner	[40]
Mice's leukemia cells (L1210)	*In vitro* *In vivo*	CU (PM 701)	-3(10^{-3}) PM701 for 24 h -3(10^{-3}) PM701 after 7 days of treatment	Apoptotic effect/damage the cell nuclei Antimitotic effect/inhibit tumor progression	[41]
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	[42]
Lung cancer cells (A549)	*In vitro*	CU (PM701,PMF, PMFK)	2-20 µg/ml for 24, 48, 72 h	Cytotoxic activity and inhibition of proliferation	[43]
Lung cancer cells (A549)	*In vitro*	CU (PMF)	-	Induction of apoptosis/caused biochemical changes such as protein, lipid and nucleic acid structures	[44]
Lung cancer cells (A549)	*In vivo*	CU (PMF)	-	Induction of apoptosis/↑pH, caused biochemical changes such as protein, lipid and nucleic acid structures	[45]
Breast cancer cell (MCF-7)	*In vitro*	CU (PM701,PMF, PMFK)	2-20 µg/ml for 24, 48, 72; 96 h	Inhibition of proliferation Induction of apoptosis	[46]
Breast carcinoma, colorectal cancer cells, glioma cells, liver carcinoma, leukemia cells, lung cancer cells	*In vitro*	CU (PMF)	0.5- 2.0 mg/mL for 4 and 8 days	anti-cancer effects by increasing apoptosis and altering cellular metabolic activity	[47]
Rodent's Lung Cancer	*In vivo*	CU (PMF)	120 mg PM/kg/day; 4-6 months	Anti-neoplastic effect but with long time treatment	[48]
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	[49]

Breast cancer (MDA-MB-231, MCF-7), breast epithelial cells (MCF 10A), Medulloblastoma cells (DAOY, MED-4, MED-13 and MED-8), osteosarcoma (U2OS), and the colon cancer (LoVo and HCT-116) cells	*In vitro*	CU	16 mg/ml for 0-72 h	Selective cytotoxic effect Inhibition of proliferation/↑cyclin dependent kinase inhibitor p21, ↓ b-catenin and cyclin D1 Induction of apoptosis/↓Bcl-2, ↑ Bax, active cleaved caspase 3 Immune modulatory effect/↑inflammatory cytokines	[50]
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 h	Effective and selective anti-cancer properties	[51]
Human breast cancer cell (BT-474)	*In vitro*	Lyophilized CM	2.5-30 mg/mL for 24 h	Repressed cells growth and proliferation/initiation of the intrinsic and extrinsic apoptotic pathways	[88]
HepG2 and HeLa cell lines	*In vitro*	CM (Casein)	0.5- 2.0 mg/mL for 4 and 8 days	casein (with α-lactalbumin) initiate cellular apoptotic cascade	[89]
CM: Camel Milk; CU: Camel Urine					

Table 1: Anti-cancer properties and safety profiles of camel milk, urine and extracted compounds demonstrated at preclinical and clinical levels.

transcriptional level through AhR-dependent transcriptional control. This is attributed to AhR antagonistic effect of these products and subsequent inhibition of *Cyp1a1* induction by TCDD. In *in vitro* study, urine of virgin camel but not pregnant and lactating camel efficiently bound to and inhibited the transformation of cytosolic AhR to a DNA-binding form [23], necessitating to assess binding and affinity of ligand to the AhR [52]. Regarding translational level effect, these natural camel products inhibit TCDD-mediated translation of Cyp1a1 mRNA into a functional protein. Furthermore, Cyp1a1 catalytic activity can be altered through several posttranslational mechanisms, such as phosphorylation, proteasomal degradations, and modulation of *HO-1* gene expression [53,54]. *HO-1* gene expression, a rate-limiting enzyme in heme catabolism, is found to alter cellular heme, the prosthetic group of CYP450, content and hence the enzyme activity [55]. Evidently, camel milk (fat-free) was found to induce the expression of Ho-1 mRNA and decreased the Cyp1a1 activity levels by degrading its heme content [36].

Meanwhile, camel's milk and urine are able to increase the expression of chemo-protective genes, *Nqo1* and *Gsta1* mRNA levels pertaining to increase the levels of several antioxidant enzymes which prevent the formation of highly reactive oxygen radicals and then protect DNA adduct and cell damage [23,38,56]. In addition, over expression of *Nqo1* in several human solid tumors and cancer cells is shown to activate bio-reductive chemotherapeutic agents in tumor cells that allow tumor cytotoxicity without corresponding toxicity to normal cells [57].

Various mediators in camel milk are implicated to offer such cytotoxic property against different cancer cells. These include: antioxidant vitamins, such as vitamin E and C [58], casein, lactoferrins, fatty acids, immunoglobulines and various trace elements [23,59]. High level of vitamin C in camel milk offered nucleophilic, anticlastogenic and antimutagenic role [60-65]. Selenium and zinc protect against the genotoxic effect of toxic compounds [66-69]. Casein and its product formed during pepsin hydrolysis protect mammalian cells against certain genotoxic compounds [70-72]. Lactoferrin is an important iron-binding glycoprotein possesses immune-inducing and immunomodulatory properties thereby exert antitumor activity [73-75]. Conjugated linoleic acid (CLA) serve as useful food antioxidants and inhibit activation of carcinogen by opposing direct interaction of procarcinogen, scavenging of electrophiles or selective induction of phase I detoxification pathways [76-81]. Selenium is a constituent of various oxidant defense selenioproteins and a cofactor of glutathione peroxidase in the elimination of peroxide radicals and hence prevents cancer development. Zinc plays pivotal role during DNA and RNA synthesis and serve as a cofactor in superoxide dismutase activity [82].

Apoptotic Effect

Apoptosisis a physiological cellular process of cell death initiate by wide variety of extrinsic and intrinsic signals and stimuli [83]. These signals instruct the cells to undergo apoptosis through the activation of a family of proteins known as caspases. The intrinsic signals initiate apoptosis through mitochondrial oxidative stress caused by free radicals [84] while the extrinsic signals induce apoptosis through binding of cell surface death receptors, such as tumor necrosis factor (TNF) receptor 1 (TNFR-1), TNF related apoptosis-inducing ligand receptor 1 (TRAILR-1), death receptor (DR4, and DR5) [83-85]. Signals in both pathways activate effector caspases such as caspase-3 [86]. Apoptosis is an important phenomenon in chemotherapy-induced killing of tumor cells as many anti-cancer drugs and natural products act through the induction of apoptosis to prevent tumor promotion and progression (Table 1) [87]. Camel's milk and urine induce apoptosis in various cancer cell lines through activating both extrinsic and intrinsic apoptotic pathways (Table 1) [49,88,89]. It would induce apoptosis through activation of caspase-3 at mRNA and activity levels. Camel milk significantly induces the expression of DR4 and oxidative stress marker (HO-1) mRNA, and enhances ROS production, thus mediate apoptotic cell death through both extrinsic and intrinsic apoptotic pathways. Recent findings have been shown that camel milk-mediated caspase-3 mRNA expression is associated with MAPK cascades, which play important roles in cell death and survival signaling [90,91]. Importantly, inhibition of JNK and p38 MAPK has significantly decreased activation of caspase-3 mRNA in response to camel milk [92], can be suggested that both kinases pertain proaptotic effect. Moreover, lyophilized camel's milk is found to differentially initiate apoptosis in BT-474 and HEp 2 cell lines as estrogen receptor-mediated apoptosis is performed in the former cell line whereas an alternative non-estrogen receptors pathway could mediate apoptosis in HEp 2 cell line [88].Thus, further investigation is required to understand the receptor involved on camel milk mediated apoptosis in the later cell line. Overall, the exact potential mediator of camel milk involved in apoptosis is not well known, but α-lactalbumin purified from camel casein is found to initiate apoptosis cascade in HepG2 and HeLa cells [89].

Meanwhile, many line of evidences revealed that different forms of camel urine, including PM701, PMF and PMFK significantly induced apoptosis in several cancer cell lines (Table 1) [40-50]. The possible mechanisms suggested include; decreasing Bcl-2, downregulating the expression of several cancer-related genes such as *b-catenin*, *cyclin D1*, and the anti-apoptotic survivin protein.

Anti-proliferative Effect

The anti-cancer effect of Camel's milk and urine is not only

attributed to cytotoxic and anti-apoptotic characteristics but also the anti-proliferative effect. Those camel products caused potent anti-proliferative effect on various cancer cell lines, largely through apoptotic and oxidative stress-mediated mechanisms (Table 1) [16,38,43,46,49,50,88]. Lactoferrin is an important camel milk component which is well studied in this regards. Lactoferrin inhibit the proliferation of cancer cells by various mechanisms. One of such mechanism includes that it interacts with polysaccharides ligands on cell surfaces and activate cell signaling pathways such as the Fas pathway thereby inhibit the growth of tumor by apoptosis [93]. Lactoferrin can also penetrate cells and function as a transcription factor and activating the transcription of specific DNA sequences [38,94]. Moreover, lactoferrin down-regulate cell proliferation through growth arrest at the G1 to S transition of the cell cycle and induce an increase in cyclin-dependent kinase (CDK) inhibitor p21 cip1 protein levels through a p53-independent mechanism [95,96]. Its effect on cell cycle can be attributed to; decrease in pAkt, increase in p27, and a reduction in cyclinE and pRb protein levels. Lactoferrin is found to bind with insulin-like growth factor-binding protein-3 [97], thereby act by altering the availability or stability of insulin-like growth factor, a known regulator of the phosphatidylinositol 3-kinase/Akt pathway [98].

Accordingly, camel urine possess supreme anti-proliferative effect on many lines of cancer cell possibly through the induction of the cyclin dependent kinase inhibitor p21 as it is found to up-regulates p21 in the p53-defective cancer cells [39,99]. Anti-proliferative effect of camel urine is significantly influenced by breeds, age, sex and other camel characteristics. *In vitro* study conducted by Alghamdi and Khorshid to understand the effect of urines obtained from Magateer and Majaheem camels of different age and sex groups on the growth of lung cancer cells (A549) showed that urine obtained from young and adult Magateer significantly down-regulate proliferation of cancer cells than their respective encounter breed. Importantly, urine obtained from adult male Magateer showed substantial anti-proliferative effects in lung cancer cells. Despite such outstanding study, the potential bioactive ingredients responsible for the observed variations is not examined, and hence further investigation aimed at identifying entailed agents is underscored in this line.

Camel's Milk and Urine Nanoparticles

Nanomedicine becomes an emerging discipline entailing production of varieties of nanoparticles for different medical applications, including for the treatment of disease, diagnosis, monitoring, and control of biological systems [100]. Importantly, entailed problems associated with targeting particular cells or body systems and degradability by various body systems such as lytic enzymes and extreme pH, and subsequent need of high dose, led currently prescribed drugs to be less effective and to cause toxic effect in the patients. On the other hand, the emergence of nanotechnology pertains to produce varieties of nanoparticles capable of targeting particular cells or body systems thereby contributing to efficient antigens/proteins/drugs/oligonucleotides delivery and thus required lower dosage. NPs can act as both carriers and adjuvants, hence removing the need for conventional adjuvants altogether [101].

In light of this, camel's milk and urine are natural products endowed with numerous agents suitable for such applications. Camel's milk phospholipids, such as phosphatidyl-ethanolamine (PE), phosphatidyl-choline (PC), lysophosphatidylcholine (LPC) and phosphatidylinositol (PI); proteins, including immunoglobulin are among well studied molecules in this regards [102]. Camel milk has unique immunoglobulin called the VHH (variable heavy heavy) antibodies or nanobodies devoid of the typical light chains present in normal antibodies. This offers camel antibodies much smaller in size as compared to the normal antibodies and pertaining to increase tissue penetration while retaining the specificity [103,104]. Camel IgGs (which also exist in the milk, besides being present in blood) are able to penetrate within tissues unlike human IgGs. Therefore, they can enter inside the cells where they would perform various functions under pathological conditions (Table 2) [105-107].

Camel urine is rich in many organic and inorganic compounds. PMF and PM701 of camel urine possess different nanoparticles, crystals and nano-rods with varying shapes and sizes. PMF crystals contain various compounds such as calcium oxalate, cystine, tyrosine, uric acid crystals, ammonium urate, calcium phosphate, hippuric and benzoic acids [108,109]. El-Shahawy et al. [110] detected the presence of glycine, alanine, and arginine in PMF. It also contain several ions, but Cs, Rb, K, Ca, Cd, Y, Eu, Th and Zn are present in relatively high concentration. Zinc is present in the form of ZnO and Ca, Cd & Y are in the form of sulfates (Table 2) [108,109].

The aforementioned components of PMF offer potent selective cytotoxic activity against several lines of cancer cells. Mechanistically, macro and nanoshells of PMF which contain different type of metals such as K+, Ca2+, Eu+3 attack cancer cell membrane by influencing on the permeability of the membrane. There are few clinically approved nanocarriers that incorporate molecules to selectively bind and target cancer cells [111]. Glycine and other amino acids remarkably offer unique selectivity of various PMF elements to cancer cells, hence can be utilized for many applications. ZnO NP is one of the most important metal oxide nanomaterials due to its various medicinal use and biological applications. Notably, its selective cytotoxic effect on cancer cells is among its important features in this regard [112,113]. NPs induced ROS generation and consequent OS is frequently observed and is the most discussed paradigm for NP toxicity [114,115]. Cytotoxic potential of ZnO is attributed to many features, including induction of oxidative stress through generation of ROS on the surface of particles [115-117], dissolution and release of Zn2+ ions and physical interaction of ZnO NPs with the membrane wall cause deformation and rupture of membrane [118]. In addition to these NPs, Cs- and Rb- can specifically enter cancer cells and embryonic cells but not normal adult cells [119,120]. PMF contain 70.9128 and 8.04 ppm Rb and Cs respectively and thus may indicate the selectivity action of this new anticancer agent (PMF). Cs and Rb nanoparticles of PMF selectively attack cancer cells by elevating the pH [111]. Cd and Y of PMF are the core of nanoshell, and have high magnetic property thereby enhance its selective cytotoxicity against various cancer cells [44,111].

Numerous amino acids of PMF regulate various functions in normal cells and in oncogenesis. Receptor tyrosine-specific protein kinases are a subclass of cell-surface growth-factor receptors with an intrinsic, ligand-controlled tyrosine-kinase activity, and they are important target because they play an important role in the modulation of growth factor signaling [121]. Meanwhile, presence of tyrosine enhances the efficiency and selectivity of PMF on cancer cells. Glycine and cysteine, amino acids entering to glutathione structure, enhance its antioxidant activity and further improve the immune system [122]. Arginine has immunomodulatory effects, such as stimulating T- and natural killer cells activity, and influencing pro-inflammatory cytokine levels through activating interleukin-12 (IL-12) [123]. It also induces IL-23 that leads to the production of interferons (IFNs) and other tumor-suppressive factors. These molecules are activated as part of the antitumor immunity response and promote apoptosis to tumor cells [124].

Active compounds	Dose	Cancer cell (cell lines)	Major effects/mechanisms of actions	Status	References
α-lactalbumin	0.5 and 2.0 mg/mL	Liver and blood cancer (HepG2 and HeLa cells)	Induce Apoptosis	*In Vitro*	[105]
PMF nanoparticles; Zn, Ag, Y, Cs, Rb and hippuric and benzoic Acids. Mainly a nanoshell of Glycine	PMF added to the ordinary media with ratio 2.5 µg: 1 ml media	lung cancer cells (A549)	Induction of apoptosis/attack the nuclear membrane and the other cell organelles resulting completely paralyzing the cells	*In vitro*	[108]
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*	[109]
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*	[110]
PMF (Cesium (Cs) and Rubidium (Rb) nanoparticles)	2.5 µg/ml up to 30 min	human lung cancer cells (A549)	Induction of apoptosis/caused biochemical changes such as protein, lipid and nucleic acid structures	*In vitro*	[111]
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 anticancer efficacy of etoposide, encapsulated with PE-containing liposomes	*In vitro*	[132]
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*	[133]
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* and *In vivo*	[134]
α-Lactalbumin (α-La)	2-40 µM α-La with oleic acid or linoleic acid	human prostate cancer cells (DU145)	Cytotoxic effect Inhibition of proliferation		[138]
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*	[139]
Camel antibody's single domain fragments (cAb-Lys2 & cAb-Lys3) univalent or bivalent format	10 µg/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*	[141]
CAR-T cells expressed camelid single domain antibody	10^7 cells/mouse	CEACAM6-expressing pancreatic cell line BxPC3	Reduced cell viability growth inhibition	*In vivo*	[142]
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 Tumor growth inhibition	*In vitro* *In vivo*	[143]
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*	[146]
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*	[148]

Table 2: *In vitro* and *In vivo* experimental studies on therapeutic properties of camel milk and urine nanoparticles against various cancer cells and cell lines.

Development Efforts on Camel Products Based Anti-Cancer Nanoparticles

NPs can be utilized for cancer therapy in various forms, including conjugated with antigens, encapsulate antigens/peptides/DNA and labeled in fluorescent, and thereby can trigger and manipulate different signaling mechanisms. NPs used for such matters are mostly designed to be drug-compatible, biocompatible, biodegradable, and easy to process, efficient in loading and controlling drug release [125]. In addition, modern developments in polymeric nano-formulations involve a number of homo and co-polymer combinations pertaining for sustained and controlled delivery of anti-cancer agents [126-131].

Various phospholipids of camel milk, including PE, PC, LPC and PI have been demonstrated for application of cancer therapy (Table 2)

[132-134]. Liposomes prepared from these phospholipids were used as drug delivery systems for various anticancer drugs, and have shown promising anticancer activity in the murine/mouse model. Etoposide entrapped in camel milk phospholipid liposomes has showed greater anticancer activity against fibrosarcoma in a murine model compared to free etoposide or etoposide entrapped in 1,2-Dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC) liposomes [132]. Combination of doxorubicin (Dox) and etoposide (ETP) loaded into camel milk phospholipids liposomes (CML-Lip) is found also to increase survival and to reduce tumor growth in the mice than the combination of Dox and ETP in DPPC-Lip [133]. The presence of PE in camel milk phospholipid liposomes could play important role in increasing the anticancer efficacy of etoposide.

Liposomes comprised of a variety of lipid molecules with high proportion of PC and cholesterol being mostly prepared for cisplatin offered low cisplatin encapsulation and drug loading efficiencies. On the other hand, camel milk's PE liposomes overcome such limitations. PE liposomes significantly promote the entrapment efficiency of cisplatin; reduce the vesicle size, target delivery and offer controlled cisplatin release. Incorporation of polyethylene glycol (PEG) derivatives in PE liposomes further enhances its cytotoxicity. Toxicity to normal cells has been reported with commonly used cationic liposomes such as DOTAP, but PE liposomes with negative surface charges overcome such drawback (Table 2) [134-137].

Camel proteins are unique that they able to maintain a high degree of thermal stability and remain functional even at elevated temperatures. Their extraordinary stability is attributable to efficient refolding after chemical or thermal denaturation and increased resistance against denaturation [138]. At high temperature (60°C), camel milk α-lactalbumin and its complexes combined with oleic acid and linoleic acid can have a stable structure, and exhibit a cytotoxic effect on a human prostate cancer cell even after exposure to such temperature [138]. It is known that camels Lactoferrin (cLF) possess supreme immunoregulatory and anti-cancer effect. Further investigation on evaluating entailed cLF active component indicates that it's C-lobe but not N-lobe has shown significant cytotoxic effect (Table 2) [139].

The use of convectional antibodies, owning both heavy and light chains in the variable region, and cloned single domain antibodies as delivery tools for diagnostic and therapeutic purpose remain very challenging. This is mainly attributed to; loss of stability, sticky nature of rendered VH hydrophobic portion and subsequent difficulties on handling [140]. Camel milk antibodies naturally possess single-domain antigen-binding units. The variable domains of these camel heavy-chain antibodies (VHHs) show a high sequence homology to human VHs. Moreover, specific mutations in the framework 2 region of the variable domain of camel VHH make it less hydrophilic [140]. Such features of VHHs overcome the problems of stickiness encountered with conventional VH. Further, camel single VHH domains are non-immunogenic molecules that exhibit a rapid pharmacokinetic clearance and specifically target solid tumors and metastatic lesions [141]. Camel antibodies also recognize and bind on the surface of inorganic material [142,143]. Such property together with the ease to produce functional and stable cAb constructs and their ability to recognize epitopes which are less antigenic for conventional antibodies [144,145], has offered unique advantages when targeting tumors for diagnostic or therapeutic purposes [141].

Accordingly, numerous of camel urine compounds have been also used for such applications. Notably, multifunctional zinc oxide (ZnO) is used in various forms such as NPs or nanorods for biomedical applications including biosensing, imaging, drug delivery, and clinical implants [113,114,146] the additive or synergistic effects of ZnO NPs with anti-cancer compounds (or drugs) was found to up-regulate induction of apoptosis in cancer cells [147]. Hippuric acid nanocomposite (HAN) (a preparation from hippuric acid (HA) and ZnO) combination with doxorubicin and/or with oxaliplatin induce suppression of cell proliferation and exhibit supreme cytotoxicity in several cancer cell lines as compared to individual effects. Importantly, the nanocomposite entails the drugs to reach the tumor cell membrane without early decomposition and the intercalation reaction enhances the permeability of the drug into the target cell without any noticeable side effects (Table 2) [148,149].

Conclusion and Future Perspectives

Camel products and byproducts are important sources of many natural agents used for various medical applications. Despite owing remarkable therapeutic agents, scientific research in this area remains at young stage. Prominent gap is evident in regards to advanced research geared towards identifying and designing suitable nano-materials. Meanwhile, multifunctional proteins, lipids and inorganic compounds of such natural products deemed capable of carrying both therapeutic and diagnostic agents are now being explored for more effective cancer management. Hence, additional study entailing to identify active agents, and formulation of toxicology on existing nano-materials in humans still needs to be fully studied and evaluated as studies conducted thus far have been small and limited to short-term exposure. Investigation on nano-toxicity and nano-therapy should be intended on long-term exposure in humans, animals and the environment. By critically understanding nanomaterial's behaviors in the tumor microenvironment and their molecular characteristics as well as formulations of cloned molecules, rapid discovery of large numbers of safe and high-potency nano-materials for cancer therapy can be achieved.

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