

Sodium dodecyl sulfate as a viral inactivator and future perspectives in the control of small ruminant lentiviruses

Emprego do dodecil sulfato de sódio como inativador viral e suas perspectivas no controle de lentivírus de pequenos ruminantes

Ana Lídia Madeira de Sousa^{1*} , Raymundo Rizaldo Pinheiro² , Juscilânia Furtado Araújo¹ , Dalva Alana Aragão de Azevedo¹ , Renato Mesquita Peixoto¹ , Alice Andrioli² , Sabrina Tainah da Cruz Silva Bezerra¹ , Maria Fátima da Silva Teixeira¹ 

ABSTRACT: Infections by small ruminant lentiviruses (SRLVs) affect goats and sheep causing chronic multisystemic diseases that generate great economic losses. The caprine lentivirus (CLV) and the ovine lentivirus (OLV) present tropism for cells of the monocyte/macrophage lineage, which are directly associated with the main route of transmission through the ingestion of milk and colostrum from infected animals. In this manner, controlling this route is of paramount importance. Currently, researches have investigated the use of chemical additives in milk that can preserve colostrum or milk and inactivate microbiological agents. Among the compounds, sodium dodecyl sulfate (SDS) has been shown to be satisfactory in the chemical inactivation of HIV and CLV in milk, and also as a biocide in goat colostrum.

KEYWORDS: colostrum; chemical inactivation; milk; monocyte/macrophage system.

RESUMO: As lentivirose de pequenos ruminantes (LVPRs) são infecções que afetam caprinos e ovinos, causando doenças multissistêmicas crônicas, ocasionando grandes perdas econômicas. Os agentes causadores, lentivírus caprino (LVC) e o lentivírus ovino (LVO), apresentam tropismo por células da linhagem monocítico-fagocitária, as quais estão diretamente associadas à principal via de transmissão, por meio da ingestão de leite e colostro provindos de animais infectados. Desse modo, o controle por esta via é de suma importância. Atualmente, pesquisas vêm sendo desenvolvidas para o uso de aditivos químicos no leite, que possam conservar o colostro ou leite, e inativar agentes microbiológicos presentes. Dentre estes, o dodecil sulfato de sódio (SDS) vem apresentando resultados satisfatórios na inativação química do HIV e LVC em leite, e ainda como biocida em colostro caprino.

PALAVRAS-CHAVE: colostro; inativação química; leite; sistema monocítico-fagocitário.

¹State University of Ceará – Fortaleza (CE), Brazil.

²Embrapa Goats and Sheep – Sobral (CE), Brazil.

*Corresponding author: analidiams10@yahoo.com.br

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INTRODUCTION

The use of chemical compounds as antivirals in humans has been investigated as possible control forms of sexually transmitted diseases, especially in association with preservatives and topical microbicides (KABAMBA et al., 2016). Most of these compounds are surfactants that solubilize bacterial and viral membranes, inactivating the pathogens. Among studies, the most investigated substances are nonoxynol-9, C31G or SAVVY® (Cellegy Pharmaceuticals, Quakertown, PA, EUA), n-Lauroylsarcosine and sodium-dodecyl-sulfate (SDS) (KABAMBA et al., 2016; KREBS et al., 1999; ROY et al., 2001).

SDS is a broad-spectrum surfactant (URDANETA et al., 2005) that have presented efficient activity as a topical microbicide and viral inactivator against HIV (human immunodeficiency virus), HPV (human papillomavirus) and HSV (herpes simplex virus) (PIRET et al., 2002). Antiviral activity in human milk was also investigated in an *in vitro* study performed by URDANETA et al. (2005). The microbicide effect has also been evaluated in caprine colostrum, which presented effective results (MORALES-DE LA NUEZ et al., 2011). In addition, SOUSA (2016) aimed to prevent milk transmission of the caprine arthritis encephalitis virus (CAEV) with SDS acting as a prophylactic microbicide and observed a possible reduction of the viral load in milk and colostrum.

Hence, this study aimed to briefly review general characteristics and toxicity levels of SDS in addition to its potential as a viral inactivator.

SODIUM DODECYL SULFATE: BIOCHEMICAL CHARACTERIZATION AND VIRAL INACTIVATION

General characteristics

Sodium dodecyl sulfate (SDS) or sodium lauryl sulfate (SLS), chemical formula $\text{NaC}_{12}\text{H}_{25}\text{SO}_4$ (IUPAC, 2014), is a tensoactive agent that has detergent properties. SDS possesses a zwitterionic form in aqueous solution with two distinct portions, polar and apolar, at opposite ends of a single molecule (Fig. 1). The polar end is formed by a sulfate group while the opposite end, apolar, is composed by a long chain hydrocarbon, which

may be linear, branched or aromatic according to the diluent solution (SINGER; TJEERDEMA, 1993).

SDS chemical structure was described for the first time by Lottermoser and Stoll in Germany, 1993. Afterwards, this compound was classified as tensoactive or surfactant containing 6 – 18 carbon atoms. Its use as a detergent propagated the chemistry technology in the first half of the 19th century when synthetic alternatives were developed to substitute detergents of animal origin, which were often used at the time (KIRK-OTHEMER, 1984).

SDS is useful due to its chemical nature that provides adequate ionic balance, solubilizing fats and oils, and the formation of microemulsions. Hence, there are different uses for this substance, such as an ingredient in cleaning products, cosmetic production and in biological research (SINGER; TJEERDEMA, 1993). SDS has cytolytic properties, which are useful in the preparation of subcellular materials for biochemical studies, such as plasmatic membranes, organelles and genetic material. In addition, it also aided in the development of proteomics, identification of proteins and determination of structures with polyacrylamide gel electrophoresis (SDS-PAGE) (SHAPIRO et al., 1967).

Cytolytic activities

Cell membranes are characterized by an architecture containing lipid bilayers. These lipids are amphipathic with a hydrophobic and a hydrophilic end in the same molecule. These membranes are impermeable to most polar or charged solutes but are permeable to apolar compounds (NELSON; COX, 2011).

In direct contact with cells, SDS cause physical and biochemical effects. The main targeted structure is the cell membrane in every type of cell, and it is able to undo its barrier capacity (BENOIT et al., 1987; PARTEARROYO et al., 1990). The cytotoxic effects are dependent of absolute concentrations and lipid/surfactant molar ratios. When in low concentrations of surfactants, cell membranes lose their barrier capacity increasing permeability (KALMANZON et al., 1992). On the other hand, equal or superior surfactant/lipid ratios cause cell lysis (PARTEARROYO et al., 1990).

According to BARTNIK (1992), three interaction phases may be established when SDS is added in high concentrations and surfactant levels surpass those of cellular lipids. Initially, the tensoactive may cause membrane permeability alterations.

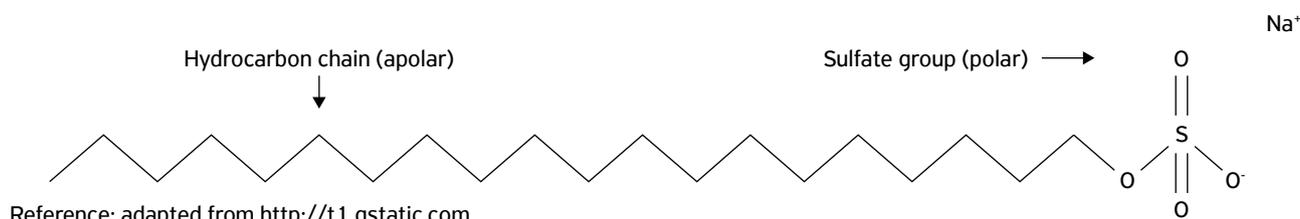


Figure 1. Chemical representation of sodium dodecyl sulfate.

Then, if it exceeds cytolytic concentrations, the lamellar structure of the membrane is solubilized releasing proteins, lipoproteins and micelles, determining a complete cell lysis. In the third phase, phospholipid separation and structural denaturation of proteins occur. SDS is one of the ionic tensoactives that can perform covalent bonds, which usually results in conformational alterations and simultaneous loss of biological activity.

Toxicity levels

SDS toxicity is attributed to the use of high doses of the product. According to the data provided by the United Nations Environment Programme (UNEP, 1997), this substance may be considered with a low potential risk for humans and the environment. Table 1 shows toxicity levels of SDS in several species.

The estimated human exposure results reported by UNEP (1997) revealed that SDS does not present risk to the human health. According to the data, daily use of SDS in kids (15 kg) and in babies (5 kg) was considered safe with doses of 0.158 and 0.034 mg/kg/day, respectively. In addition, maximum consumption of SDS was 1 g/kg/day for kids. This includes exposure to body lotions and oral ingestion of contaminated water or toothpaste (DREISBACH; ROBERTSON, 1987).

Use as a viral inactivator

SDS has showed potent inhibition of enveloped and non-enveloped viruses causing dissociation of the viral envelope and capsid proteins through denaturation. These proteins play different roles in the viral replication cycle from adhesion to viral encapsidation (PIRET et al., 2002).

Sexually transmitted diseases have global incidence, morbidity and mortality with significant levels. The human immunodeficiency virus type 1 (HIV-1), herpes simplex virus (HSV) and human papillomavirus (HPV) are part of these rates (BRUGHA et al., 1997). SDS mechanism of action has shown efficiency in chemically inactivating these viruses, denaturing proteins from the envelope and/or capsid in HeLa cell culture (human cells from Henrietta Lacks) (PIRET et al., 2002; KREBS et al., 1999). Furthermore, this surfactant does not compromise the vaginal mucosa of rabbits. Hence, it is a good option for use as a topical microbicide to prevent sexually transmitted pathogenic agents, which could be a high impact tool to the public health (PIRET et al., 2000, 2002).

Figure 2 demonstrates a dose-dependent effect of SDS against HSV-1 in VERO cells (African green monkey kidney cells). Low concentrations ($\leq 50 \mu\text{M}$) did not reduce synthesis of viral glycoprotein D (gD). However, viral infectivity was

Table 1. Sodium dodecyl sulfate toxicity levels in different species.

Species	Application	Results	Reference
Rats	Intraperitoneal	LD ₅₀ = 210 mg/kg	EPSTEIN et al. (1939)
	5 and 10% in water for 5 days	100% lethality	EPSTEIN et al. (1939)
	2 and 4% in feed for 4 months	No reaction and growth reduction, respectively.	FITZHUGH; NELSON (1948)
	Intravenous	LD ₅₀ = 188 mg/kg	CASCORBI et al. (1963)
	Acute oral Repeated doses	LD ₅₀ ¹ = 1200 mg/kg	UNEP (1997)
	(oral hepatotoxicity)	NOAEL ² = 100 mg/kg/day	UNEP (1997)
Guinea pigs	Acute dermal	LD ₅₀ => 1200 mg/kg	UNEP (1997)
Rabbits and mouse	Toxicity for development/ teratogenicity	NOAEL \leq 300 mg/kg/day (maternal toxicity) NOAEL = 600 mg/kg/day (fetal malformation)	UNEP (1997)
Rabbits	Acute dermal toxicity	LD ₅₀ = 600 mg/kg	UNEP (1997)
Mouse	Intraperitoneal	LD ₅₀ = 250 mg/kg	GALE; SCOTT (1953)
	Oral	LD ₅₀ = 2700 mg/kg	GLOXHUBER (1972)
	Reproductive route (male fertility)	NOAEL = 1000 mg/kg/day	UNEP (1997)
Dogs	Oral: 135 mg/kg/day for 10 months	No reaction	FOGELSON; SHOCH (1944)
Goat kids	Oral: 0.5% in milk	Apathy and light diarrhea in 7 days of treatment	SOUSA (2016)
	Oral: 1% in milk	Apathy, severe diarrhea and death in 72 hours of treatment	SOUSA (2016)

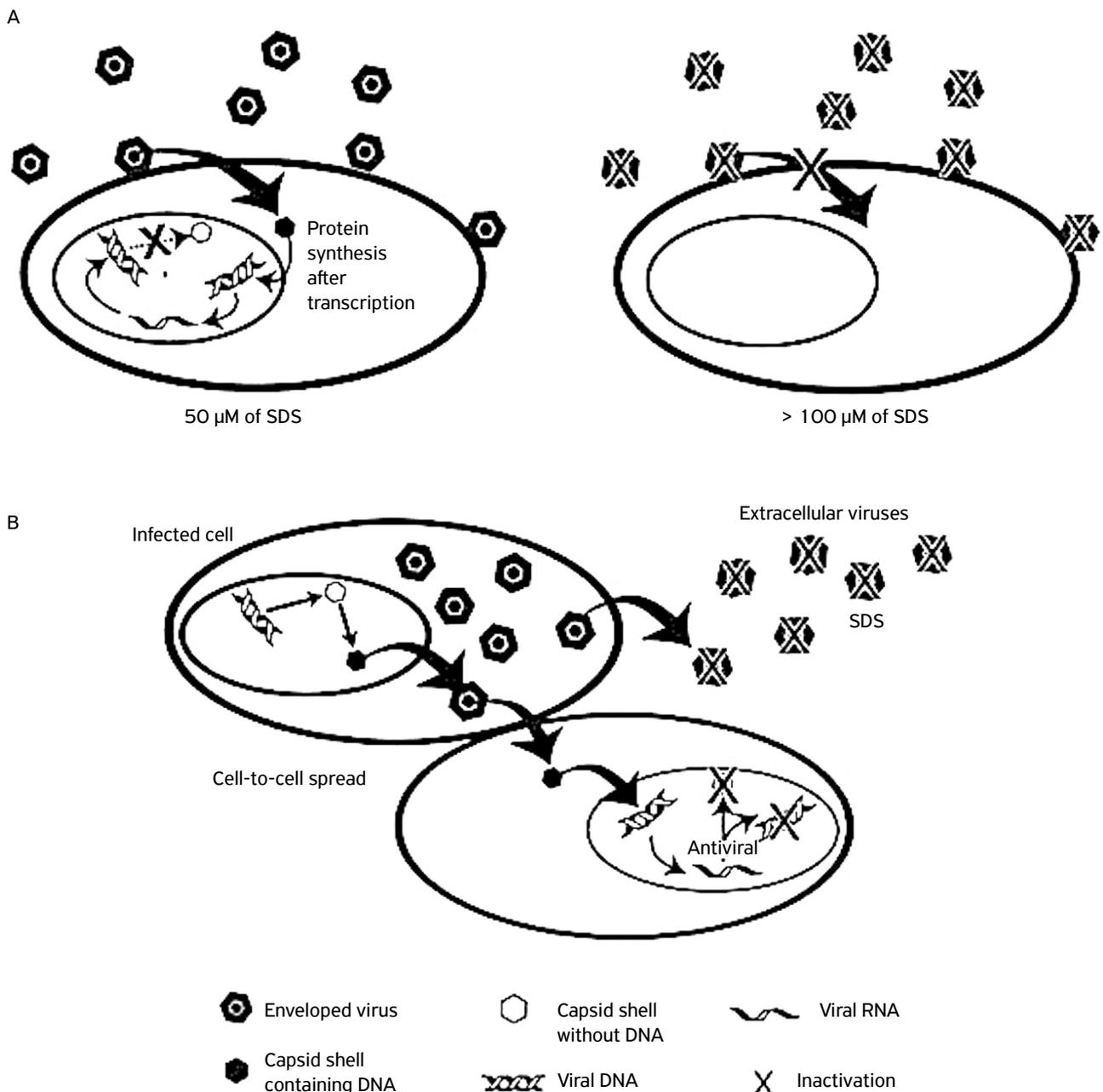
¹: average lethal concentration, ²: no adverse effects were observed.

completely inhibited, which suggests that the surfactant could interfere with the maturation of nucleocapsids and with encapsidation of nucleic acids (Fig. 2A). In contrast, viral activity in SDS concentrations higher than 100 μM caused a reduction of 65.1% in gD synthesis. In these conditions, envelope solubilization of most of the investigated viruses was observed and the remaining particles were not able to penetrate cells and continue with the natural replication process (Fig. 2B) (PIRET et al., 2000, 2002).

URDANETA et al. (2005) demonstrated that 0.1% SDS could effectively inactivate HIV-1 in milk and the proposed treatment concentrations were within the safe limits for SDS

ingestion in kids. These authors evaluated their samples in a rapid in vitro system (Multinuclear Activation of Galactosidase Indicator — MAGI) that quantifies viral infectivity after microbicide treatment. The results showed that SDS use for 10 minutes at 0.1 and 0.5% in HeLa cell culture was sufficient to totally inhibit viral infection caused by HIV-1 in maternal milk.

URDANETA et al. (2005) and HARTMANN et al. (2006) described SDS as an efficient microbicide in the treatment of human milk against HIV-1 with the following characteristics: efficiency in low doses, low toxicity level, broad-spectrum of microbicide activity, odorless and tasteless properties. Hence, it can be used to conserve nutritional and immune-related traits



Source: PIRET et al. (2002) with modifications.

Figure 2. Dose-dependent mechanism of action of sodium dodecyl sulfate against HSV-1.

of milk. Due to the broad-spectrum, SDS may also eliminate other pathogens from milk (secondary contaminant bacteria), which could potentially contaminate it during manipulation.

In goat production, MORALES-DE LA NUEZ et al. (2011) demonstrated that caprine colostrum treated with SDS at 1% reduced bacterial load at a rate similar to pasteurization. However, IgG destruction in SDS treated colostrum is significantly lower than pasteurized colostrum. In addition, goat kids fed with colostrum added 1% of SDS did not present pathological deficit or alterations in the transmission of passive immunity.

An *in vitro* study with SDS at 0.25, 0.5 and 1% in colostrum and milk performed by SOUSA (2016) revealed dose-dependent effects in caprine synovial membrane cell cultures (CSM). According to the SDS concentration in treatments (0.25 and 0.5%), a gradual reduction of cytopathic effects occurred (CPE). On the other hand, cells with signs of viral infection were not observed in colostrum treated with 1% SDS. In milk, the absence of CPE was more relevant, which was observed in concentrations of 0.5 and 1%. In addition, CLV particles were not identified in milk samples treated with 1% SDS and investigated with nested polymerase chain reaction (nPCR), which demonstrates antiviral activity against this pathogen.

The same author performed *in vivo* studies, in which goat kids were fed with colostrum and milk from CAE positive goat nannies and treated with SDS in the same concentrations used in the *in vitro* experiment. Hence, animals that received SDS in 0.25 and 0.5% presented positive results for the CLV in the early phases of monitoring. However, animals that received 1% SDS presented positive result only after 90 days of study. Probably, this dosage diminished the viral load and consequently delayed the infection but did not fully prevent it. Nonetheless, this concentration promoted gastrointestinal complications, such as profuse diarrhea.

GENERAL CHARACTERISTICS OF SMALL RUMINANT LENTIVIRUS INFECTIONS

Goat and sheep production are associated with traditional systems of subsistence and with economic factors, where animal production tends to be more intensive and demands more efficient production systems (GUILHERME et al., 2017). However, health management with late diagnoses of diverse diseases of different etiologies drastically interferes in the performance of these activities (AZEVEDO et al., 2017). Among the most relevant health problems are the infections caused by small ruminant lentiviruses (SRLVs). These pathogens are classified in two phylogenetic groups, the CAEV or caprine lentivirus (CLV), and the Maedi-Visna virus (MVV) or ovine lentivirus (OLV) (BLACKLAWS, 2012).

These diseases cause considerable losses in goat and sheep productions, which may compromise the profitability

of the animal farm (AZEVEDO et al., 2017). In addition, the main clinical signs of both infections include arthritis, encephalitis, mastitis and, less frequently, respiratory conditions. Furthermore, animals from all ages, sex and races are susceptible (FRANKE, 1998).

SRLV have several transmission pathways, such as the lactogenic route, either through contaminated milk or colostrum (PISONI et al., 2010). The reproductive transmission may occur through the presence of the virus in the semen of infected breeders (TRAVASSOS et al., 1999; ANDRIOLI et al., 2002, 2006; SOUZA, 2013). The horizontal route may occur in direct contact between animals through feces, saliva, urogenital and respiratory secretions (RADOSTITS et al., 2002; SOUZA et al., 2015). The vertical transmission may occur via transplacental passage (RODRIGUES et al., 2017).

LACTOGENIC TRANSMISSION OF SMALL RUMINANT LENTIVIRUSES

Mononuclear phagocyte system

Monocytes and macrophages play a key role in the regulation of the immune system, guiding innate and specific immune responses (FLORES, 2007). A monocyte circulates the bloodstream until it migrates to a tissue and matures into a macrophage (TIZARD, 2014).

These cells are present in tissues, blood, colostrum and milk, among other biological fluids, which are related to the main transmission pathways of SRLV (ZINK; JOHNSON, 1994). SRLV-free flocks usually get infected through contact with carrier animals short after introduction (PISONI et al., 2010).

Pathogeny of these lentivirus infections is directly related to cells of the mononuclear phagocyte system with a focus on differentiation and maturation of monocytes into macrophages, where the viral multiplication occurs (NARAYAN et al., 1983; GENDELMAN et al., 1986). However, when *in vivo*, macrophages are the most infected cells (NARAYAN; CLEMENTS, 1989; LUJÁN et al., 1994; BRODIE et al., 1995). Lymphocytes may also be targeted with a less efficient viral multiplication (ZINK; JOHNSON, 1994).

Milk and colostrum cells

Colostrum is characterized as a secretion from the mammary gland produced in the last weeks of pregnancy that holds essential nutrients for the nutrition and immunological development of the newborn (HERNÁNDEZ-CASTELLANO et al., 2014; SÁNCHEZ-MACÍAS et al., 2014; TIZARD, 2014). Milk is defined as a lacteous secretion practically free of colostrum. It is composed in general by 87% of water, carbohydrates, lipids, proteins, numerous mineral salts, lactose, urea,

lactic acid, creatinine, amino acids and water-soluble vitamins (SERTÃOBRAS, 1952; SÁNCHEZ-MACÍAS et al., 2014).

Somatic cells that compose milk and colostrum may originate from epithelium or the immune system. Epithelial cells are derived from natural peeling of the secretory epithelium of the mammary gland. Cells from the immune system, usually leukocytes (macrophages, lymphocytes and neutrophils), are those that migrate from the bloodstream to the alveoli (HERNÁNDEZ-CASTELLANO et al., 2014; SÁNCHEZ-MACÍAS et al., 2014; TIZARD, 2014).

Lactogenic transmission via

Lactogenic transmission is a natural model of infection that is more effective in lentiviruses. It plays a key role in SRLV biology, as in other lentiviruses, such as HIV and SIV. In fact, it is considered the main pathway of SRLV transmission in goats, since it guarantees the dissemination between generations and the persistence in flocks on a population level. Maternal leukocytes are absorbed by the intestine of newborns and enter their peripheral circulation. The great intestinal permeability in this phase favors the entry of the virus through the ingestion of contaminated colostrum (PISONI et al., 2010).

According to HERRMANN-HOESING et al. (2007), animals are exposed to infection after ingesting colostrum, either by free viruses or proviruses within monocytes/macrophages, which demonstrates efficient transmission between mother and offspring. Goat kids that are born from seronegative nannies and receive colostrum and/or milk from seropositive females soon become infected. Hence, a single ingestion of these fluids is sufficient to start the infection (RADOSTITS et al., 2002).

Furthermore, lactogenic transmission was also observed in interspecies contact as described by SOUZA et al. (2015). In this study, newborn lambs received colostrum from goat nannies positive for CAE and during the seven days of the experiment, seven out of nine (77.78%) of the group were positive for the virus in nPCR.

METHODS FOR BLOCKING THE LACTOGENIC TRANSMISSION

Several prophylactic measures for SRLV have been suggested in studies throughout the years (ROWE et al. 1992; PERETZ, et al., 1993; ALVES, 1999; NOGUEIRA et al., 2009). Among these, the control of the lactogenic pathway is critical due to its potential of transmission from breeders to their offspring (ROWE et al., 1992; PERETZ, et al., 1993; PISONI et al., 2010; RADOSTITS et al., 2002; SOUZA et al. 2015). The most used techniques by farmers are:

- **Use of artificial colostrum:** this is composed by 700 mL of bovine milk (healthy and specifically free of bovine viral diarrhea — BVD), 300 mL of blood serum from

negative goats or sheep, and one chicken egg (ALVES, 1999). The serum is obtained through blood collection without anticoagulant following centrifugation.

- **Use of bovine colostrum:** colostrum from cows is also recommended to feed goats and sheep. However, donors for this purpose must be healthy, especially concerning bovine leukosis to prevent interspecies transmission (PERETZ et al., 1993; NOGUEIRA et al., 2009).
- **Thermal treatment of colostrum and milk:** thermization procedure may be performed in colostrum, transition milk and common milk. For example, colostrum is collected in plastic bottles from females after delivering, which are sealed and heated at 56°C in water bath for one hour. Then, bottles are removed and cooled naturally to room temperature before being stocked at -15°C (PERETZ, et al., 1993; ANDRADE, 2008; NOGUEIRA et al., 2009).
- **Milk pasteurization:** milk may be conserved through pasteurization, which is a method that maintains organoleptic and nutritional characteristics and ensures destruction of pathogenic micro-organisms guaranteeing a healthy food (CHEFTEL et al., 1989; RIEDEL, 1996). There are two types of pasteurization, which are slow and fast. In slow pasteurization, milk is heated to 63 to 65°C for 30 minutes and cooled to 4°C. During the heating period, milk is moderately agitated to avoid adhesion to the walls of the bottle, to promote uniform heating of all particles and in the same time to avoid foam formation (PRATA, 2001; LEITE et al., 2006). Fast pasteurization of the High Temperature Short Time (HTST) method consists of heating the milk to 72 to 75°C for 15 to 20 seconds following immediate cooling to 5°C, which causes a thermal shock (LEITE et al., 2006).

However, these methods may be considered costly due to the need for trained laborers and equipment, such as water baths or thermizators, and centrifuges. Hence, the search for practical and low-cost alternatives that are efficient in blocking SRLV transmission in colostrum and milk are necessary for farmers to control the dissemination of these diseases in flocks.

CONCLUSION

This study demonstrated the antiviral potential of SDS in the prevention of sexually transmitted diseases and in SRLV prophylaxis. In addition, general aspects of the lactogenic transmission of CLV, advantages of SDS use as a viral inactivator in human research and promising results of its application as a chemical inactivator of CLV were presented. Although several studies have reported the antiviral activity of SDS, there is still a lack of data that can assess its effects on SRLV and the application as a control measure for the lactogenic transmission.

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