

REVIEW ARTICLE

Therapeutic potential of camel milk

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ABSTRACT

Camel milk is recognized for its therapeutic potential against many diseases. It is reported to have microbicidal and immuno stimulatory properties as it contains immunoactive proteins like lysozyme, lactoperoxidase and lactoferrin. Camelid antibodies have a unique structure. They possess the heavy chains but are devoid of the usual light chains. This special feature enhances their penetration. Camelid proteins have a very high degree of thermal stability and are resistant to acid hydrolysis. Camel milk components act like a ligand to the aryl hydrocarbon receptor. They significantly inhibit the induction of some cancer-activating genes and also induce tumor suppressor genes. Modulation of aryl hydrocarbon receptors is now recognized to have a vital role in cancer therapy. The present review deals with clinical significance of camel milk with special reference to cancer. It also encompasses its unique composition, relevance to other diseases and special properties as compared to human milk.

Keywords: Antibodies; Camel; Cancer; Disease; Milk

INTRODUCTION

Over millenniums nature has evolved to ensure survival of diverse species against adverse environmental and pathological conditions. In case of mammals, maternal milk has paramount preventive and therapeutic benefit against vast variety of diseases, including cancer. Numerous studies in humans testify the immunological potential of human milk (Davanzo et al., 2012; Davis, 1998; Harikrishnan, 2006; Mathur et al., 1993; Newman, 1995; Parodi, 2007; Shamsia, 2009; Singh et al., 2012). The global epidemic of cancer is rising with this disease killing more people across the world than tuberculosis, AIDS, and malaria combined. According to GLOBOCAN, an estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012. This amounts to nearly 13% of all deaths. By 2030, the global cancer burden is expected to mount by about 75%, increasing to 21.4 million new cases and culminating in 13.2 million deaths (Bray et al., 2013). Cure of cancer still remains a worldwide challenge.

Camel milk not only serves as a nutritional supplement well adapted to human needs but also has microbicidal and immuno-stimulatory properties (El-Agamy et al., 1992; El-Fakhary et al., 2008; Hamad et al., 2011; Shabo

et al., 2005; Yagil, 2013). It has been traditionally believed in the Middle Eastern countries that camel milk has both preventive and therapeutic potential against cancer. Recently there have been many upcoming scientific evidences to lend support to this belief (Korashy et al., 2012a; Korashy et al., 2012b; Magjeed, 2005). Camel milk is generally consumed without boiling, thereby retaining its various biological and immunological properties that are normally lost in milk preservation processes (Agrawal et al., 2007). Camel is a mammal well adapted to deal with stressful conditions like high temperature and water deficiency (Faye, 2014). Its proteins are highly thermo-stable and resistant to acid hydrolysis (Maliheh et al., 2011). The ability of camel to withstand elevated temperatures may be useful in killing pathogenic thermo sensitive infectious agents. This may be the speculated cause behind the so called pathogen free state of its milk. Therefore, camel milk rarely ever causes any disease even though it is normally consumed raw.

Camel milk is supposed to have medicinal properties (El-Agamy et al., 1992). It is expected to have a therapeutic potential against many diseases including cancer. It has long been utilized for its benefit in broad range of diseases like Insulin Dependent Diabetes Mellitus (IDDM) (Agrawal et al., 2002; Agrawal et al., 2003; Agrawal et al., 2005),

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infant diarrhea (Yagil, 2013), hepatitis (El-Fakharany et al., 2008), allergy, lactose intolerance (El-Agamy et al., 2009; Konuspayeva et al., 2009; Cardoso et al. 2010) and alcohol induced liver damage (Ahmed et al., 2011). Its benefits can be attributed to the presence of many immunologically important molecules such as lysozymes, lactoferrin, lactoperoxidase, etc. (El-Agamy et al., 1996). The level of lactoferrin is comparable to cow's milk although its bioactivity is slightly higher (Konuspayeva et al., 2006; Conesa et al., 2008). It contains extraordinarily high levels of insulin like molecule (Agrawal et al., 2002; 2003; 2005). Besides this, its antibodies have a very specialized structure and function which may lead to its therapeutic benefit by modulating the immunoregulation. Camels unlike all other species (except shark) produce very special antibodies devoid of any light chains yet fully capable of antigen binding (De Genst et al., 2006; Desmyter et al., 2001; Hamers-Casterman et al., 1993; Harmsen et al., 2000; Harmsen and DeHaard, 2007; Muyldermans et al., 1994; Nguyen et al., 2000; Spinelli et al., 1996; Van der Linden et al., 1999; Vu et al., 1997; Yoo et al., 1967). Heavy chain antibodies can be expressed in microorganisms and have a high stability and solubility. Furthermore, camel milk IgGs are well suited for construction of larger molecules. It can also be used for selection systems such as phage, yeast, or ribosome display (Harmsen and DeHaard, 2007). Therefore the special features of these antibodies and the presence of other biologically important molecules and/or their derivatives confer camel milk with unique medicinal properties.

It is a commonly expected notion that proteins/polypeptides are enzymatically broken down completely to amino acids before their assimilation. It has been observed that there exist cellular mechanisms by which proteins/large polypeptides maybe carried across the cell intact. These molecules cross the basolateral border by co-transporters and facilitated transporters. Some large peptides or proteins can be carried across the cell by transcytosis. This is particularly true in infants where the intestinal tract is not completely developed and the pH of stomach is not as low as adults. It is the mechanism whereby the immunoglobulins in maternal milk along with all its immunological properties is transferred to the child. The enterocytes that do this are probably situated in the Crypts of Lieberkuhn. This mechanism also operates in adults but to a lesser extent. It has been observed that, indeed in infants the openings to the pits are much wider than in older children and adults (Gullberg, 2005; Ziv and Bendayan, 2000).

To prevent degradation of protein drugs from action of digestive juices in the stomach and to further enhance their absorption, various agents and techniques have been developed. Certain enzyme inhibitors like pancreatic inhibitor, soybean trypsin inhibitor and aprotinin have

been used to minimize the degradation of protein drugs by various proteolytic enzymes (Laskowski et al., 1958; Yamamoto et al., 1994). Absorption of protein drugs through intestinal walls could be improved using absorption enhancers which include surfactants, detergents, bile salts and Ca²⁺ chelating agents (Aungst, 2000; LeCluyse and Sutton, 1997). Researchers have also designed mucoadhesive polymeric systems which are capable of extending the residence time for protein drugs at their site of absorption (Hejazi and Amiji, 2003; Peppas, 2004). On the similar lines, various particulate carriers have been used to deliver protein drugs via the oral route. These carriers include nanoparticles, microspheres and liposomes. They play a vital role in preventing the degradation of protein drugs in the harsh environment of the GI tract (Okada et al., 1998; Singh et al., 2008; Behrens et al., 2002).

Anti-cancer properties of milk

Animal models for colon and mammary tumorigenesis have shown that whey proteins are better than other dietary proteins in suppressing tumor development (Parodi, 2007).

Survival value of maternal milk

Milk has a wide range of immunological molecules that enhance the survival value of infants feeding on mother's milk directly. Many of these molecules are present across mammalian species. Human milk too has numerous compounds with immune modulatory, antimicrobial and anti-neoplastic properties and/or the combination of the above. It also contains various bioactive components having an anti-cancer action. Some vital biologically active molecules present in milk are listed in Table 1.

Some molecules with anti-cancer activity present in human milk are Conjugated linoleic acids (CLAs), lactoferrin, TRAIL (TNF-related apoptosis inducing ligand) and HAMLET (Human alpha-lactalbumin made lethal to tumors). Structurally and functionally similar molecules with anti-cancer properties have been discovered in milk across diverse mammalian species (Zhang et al., 2009). For example, HAMLET, a conjugate of α -lactalbumin and oleic acid, is an antitumor biomolecule known to act not only against a wide range of cell lines, but also against some human tumors. It has shown significant positive response in treating glioblastomas skin papillomas, and bladder cancers. Interestingly, a variety of HAMLET-like substances from milk of other mammalian species have been discovered (Zhangetal., 2009). These molecular species with anticancer activity have been referred to as XAMLET, just for the sake of generalization.

Recently, the toxicity of bovine α -lactalbumin made lethal to tumor cells (BAMLET) has also been studied against cell lines. The toxicity of raw bovine milk is highly dependent

Table 1: Bioactive components in human milk

Type of molecule	Biomolecule present in milk	Biochemical nature	Significant property	Reference
Immunomodulatory	Fibronectin	Glycoprotein	Increases antimicrobial activity of macrophage Carcinoma development	Goldsby et al., 2003; Han et al., 2006
	Hormones and growth Factors	Peptides and proteins	Development of infants GIT against microbes	Newman, 1995
	Interferons	Proteins	Enhances antimicrobial activity of immune competent cells and signals adjacent cell on being virally infected to take preventive measure	Watanabe, 2004
	Lactoferrin	Globular glycoprotein	Makes Iron unavailable for bacteria thereby inhibiting its growth Enhances lactose tolerance	El-Fakharany, et al., 2008; Cardoso et. al., 2010; Conesa et al., 2008.
Antimicrobial	Secretory Immunoglobulins	Glycoproteins	Prevent microbial infiltration in tissue by blocking entry	Harmsen et al., 2007; Cortez et al., 2002
	B ₁₂ binding protein	Protein	Retards bacterial growth by reducing the amount of available vitamin B ₁₂	Newman, 1995
	Fatty acids	Lipid	Disruption of some viral membrane	Newman, 1995
	Bifidus factor	methyl-N-acetyl D-glucosamine	Promotes growth of harmless <i>L. Bifidusto</i> out compete pathogenic strains	Newman, 1995
	Lysozyme	Protein	Kills bacteria by disrupting its wall	El-Agamy et al., 1992
	Mucins	Glycosylated proteins	Prevent bacterial & viral attachment to mucosal surfaces	Newman, 1995
	Oligosaccharides	Carbohydrates	Prevent microbes from binding to mucosal surface by attaching to the microbes	Newman, 1995
Anticancer	Lactoferrin	Globular glycoproteins	Induction of apoptosis, inhibition of angiogenesis and modulation of carcinogen metabolizing enzymes	El-Agamy et al., 1996
	Casein and its peptides	Phosphoproteins	Antimutagenic properties	Parodi et al., 2007
	TRAIL (TNF-related apoptosis inducing ligand)	Cytokine (proteins)	A member of TNF family, kills cancer cells in vitro and in vivo	Horinaka et al., 2010
	XAMLET	Lipoprotein	Induces cell death in certain cancers and cell lines without effecting normal tissue	Zhang et al., 2009
	CLA (conjugated linoleic acids)	Fatty Acid	Antimutagenic activity	Amarù et al., 2009

on oleic acid and induces killing in cancer cell lines but up to now only human milk has been most predominantly studied. There is a conservation of molecules in evolutionarily closely related species thus it is likely that homologous molecules may also be present in other mammalian species. We postulate the presence of similar molecule in camel milk (CAMLET), because camel milk too, is known to possess relatively high concentration of oleic acid and alpha lactalbumin (Konuspayeva et al., 2008).

Supplementing cow's milk with selenium increases the content of selenoproteins in milk. These selenoproteins on isolation were able to inhibit colon tumor genesis in rats (Parodi, 2007). In the traditional Indian system of medicine, namely *Ayurveda*, raw cow's milk and its derivatives have also been used as a component of various medicines against wide range of ailments (Harikrishnan, 2006).

Epidemiological evidences of anti-cancer properties of Human milk

Epidemiological evidences strongly suggest benefits of mother's milk against cancer in humans. A qualitative

review assessing the association between infant feeding and childhood cancer was undertaken by Davis et al., in 1998. The results of suggested that children who were never breast-fed or fed for short-term (< 6 months) were at a higher risk of developing Hodgkin's lymphoma. In another study, the total duration of breastfeeding and of exclusive breastfeeding was compared in 99 childhood cancer cases and 90 controls. The outcome suggested that breast feeding had a protective effect against childhood cancer. The study also indicated that exclusive breast feeding provided more beneficial immunological effects than breast feeding supplemented by artificial feeding (Mathur et al., 1993). The high rate of breast feeding in India may explain the low incidence of childhood cancer in India as compared to many countries such as Israel (6/100,000 vs. 18/100,000 respectively).

There exists no substitute for mother's milk in any mammalian species other than humans. In animals, infants deprived of mother milk are likely to simply die away due malnutrition and disease. The research conducted in human shows presence of vital immunological factors

in milk (Goldsby et al., 2003). Similar benefits are likely in other mammalian species too although not many studies have been done. Benefits of maternal milk may be presumed because there is an evolutionary preservation of vital molecules, required for survival, across diverse species. Molecules present in maternal milk may help to optimize the function of the immune system and regulate cell proliferation to avoid tumor development in the rapidly growing neonatal cells.

Anticancer molecules present in human milk

The anti-cancer properties of human milk are far better studied than any other species. Before emphasizing upon the anticancer properties of camel milk it might be relevant to appreciate some evolutionarily conserved relevant molecules from human milk with an anti-cancer property. As we shall see later, many of these are also present in camel milk.

HAMLET (Human α - lactalbumin made lethal to tumors)

HAMLET is a very promising anticancer agent derived from human milk. It induces massive cell death in various types of cancers without causing any damage to normal tissues. *In vitro* it was able to induce programmed cell death in many human and murine cell lines such as Jurkat, L1210 (a leukemia cell line), A549 (a lung carcinoma line), and A-498 (a kidney carcinoma cell line). It also effectively destroys a great variety of tumor cells ranging from carcinomas of lung, throat, kidney, colon, bladder, prostate, ovaries; melanomas, to glioblastomas of the brain and leukemia (Svensson et al., 2000; Spolaore et al., 2010).

Mossberg et al., (2007) examined the effect of HAMLET on plasma membrane vesicles (PMVs) obtained from tumor cells. The treatment of bladder tumors by intravesicle HAMLET delivery resulted in a significant reduction in 8 out of 9 treated patients. HAMLET has shown striking effects in a rat model xenografted with human glioblastomas (Fischer, 2004).

HAMLET treated cells underwent shrinkage, nuclear condensation, caspase activation and DNA fragmentation, the characteristic features of programmed cell death (Hakansson et al., 1995). HAMLET-induced cell death is p53-independent and it also triggers an autophagic response (Aits et al., 2009). HAMLET not only translocates into tumor cells, activates cell death pathways but also induces adherent cell detachment *in vitro* (Trulsson et al., 2011). It also triggers tumor cell detachment *in vivo* in bladder cancer patients (Mossberg et al., 2007).

The interaction of tumor cell plasma membrane with HAMLET results in change in the fluidity of lipid bilayer leading to membrane elongation (Mossberg et al., 2010).

Membranes of tumor cells have altered lipid composition and fluidity. This may alter membrane-bound receptors and endocytic pathways and thereby affecting the activation of cell death in a manner that discriminates tumor cells from normal cells. After passing through the first barrier of plasma membrane, HAMLET enters cytoplasm and translocates into the nucleus (Durringer et al., 2003). HAMLET, being a partially unfolded protein, triggers endoplasmic reticulum stress signal in the cytoplasm, and is directed to 20S proteasome for degradation. Here it triggers a change in structure of proteasome and resists its own degradation by proteolytic enzymes (Gustafsson et al., 2009). In the nucleus histone proteins, mainly H3 and H4 act as nuclear receptors for HAMLET. In their study in 2007, Brest et al., have shown that histone deacetylase inhibitors enhance the tumoricidal effects of HAMLET. They acted by enhancing the hyperacetylation response which disrupts chromatin structure.

TNF - Related Apoptosis Inducing Ligand (TRAIL)

TRAIL is a member of the tumor necrosis factor (TNF) super family of cytokines. It may be present either in a trans-membrane form or occur in the cytoplasm as a soluble protein. Extremely high levels of TRAIL have been detected in human colostrum and milk (Davanzo et al., 2012). TRAIL is a pleiotropic cytokine with important functions in regulating immune response and inflammation. It plays a key role in controlling cell death and cell proliferation in various organs and tissues. The best characterized activity of TRAIL is its ability to kill cancer cells both *in vitro* and *in vivo*. It is currently being used as a recombinant protein in many clinical trials against a wide variety of human cancers. Moreover, it has recently been shown that certain *Lactobacillus* strains induce the production of TRAIL. This further facilitates natural killer activity against cancer cells (Horinaka et al., 2010). Endogenous soluble TRAIL itself represents a strong candidate to explain the overall biological effect of breastfeeding against cancer.

Immunological and anti-cancer properties of casein and whey components of milk

Many milk components act not only as nutrients but also have very important immunological and anticancer properties. Casein breakdown products have the ability to prevent mutations. The high content of cystine/cysteine and gamma-glutamylcyst(e)ine dipeptides have been implicated for this activity. Dipeptides are efficient substrates for the synthesis of glutathione. Glutathione is a well-known ubiquitous cellular antioxidant that either directly or through its associated enzymes destroys reactive oxygen species (ROS). It also detoxifies carcinogens, maintains proteins in a reduced state and ensures immunocompetence. Increased glutathione levels

in serum and tissues accompany tumor prevention by dietary whey proteins. Enhanced glutathione level has been found to be associated with an enhanced splenocyte proliferation and phagocytosis. It is also involved in immune regulation by T Helper cells, cytotoxicity mediated by natural killer cells and CTLs. The minor whey component, lactoferrin, inhibits intestinal tumors. It acts by inducing apoptosis, inhibiting angiogenesis and modulating carcinogen metabolizing enzymes. It also acts as an iron scavenger (Parodi, 2007).

Medicinal value of camel milk

Camel milk is emerging as a potent therapeutic alternative which can help in reducing insulin doses in diabetic patients. It's well established role in management of Diabetes has rendered it the title of "white gold of desert". Epidemiological surveys strongly indicate low prevalence of diabetes in communities consuming camel milk. (Agrawal et al., 2013). Global market potential for camel milk needs to be further exploited.

Camel milk has been successfully used in the treatment of various diseases such as diabetes (Agrawal et al., 2002; Agrawal et al., 2005), hepatitis (El-Fakharany, 2008), allergy (El Agamy et al., 2009) and to counter alcoholism (Ahmed et al., 2011) as explained in Table 2. Similar to human milk as described earlier, camel milk also contains protective proteins like lysozyme, lactoperoxidase, lactoferrin, polypeptide recognition protein and N-acetyl-beta-D-glucosamidase (Shamsia, 2009; El-Agamy et al., 1996).

Camel milk has an amazing immunological profile. It contains very special types of immunoglobulins called the

VHH (variable heavy heavy) antibodies or Nanobodies. Camel antibodies are much smaller in size as compared to the normal antibodies as they lack the typical light chains present in normal antibodies. This increases their tissue penetration while retaining the specificity (Harmsenand De Haard, 2007; Cortez et al., 2002). Camel IgGs (which also exist in the milk, besides being present in blood) are able to penetrate within tissues unlike human IgGs. Therefore, they are able to enter into organs like liver and kidney. Furthermore, they can enter inside a cell where they may perform various functions under pathological conditions (Al-Fartosi et al., 2011; Mohamed, 2010; Jadambaa et al., 2000; Hamad et al., 2011; Sharmanov and Kadyrova, 1978). As mentioned earlier, camel milk lactoferrin also has anti-viral and anti-bacterial properties (El Agamy, 1996; Konuspayeva et al., 2006).

Special composition of camel milk

Functional foods and their dietary constituents have a well-established beneficial role in health promotion and have emerged as an adjunct for cancers chemoprevention (Kontou et al., 2011). Camel milk is given to the sick, elderly and very young because of the belief that it is not only healthier, but works especially well in bone formation. A high content of unsaturated fatty acids (such as oleic acid) further improves its overall dietary quality (Konuspayeva et al., 2009; Jadambaa, 2000; Nikkhah, 2011; Shabo et al., 2005; Shamsia, 2009; El-Agamy et al., 2009).

Camel milk is mostly consumed fresh and raw by some native communities in India. In this way its medicinal properties are not destroyed by preservation techniques like boiling, pasteurization, etc., Also it does not form coagulum in acidic environment (Wangoh et al., 1998). This lack of

Table 2: Application of camel milk in various diseases

S. no.	Treatment against disease conditions	Molecule implicated	Reference
1.	Diabetes	Insulin like molecule	Agrawal, et al., 2013; Agrawal, et al., 2002; Beg et al., 1986; Singh, 2001
2.	Hepatitis C Virus	Amylase & lactoferrin	El-Fakharany, 2008
3.	Allergy	Low levels of β -Casein & lack of β -lactalbumin	El Agamy et al., 2009; Shabo et al., 2005
4.	Liver and kidney function	Alanine amino transferase and aspartate aminotransferase	Hamad et al., 2011; Jadambaa et al., 2000; Sharmanov et al., 1978
5.	Slimming properties	Low protein content and reasonable cholesterol content	Yasin and Wahid, 1957 Faye et al., 2015
6.	Bacterial infection	Lysozyme, lactoperoxidase	El Agamy et al., 1992
7.	Nutritional supplements	Unsaturated fatty acids	Konuspayeva et al., 2009
8.	Immuno enhancer	Peptidoglycan recognition protein	El Agamy et al., 1992
9.	Lactase deficiency and easy assimilation	L-lactate	Cardoso et al., 2010; Baubekova et al., 2015
10.	Bone formation	High level of calcium	Riad et al., 1994
11.	Diarrhea	High level of sodium and potassium	Yagil, 2013; El Agamy et al., 2009

coagulum formation allows the camel milk to pass rapidly through stomach with proteins available for absorption in intestine. The pH of camel milk is between 6.5–6.7. Camel milk is different from other ruminant milk because it has reasonable content of cholesterol, high minerals (sodium, potassium, iron, copper, zinc and magnesium), high vitamin C, B2, A and E, low protein and high concentrations of an insulin-like protein (Konuspayeva et al., 2009; Shamsia, 2009; Faye et al., 2015).

One liter of camel milk has ample amount of minerals to meet 100% of the daily human requirements for calcium and phosphorus, 57.6% for potassium, 40% for iron, copper, zinc and magnesium, and 24% for sodium. It helps treat liver problems, lowers bilirubin output, lightens vitamin inadequacy and nutrient deficiency, besides boosting immunity. Camel milk contains substantially less vitamins A and B2, similar vitamin E content and about 3-10 times greater vitamin C as compared to cow milk (Nikkhah, 2011; Konuspayeva et al., 2011).

In the Middle Eastern countries fresh butter derived from camel milk is often used as a base for many medicines. Not only is it totally devoid of any allergic properties but it also heals food allergies and gut problems. It can be conveniently consumed by lactase deficient people and even by those who have a weak immune system. The hypo-allergic effect of camel milk is associated with a low level of beta-casein and lack of beta-lactoglobulin. This milk also apparently has slimming properties attributed to camel milk owing to its cholesterol level, which however remains a matter of debate (El-Agamy et al., 2009; Faye et al., 2015).

Immunologically important molecules in camel milk (Table 3)

Medicinal properties present in camel milk have been attributed to a wide array of immunologically significant protective proteins present in it. The level of peptidoglycan recognition protein (PRP) is very high in camel milk. PRP not only stimulates the host's immune response but also has an antimicrobial activity (El-Agamy et al., 1992). It acts by preventing microbial overgrowth and inhibiting pathogenic invasion. Recent studies have shown that the amount of Lactoferrin is almost similar to that in cow milk however its bioactivity is higher (Konuspayeva et al., 2006; Conesa et al., 2008). The camel milk has the same quantity of sugar (lactose) but the only difference is the better lactose tolerance for consumers (Cardoso et al., 2010). Lactoperoxidase present in camel milk has bactericidal activity on gram-negative bacteria. Its antitumor activity has also been suggested. Lysozyme is a part of the soluble components of the innate immune system and targets gram-positive bacteria. N-acetyl-beta-D-glucosamidase is found in similar

quantities as in human milk where it has antibacterial activity. Lactoferrin, lactoperoxidase, lysozyme, immunoglobulin G and secretory immunoglobulin A were extracted from camel milk (El-Agamy, 1992). The activity of these protective proteins was assayed against *Lactococcus lactis*, *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhimurium* & rotavirus and compared with egg white lysozyme, bovine lysozyme and bovine lactoferrin. The spectrum of antibacterial activity of camel milk lysozyme was similar to that of egg white lysozyme, but differed from bovine milk lysozyme. The camel milk lactoperoxidase was bacteriostatic against the gram-positive strains and was bactericidal against gram-negative cultures. The immunoglobulins had little effect against the bacteria but high titers of antibodies against rotavirus were found in camel milk. The lactoperoxidase system was ineffective against rotavirus (El-Agamy et al., 1996).

As compared to human milk, camel milk has a higher ratio of immunoglobulins but a lower ratio of both lysozyme and lactoferrin. A comparative lipid profile indicates that the short chain fatty acids (C4–C12) although were present in small amounts but they were higher than in human milk fat. On the contrary the concentration of higher chain fatty acids such as C14:0, C16:1 and C18:0 were relatively high in camel's milk fat as compared to human milk fat. Appreciable amounts of essential fatty acids were also present in camel milk (Shamsia, 2009; Konuspayeva et al., 2009).

Ahmed et al., in 2011 studied the role of camel milk in the reactivation of liver damage caused by Sudanese liquor, popularly known as *Aragi*. Their study showed a statistically significant increase in the liver enzyme markers in the group given liquor as compared to the controls. Camel milk was observed to reduce the level of vital liver enzymes. It was thus suggested that camel milk can be used as a remedy for treatment of alcoholism and other liver diseases.

A study was conducted to see if the consumption of camel milk was beneficial for diabetes. A significant improvement in glycosylated hemoglobin (HbA1c) and fasting blood sugar levels was observed. Also a significant reduction in insulin requirement in patients receiving camel milk was noted. Although there was a 30% reduction in doses of insulin in 92% of patients but there were no statistically significant change in lipid profile, plasma insulin and c peptide (Agrawal et al., 2003; Agrawal et al., 2007). It has been reported that one of its milk protein has many characteristics similar to insulin (Beg et al., 1986).

Camel proteins are able to maintain a high degree of thermal stability and remain functional even at elevated temperatures. Their extraordinary stability is attributed mainly to their

Table 3: Molecules with immune function in camel milk

S. no.	Name of molecule	Function	Reference
1.	Heavy chain antibodies (HCAb) or variable heavy antibodies (VHH) or nanobodies	Able to interact with less immune dominant parts of antigens More tissue penetration but similar specificity Equivalent specificity Rapid renal clearance in human	Hamers-Casterman et al. (1993); Muyldermans, 2013
2.	Peptidoglycan recognition protein (PRP)	Stimulates immune response and has antimicrobial activity	El Agamy et al., 1992
3.	Lactoferrin	Prevents pathogenic invasion and microbial overgrowth	El Agamy et al., 1992; Konuspayeva et al., 2006
4.	Lactoperoxidase	Antitumor activity Antibacterial against gram negative bacteria like <i>E. Coli</i> , <i>Salmonella</i> and <i>Pseudomonas</i> Bacteriostatic against gram positive	El Agamy et al., 1996
5.	Lysozyme	Targets Gram positive bacteria	El Agamy et al., 1992
6.	N-acetyl-glucosaminidase (NAGase)	Antibacterial and antiviral activity	Jassim and Naji, 2001

efficient refolding after chemical or thermal denaturation. To a lesser extent, an increased resistance against denaturation may be responsible for it (Maliheh et al., 2011).

Special features of camelid antibodies

Structurally, a classical antibody present in mammals consists of two heavy and two light chains interconnected by disulfide bonds. The antibodies present in humans and most other mammalian species are essentially Y-shaped proteins which have a vital role in various antigen-elimination mechanisms and also act against cancer. The classical antibody contains an N-linked oligosaccharide attached to the second heavy-chain constant domain (CH2) that is essential for antibody effector functions such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and for retaining a long serum half-life. Even after isolation, the heavy (Utsumi and Karush, 1964) and light chains (Yoo et al., 1967) of an antibody can retain their antigen binding specificity; however reduction in their affinity and solubility is often observed (Ward et al., 1989).

Camelids (Bactrian and dromedaries camels, as well as llamas) generate antibodies devoid of light chains (Hamers-Casterman et al., 1993). The single N-terminal domain of these heavy chain antibodies is fully capable of binding with the antigen.

Another specialty of these antibodies is that they lack the CH1 domain, which remains associated with the light chain as well as to some extent with the V_H domain, in case of classical antibodies. Besides these special antibodies, camelids also have the normal type of mammalian antibodies. The affinities of VHHs are generally comparable to those of conventional antibody fragments (Maliheh et al., 2011). Dedicated Immunoglobulin Heavy chain genes are used to produce heavy chain antibodies in camels. Similar to conventional

antibody genes, the dromedary genes have identity in the organization of relevant regions such as exons and introns of the immunoglobulins (Muyldermans, 2013).

The sequence study (Hamers-Casterman et al., 1993) and revelation of crystal structure (Desmyter et al., 2001; Spinelli et al., 1996) have exposed various structural characteristics of VHH domains of camelid antibodies. The structural organization of VHH domains consist of four framework regions (FRs) which together form the core structural configuration of the immunoglobulin and three Complementarity Determining Regions (CDRs) that are involved in the interaction with antigen. The V_H domains of classical antibodies contain conserved amino acid sequences at positions 37, 44, 45, and 47 (Kabat numbering) of FR2. These amino acids are responsible for the hydrophobic interaction of V_H domains with the V_L domains. However VHHs have substituted amino acids at the above four mentioned FR2 positions due to which they attain an increased hydrophilic character. Also some of the amino acids at positions forming hydrophobic patch in classical antibody's V_H domain contacting CH1 (Lesk and Chothia, 1988) are also replaced by hydrophilic residues in VHHs. Additional features are also present in case of CDRs of VHHs which includes the increased variability of N-terminal part of CDR1 (Vu et al., 1997; Harmsen et al., 2000; Nguyen et al., 2000) and an extended CDR3 in case of many dromedary VHHs which is often stabilized by an extra disulfide bond in CDR1 or FR2 (Muyldermans et al., 1994).

In comparison to classical antibodies, the VHHs are more stable at higher temperatures. VHHs remain functional even at 90°C or even when subjected to incubation at high temperatures (Van der Linden et al., 1999). The efficient refolding of VHHs after chemical or thermal denaturation provides them with enhanced stability and to some extent is also attained because of their increased resistance to denaturation (Dumoulin et al., 2002;

Ewert et al., 2002). Additionally the refolding of VHHs involve only domain refolding while in case of classical antibodies, interaction between V_H and V_L domains is also required.

VHHs can even recognize antigenic sites that are normally not recognized by classical antibodies, for instance the active sites of enzymes (Lauwereys et al., 1998; De Genst et al., 2006) and conserved cryptic epitopes (Stijlemans et al., 2004). Hence the VHHs can be utilized as enzyme inhibitors. The smaller size of VHHs gives them an added advantage to access and recognize hidden antigenic sites. Even their extended CDR3 loop has the ability to penetrate and access such sites (Desmyter et al., 1996; De Genst et al., 2006).

The smaller size of VHHs (12-15 kDa) as compared to common antibodies (150-160kDa), allows them to rapidly pass the renal filter, which has cutoff of around 60kDa, thereby facilitating their rapid blood clearance. In addition to this the small size also aids in quick tissue penetration which can be used for targeting tumors by VHHs coupled to cytotoxic drugs (Cortez-Retamozo et al., 2004). VHH coupled tumor targeting can be used for *in vivo* diagnosis in association with imaging techniques. Furthermore, it can even be used in the treatment of snake bites (Harrison et al., 2006).

Anticancer properties of camel milk

Middle Eastern countries have traditionally used camel milk for therapeutic benefits against cancer. There are upcoming clear cut indications suggesting the potential role of camel milk against cancer.

Evidences supporting anti-cancer properties of camel milk

An epidemiological survey was conducted to study the prevalence of diabetes in a local Nomadic community called Raika (Agrawal et al., 2007). This community is totally dependent on camel milk for its day to day needs. During his entire study he did not come across a single case of cancer (personal communication). The low prevalence of cancer in communities consuming camel milk is indeed remarkable. Recently, Korashy et al., in 2012 have reported that camel milk has the ability to significantly inhibit the induction of the Cyp1A1, a cancer-activating gene. Further it also induces NQO1, a cancer chemo preventive gene in murine hepatoma Hepa 1c1c7 cells. Both these functions were studied at the transcriptional and posttranscriptional level. It was observed that the survival of HepG2 cells was significantly reduced upon incubation with camel milk. Further, they observed that camel milk significantly induced caspase-3 and DR4 mRNA expression levels. The induction of Caspase-3 was blocked by the action of Act-D. This

indicates that camel milk increased the caspase-3 mRNA level by the *de novo* synthesis of RNA. It was further observed that pretreatment of cells with MAPK inhibitors alone, slightly, but not significantly decreased the basal expression level of caspase-3 mRNA. Furthermore, it was reported that the induction of caspase3mRNA by camel milk in HepG2 cells was significantly decreased by both the JNK and p38 MAPKs inhibitors and was potentiated by an ERK inhibitor.

Mohamed E.M. Afifi (2010) studied the protective effect of camel milk against cisplatin-induced renal oxidative stress in mice. Cisplatin induced stress was indicated by increased level of liver tissue metabolites such as malondialdehyde, serum creatinine and urea. This stress also led to a decrease in the concentration of glutathione, vitamin C and E. At an enzymatic level cisplatin decreased both, the activity and gene expression of superoxide-dismutase, catalase glutathione reductase and glutathione peroxidase. In their study, treatment of these animals significantly increased the level of malondialdehyde as well as the enzymes viz. superoxidedismutase, catalase, glutathione reductase and glutathione peroxidase. The increase caused in catalase was not significant. The camel milk caused reduction in all these biochemical alterations and counteracted the deleterious effects of cisplatin. This study demonstrated the renoprotective potential of camel's milk against cisplatin-induced oxidative stress.

Alpha-lactalbumin upon combination with oleic acid can be converted to the complex, HAMLET, which kills tumor cells selectively. The thermal stability of camel milk α -lactalbumin and its complexes with oleic acid and linoleic acid were studied at 60°C. Both these complexes were observed to have a stable structure. They were able to exhibit a cytotoxic effect on DU145, a human prostate cancer cell line, even after exposure to temperatures as high as 60°C (Maliheh et al., 2011).

Mechanism of action of camel milk proteins

Camel milk components act as a ligand to the aryl hydrocarbon receptor (AhR). Signaling via aryl hydrocarbon receptor has a definite anticancer action. This receptor is an endogenous transcription factor known to have a preventive as well as therapeutic benefit to patients with cancers of breast, liver, prostate, etc. (Zhang et al., 2009).

Role of aryl hydrocarbon receptors

Aryl hydrocarbon receptor (AhR) is a basic helix-loop-helix (bHLH)/Per-ARNT-Sim (PAS) family of transcription factor which is found in the cytosol and is activated after binding with its ligand. This family of transcription factors regulates the pathways involved in cellular proliferation and differentiation (Kerzeeand Ramos, 2001; Whitelaw et al., 1993). In the cytosol, AhR remains

as an inactive complex when bound with Heat Shock Protein-90 (HSP90) and AhR interacting protein (AIP). The interaction of AhR with its ligands, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a polycyclic aromatic hydrocarbon (PAH), results in the dissociation of bound HSP90 and AIP and hence its activation. This subsequently leads to its translocation into the nucleus. After entering the nucleus it forms a dimer by interacting with the AhR nuclear translocator (ARNT) and then proceeds to bind with xenobiotic-responsive element (XRE) found in the promoter region of the so called AhR regulated genes. It's binding results in the transcription and translation of these genes (Whitlock, 1999; Nebert *et al.*, 2000). The group of genes regulated by AhR includes both phase I xenobiotic metabolizing enzymes such as the cytochrome P4501A1 (CYP1A1), CYP1A2, CYP1B1 and phase II enzymes such as NAD (P) H: quinone-oxidoreductase 1 (NQO1), Glutathione S-transferase A1 (GSTA1), Uridine diphosphate glucuronosyl-transferase1A6, and Aldehyde dehydrogenase-3 (Whitlock, 1999; Nebert *et al.*, 2000). Among the above mentioned genes, CYP1A1 is considered a cancer activating gene as it plays an important role in the bioactivation of procarcinogens into carcinogens and other toxic metabolites (Nebert *et al.*, 2004). On the other hand, NQO1 and GSTA1 catalyze the reduction of numerous environmental contaminants and also maintain the optimum level of endogenous antioxidants like vitamin E and ubiquinone. This helps in protecting the tissues against mutagens, carcinogens and damages induced by oxidative stress (Ross, 2004; Vasiliou *et al.*, 2006).

Modulation of aryl hydrocarbon receptors in cancer therapy

Several lines of evidence have shown that the induction of CYP1A1 strongly correlates with increased incidences of human colon, rectal, and lung cancers (Slattery *et al.*, 2004; Shah *et al.*, 2009). In addition, studies on carcinogenicity and mutagenicity of PAHs have demonstrated a significant role in induction of CYP1A1 in bioactivating these environmental toxicants into their ultimate carcinogenic forms (Shimada and Fujii-Kuriyama, 2004). Thus, CYP1A1 induction is considered a useful biomarker of exposure to carcinogenic substances (Williams *et al.*, 2000).

Accordingly, one of the strategies for protecting human cells and tissues from the toxic effects of carcinogenic and cytotoxic metabolites is to attenuate the carcinogen-activating genes, CYP1A1 signaling pathways, and/or enhancing the adaptive mechanisms by increasing the expression of detoxification and antioxidant genes, such as NQO1 and GSTA1. Therefore camel milk can be postulated to protect against or decrease the deleterious effects of many environmental toxicants and carcinogens such as PAHs, probably through modulation of AhR-regulated genes, such as CYP1A1, NQO1, and GSTA1

at the transcriptional and post transcriptional level.

Aberrant aryl hydrocarbon receptor expression and the activation of AhR pathway is involved in carcinogenesis. Exogenous AhR agonists promote differentiation in a putative mammary cancer stem cell line. Moreover, activation of the AhR is known to inhibit invasive and metastatic features of human breast cancer cells (Zhang *et al.*, 2009). It has been shown that the aryl hydrocarbon receptor functions as a suppressor of liver carcinogenesis. It has also been observed that AhR pathway activation enhances gastric cancer cell invasiveness through a c-Jun-dependent induction of matrix metalloproteinase-9.

New antitumor drugs like aminoflavone and benzothiazoles, require AhR-mediated signaling to expedite DNA damage. These drugs show antitumor activity in the estrogen receptor of positive breast cancer cell line, MCF-7. However, nude mice model having estrogen receptor negative breast cancer cells like MDA-MB-231 is less susceptible to the action of these drugs. This study indicates that these drugs, unlike other neoplastic agents, require AhR-mediated signaling to cause DNA damage. This is a new treatment strategy for breast cancers cells which have intact AhR signaling mechanisms. Camel milk constituents are known to similarly act through aryl hydrocarbon receptors (Callero and Loiaza-Perez, 2011).

CONCLUSION

Evolutionary pressures have played a vital role in accrediting milk with very significant immunological and anti-cancer properties. Camel has specially evolved to adapt under stressful conditions. As a result of these adaptations, it has an extraordinary immune system containing special feature antibodies. Camel milk proteins are thermostable and acid hydrolysis resistant, thus very relevant. Camel milk is known to contain many compounds that exhibit anti-cancer properties in other mammalian species. It is therefore immensely important to understand these special attributes to fully utilize the potential of camel milk. The future prospect includes utilization of camel milk as a nutraceutical agent with adjunct therapeutic potential.

Author contribution

All authors contributed equally in this article.

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