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REVIEW

# Bioactive compounds in sheep milk: The therapeutic potential of CLA, lactoferrin, and orotic acid in skin cancer treatment

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**ABSTRACT.** Melanoma, an aggressive form of skin cancer, poses a significant public health problem due to its rising global incidence. Therefore, there is a growing interest among patients in natural substances with potential therapeutic benefits. Sheep's milk, rich in bioactive substances such as conjugated linoleic acid (CLA), lactoferrin, and orotic acid, represents a promising candidate for adjunctive cancer therapy due to its unique biological properties. This review consolidates current knowledge on the health-promoting effects of selected bioactive substances from sheep's milk in the context of skin cancer supportive care. *In vitro*, *in vivo* and clinical studies have demonstrated that CLA isomers have anticancer activity, suppressing malignant melanoma development and progression. Lactoferrin is widely utilised in the cosmetic and pharmaceutical industries due to its antibacterial and skin repairing properties. Meanwhile, orotic acid shows potential as a breakthrough compound in skin cancer prevention and treatment through its combined anticancer and dermatoprotective effects. Considering the great anticancer potential of sheep's milk, further research is essential to fully elucidate their mechanisms and clinical applications.

## Introduction

According to the World Health Organization report, melanoma, a malignant transformation of melanocytes, ranks 17$^{th}$ out of 33 cancers in the list of most common cancer types (Roky et al., 2024). Skin cancers are broadly classified into two categories: melanoma and non-melanoma skin cancers, with the latter comprising basal cell carcinoma and squamous cell carcinoma (Rojas-Solé et al., 2024). The rising incidence of melanoma in recent years has become a pressing public health concern, primarily attributed to modern lifestyle factors and environmental changes, particularly increased ultraviolet radiation exposure (Rojas-Solé et al., 2024, Serman et al., 2022).

Surgery removal of the tumour remains the primary treatment for all stages of melanoma. Radiotherapy and chemotherapy may also be applied for palliative care or alternatives for inoperable cases. To improve treatment efficacy and reduce side effects, current research and clinical practice emphasise integrated approaches that combine conventional therapies with non-traditional methods and novel treatment strategies (Hanahan, 2022; Thapa et al., 2024). The global rise in skin cancer incidence has intensified demand for innovative solutions in both prevention and treatment, including advancements in medical devices.

Natural products serve as a crucial source of anticancer drugs, comprising approximately 50% of all pharmaceuticals and 48.6% of cancer therapeutics (Newman and Cragg, 2012; Mir et al., 2023; Asma et al., 2022). Alternatives to conventional drugs, including food-derived peptides, are being investigated to reduce the side effects of available therapies, such as chemotherapy and adjunct treatment (Ali Abdalla et al., 2022). This has led to increased consumer demand for natural health-promoting compounds (Flis and Molik, 2021; Flis et al., 2022). Sheep's milk, thanks to its rich profile of bioactive substances, represents a valuable functional food and potential therapeutic adjuvant for managing metabolic disorders and cancers, including melanoma (Mohapatra et al., 2019; Flis and Molik, 2021; Flis et al., 2022).

The unique biological properties of sheep's milk are attributed to its high content of bioactive substances such as conjugated linoleic acid (CLA), lactoferrin, or orotic acid, with proven beneficial health effects (Flis and Molik, 2021; Flis et al., 2022). These milk-derived bioactive substances show therapeutic potential for dermatological applications and cancer treatment (Flis et al., 2022, 2023). Dairy products are utilised in modern medical and cosmetic products due to its anti-inflammatory, immunomodulatory, antimicrobial, and skin barrier-enhancing properties, along with moisturising and regenerative capacities (Kazimierska and Kalinowska-Lis, 2021). Milk of small ruminants has been traditionally used for treating difficult wounds, bites, and purulent skin lesions (Sezik et al., 2001). At present, cosmetics containing sheep's or goat's milk are gaining wide popularity and consumer trust due to their moisturising, lubricating and non-toxic properties. Current research focuses on developing medical products containing small ruminant's milk, leveraging its anti-inflammatory, hydrolipid barrier-strengthening, antimicrobial, and immunomodulatory properties for treating various skin conditions (Kazimierska and Kalinowska-Lis, 2021).

Despite promising therapeutic potential, research on bioactive compounds in sheep's milks (CLA, lactoferrin, and orotic acid) for melanoma treatment remains limited, particularly in clinical settings. This review synthesises evidence for the therapeutic potential of key sheep's milk bioactive substances, including CLA, lactoferrin and orotic acid, in the context of skin cancer management.

## Clinical applications of CLA

Sheep's milk has the highest content of CLA, compared to milk of other ruminants, known for its significant role in inhibiting cancer cell growth (Table 1) (Flis and Molik, 2021; Flis et al., 2022). CLA refers to a group of isomers characterised by two conjugated double bonds in different geometrical (*cis* or *trans*) and positional positions (Gebereyowhans, 2024). These isomers are generated in the rumen as intermediates during the biohydrogenation of dietary linoleic acid to stearic acid (Salsinha et al., 2018). Additionally, *cis*-9, *trans*-11 CLA can be synthesised from vaccenic acid in mammalian tissue by delta-9 desaturase (Fukuda et al., 2006). To date, approximately 28 CLA isomers

**Table 1.** Health-promoting effects and content of selected bioactive substances in sheep's milk

| Bioactive substances | Health-promoting effect | Content in sheep's milk | Content in cow's milk |
|---|---|---|---|
| Conjugated linoleic acid (CLA) | anti-obesity, anti-diabetic, anti-cancer (Basak and Duttaroy, 2020);<br>skin cancer (Hwang et al., 2007; MacDonald, 2000) | 1.60 g/100 g (Claeys et al., 2014) | 1.10 g/100 g (Claeys et al., 2014) |
| Lactoferrin | anti-inflammatory (Kaplan et al., 2024);<br>antibacterial (Farnaud and Evans, 2003);<br>antiviral (Kaplan et al., 2024);<br>anti-inflammatory (Takayama and Aoki, 2012);<br>anti-cancer (Oginga et al., 2024; Tsuda et al., 2010);<br>colon cancer (Habib et al., 2013);<br>melanoma (Singh and Prasad, 2024) | 0.7–0.9 g/kg milk (Alichanidis et al., 2016) | 0.02–0.5 g/kg milk (Alichanidis et al., 20126 |
| Orotic acid | antiarthritic (Thakur, 2020);<br>circulatory system diseases (Czauderna et al., 2021);<br>anti-atherosclerotic (Kilari et al., 2021,<br>anti-diabetic (Fushimura et al., 2021);<br>anti-cancer (ovarian) (Marynowicz et al., 2023;)<br>anti-aging skin cells (Parfenyuk et al., 2024);<br>treatment of wounds, scars, atopic dermatitis, eczema, psoriasis (Park, 2010) | 200–400 mg/l (EFSA, 2009) | 20–100 mg/l (EFSA, 2009) |

have been identified, with *cis*-9, *trans*-11 CLA and *trans*-10 *cis*-12 CLA being the most prevalent, accounting for about 85% and 10% of all naturally occurring CLA isomers, respectively (den Hartigh, 2019). The main CLA isomers exhibit biological activity, including, anticancer, anti-obesity and antidiabetic effects (Basak and Duttaroy, 2020). The c9, t11-CLA isomer anticancer activity is based on apoptosis induction, while the t10, c12-CLA isomer inhibits cancer cell growth and triggers cell death (Basak and Duttaroy, 2020). *In vitro, in vivo* and clinical studies have confirmed the anticancer properties of CLA isomers, demonstrating its potential as an alternative or adjuvant therapy to mitigate side effects of conventional treatments (George and Ghosh, 2024). CLA isomers show efficacy against skin cancers, suppressing malignant melanoma proliferation in both animals and humans (Bhattacharya et al., 2006). *In vitro* studies have demonstrated CLA's cytotoxicity towards MCF-7 cells and human malignant melanoma cells, while animal models confirmed CLA inhibition of epidermal tumour development in mice (MacDonald, 2000). Further research by Hwang et al. (2007) demonstrated that topical administration of the c9, t11-CLA isomer inhibited skin tumorigenesis in hairless HR-1 mice. This isomer specifically inhibits TPA-induced NF-κB activation and subsequent COX-2 expression by blocking IKK and Akt signalling pathways in the skin (Hwang et al., 2007). Bergamo et al. (2013) suggested that combining the t10, c12 isomer with other specific active substances may be an effective strategy in melanoma therapy (Bergamo et al., 2013). Supporting these findings, Du et al. (2014) reported the antitumor activity of iRGD-modified liposomes containing CLA and paclitaxel (CLA-PTX) against B16-F10 melanoma in *in vitro* and *in vivo* experiments. Additionally, both c9, t11 and t10, c12 CLA isomers significantly reduced UVB-induced IL-8 secretion in human keratinocytes, indicating their photoprotective potential, which is particularly relevant in melanoma prevention (Storey et al., 2007).

## Potential lactoferrin applications

Lactoferrin is a multifunctional milk protein with diverse health benefits, which leads to its popularity in pharmaceutical and clinical applications. As an 80 kDa iron-binding glycoprotein, primarily synthesised by epithelial cells and neutrophil precursors, lactoferrin shows remarkable structural flexibility. This allows it to form various functional variants through post-transcriptional and post-translational modifications, enabling diverse biological functions *in vivo* (Zhang et al., 2024). Among ruminant milks, sheep's milk contains the highest concentration of lactoferrin (Table 1) (Flis and Molik, 2021; Flis et al., 2022; Singh and Prasad, 2024).

Milk lactoferrin stimulates immune cells to release cytotoxic agents and exerts antiangiogenic effects by restricting the blood supply to cancer cells, thereby reducing or inhibiting tumour growth (Habib et al., 2013; Cutone et al., 2020). Habib et al. (2013) demonstrated that milk lactoferrin reduced colon cancer growth by 56% while exhibiting antioxidant properties and preventing DNA damage. Its role in breast cancer development has been particularly well documented, with specific lactoferrin peptides shown to inhibit cancer cell proliferation, adhesion, and migration while inducing apoptosis, cell cycle arrest, and overexpression of apoptosis-related proteins (Zhang et al., 2024). Lactoferrin has attracted significant research interest due to its anti-inflammatory and anticancer properties, demonstrating considerable potential for clinical applications. However, further studies are needed to fully elucidate its mechanisms of action and potential interactions. The combination of lactoferrin with other milk components or therapeutic agents may offer improved treatment strategies (Habib et al., 2013). Recent research has indicated that lactoferrin-conjugated extracellular nanovesicles (LF-EVs) may serve as effective carriers for targeted delivery systems for melanoma therapy (Singh and Prasad, 2024). The latter authors have demonstrated that LF-EVs exhibit increased specificity for melanoma cells, as well as reduce off-target effects and improve drug release efficiency. Moreover, these LF-EVs interact with the tumour microenvironment, suppressing its progression and metastasis (Singh and Prasad, 2024). Lactoferrin has found applications in the cosmetic and pharmaceutical industries owing to its skin-whitening properties and capacity to repair inflammation-induced skin damage (Xie et al., 2024). Additionally, it helps strengthens the skin barrier and provides moisturising effects (Xie et al., 2024). As reported by Maru et al. (2014), inflammation plays a key role in skin carcinogenesis, particularly in melanoma initiation, progression, angiogenesis and metastasis. Chronic inflammation contributes to melanoma development through elevated production of proinflammatory mediators (Sethi et al., 2012). Studies by Takayama and Aoki (2012) demonstrated that lactoferrin can accelerate skin wound healing by modulating inflammatory responses – it strengthens initial inflammation and prevents excessive immune reactions (Takayama and Aoki, 2012). When applied to skin wounds, lactoferrin stimulates production of key inflammatory repair mediators, including IL-8, IL-6, macrophage inflammatory protein 1α (MIP-1α) and tumour necrosis factor α (TNF-α) (Takayama and Aoki, 2012).

The available literature highlights the potential of lactoferrin, present in the highest amounts in sheep's milk and its products, as a key component in strategies aimed at supporting the treatment of skin conditions and cancers, including melanoma. However, further research is needed to fully elucidate the mechanisms underlying the action of milk-derived lactoferrin in the context of skin cancer. The growing interest in natural medicinal products containing health-promoting bioactive compounds has created opportunities to develop advanced wound care materials incorporating these biologically active components, particularly for managing oncological and inflammatory skin conditions.

## Anti-cancer properties and potential applications of orotic acid

Orotic acid represents an important component of the non-protein nitrogen (NPN) fraction in mammalian milk and dairy products, with sheep's milk containing the highest concentration among ruminants (Table 1) (Bhattacharya et al., 2006; Löffler et al., 2015; Flis and Molik, 2021; Flis et al., 2022). This compound is gaining increasing popularity among researchers and consumers due to its numerous health benefits. Orotic acid is involved in regulating genes critical for the development of cells, tissues and organs (Löffler et al., 2015). Additionally, it participates in folate and vitamin $B_{12}$ metabolism while exhibiting detoxifying and anti-arthritic properties (Thakur et al., 2020). Research highlights an important role of orotic acid in the prevention of cardiovascular diseases by increasing heart contractility and reducing blood cholesterol levels (Czauderna et al., 2021). Its deficiency has been associated with serious health consequences, such as cell degeneration, premature aging, mental retardation, anaemia, reduced immunity, and dermatological disorders (Todorov et al., 2018; Czauderna et al., 2021).

Orotic acid has attracted significant attention in medical research and drug development due to its unique biochemical properties (Nath et al., 2013). This compound has been used as a valuable tool for investigating pyrimidine metabolism, monitor metabolic precursors, nucleotide pools, and RNA synthesis rates, differentiating *de novo* pathways, treating metabolic syndromes and exploring new anticancer therapies (Löffler et al., 2015). Its putative role in cancer prevention has been demonstrated through its ability to counteract carcinogenesis induced by oxidative stress (EFSA, 2009). Recent studies by Marynowicz et al. (2023) have demonstrated that orotic acid induces apoptosis in ovarian cancer granulosa cell by enhancing caspase-3/7 activity. Additionally, it has been shown to enhance mitochondrial function in healthy ovarian granulosa cells without triggering apoptosis, indicating selective action of this compound (Marynowicz et al., 2023). Certain metal complexes of orotic acid (e.g., with palladium, platinum, or tin) demonstrate significant therapeutic potential and are widely investigated as potent anticancer agents (Nath et al., 2013; Marynowicz et al., 2023). According to Marynowicz et al. (2023), orotic acid can be used as an adjuvant to improve cancer drug sensitisation in chemotherapy-resistant patients. *In vitro* screening studies in cancer cell lines, including MCF-7 (breast), HEK-293 (renal), PC-3 (prostate), HCT-15 (colon), and HepG2 (liver) (Nath et al., 2013; da Silva Gomes et al., 2022) have shown that metal orotates exert cytotoxic effects through apoptosis induction. Research by Maji et al. (2021) have demonstrated that platinum(IV) orotic acid complexes selectively target liver cancer cells, showing increased activity and higher uptake in Hep G2 cells.

Further, carboxamidotriazole orotate (CTO) has been reported to increase temozolomide sensitivity in melanoma models, potentially allowing the use of lower temozolomide doses in combination therapy while maintaining antitumor efficacy and minimising toxicity (Karmali et al., 2012). Due to its beneficial effects on the skin, orotic acid has also found applications in the cosmetic and pharmaceutical industries (Parfenyuk et al., 2024). It enhances metabolic processes in the skin, actively counteracting cellular aging (Parfenyuk et al., 2024). Moreover, orotic acid and its salts or derivatives, can be used to prevent or treat wounds, scars, atopic dermatitis, eczema or psoriasis (Park, 2010). Recent research (Kim et al., 2023) has indicated that orotic acid plays a key role in promoting a balanced distribution of beneficial microbial species in the skin environment. This finding coincides with rapid advancements in the development of natural bioactive-enriched hydrogel dressings. Orotic acid's unique combination of anticancer activity, skin-protective effects, and microbiome-regulating properties positions it as a promising candidate for innovative dermatological applications, particularly in skin cancer prevention and adjunctive therapy. Sheep's milk, as the richest natural source of orotic acid, may support the development of new formulations of bioactive dressings with improved pharmacological properties.

## Conclusions

Current evidence suggests that bioactive compounds in sheep's milk, including conjugated linoleic acid, lactoferrin and orotic acid, have therapeutic efficacy in supporting the treatment of certain types of cancer. It should be noted that sheep's milk is a natural food product and does not exert any toxic effects on the body and offers superior concentration of bioactive components compared to milk of other ruminants. However, existing studies specifically examining the effects of sheep's milks on skin cancer remain limited. For this reason, it is necessary to focus on future research directions, which should prioritise:

- long-term clinical trials to validate the anticancer efficacy of sheep milk bioactive substances;
- synergistic combinations with conventional therapies (e.g., chemotherapy) to improve treatment outcomes;
- innovative delivery systems, such as bioactive dressings, to optimise therapeutic effects;
- comparative analyses of sheep's milk and other types of milk to determine its advantages in skin cancer treatment.

In conclusion, while preliminary evidence is encouraging, further research, particularly clinical trials, is required to fully explore and confirm the therapeutic potential of sheep's milk in melanoma management.

## Conflict of interest

The Authors declare that there is no conflict of interests.

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