Journal of Dairy Research

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Supplementation with antioxidants and phenolic compounds in ruminant feeding and its effect on dairy products: a systematic review

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Invited Review

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Cite this article: Avila-Nava A, Medina-Vera I, Toledo-Alvarado H, Corona L and Márquez-Mota CC (2023). Supplementation with antioxidants and phenolic compounds in ruminant feeding and its effect on dairy products: a systematic review. *Journal of Dairy Research* **90**, 216–226. https://doi.org/10.1017/S0022029923000511

Received: 9 November 2022
Revised: 6 July 2023
Accepted: 10 July 2023
First published online: 1 September 2023

Keywords:
Bioactive compounds; dairy products; diet; milk; supplementation

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Abstract

Milk and dairy products have great importance in human nutrition related to the presence of different nutrients, including protein, fatty acid profile and bioactive compounds. Dietary supplementation with foods containing these types of compounds may influence the chemical composition of milk and dairy products and hence, potentially, the consumer. Our objective was to summarize the evidence of the effect of supplementation with antioxidants and phenolic compounds in the diets of dairy animals and their effects on milk and dairy products. We conducted a systematic search in the MEDLINE/PubMed database for studies published up until July 2022 that reported on supplementation with antioxidants and phenolic compounds in diets that included plants, herbs, seeds, grains and isolated bioactive compounds of dairy animals such as cows, sheep and goats and their effects on milk and dairy products. Of the 94 studies identified in the search, only 15 met the inclusion criteria and were analyzed. The review revealed that supplementation with false flax cake, sweet grass, *Acacia farnesiana*, mushroom myceliated grains and sweet grass promoted an effect on the milk lipid profile, whereas supplementation with dried grape pomace and tannin extract promoted an effect on the milk and cheese lipid profiles. In six studies, the addition of *Acacia farnesiana*, hesperidin or naringin, durum wheat bran, mushroom myceliated grains, dried grape pomace and olive leaves increased the antioxidant activity of milk. In conclusion, supplementation with bioactive compounds had a positive impact which ranged from an increase in antioxidant capacity to a decrease in oxidative biomarkers such as malondialdehyde.

Milk is the sole and primary source of nutrition for newborns, and it has been demonstrated to be important for children's growth and adult health (Zhang *et al*., 2021). The beneficial effects are related to the presence of different nutrients, including protein, fat, lactose, essential minerals including calcium and magnesium, fat-soluble vitamins (A, D, E, and K) and bioactive compounds (Gil and Ortega, 2019; Scholz-Ahrens *et al*., 2020). Among these bioactive compounds are polyphenols, peptides and polyunsaturated fatty acids (PUFA), which are related to improved health. For children and adults, the main sources of milk and dairy products are dairy cattle, buffaloes, goats and sheep (Ferro *et al*., 2017). However, the chemical composition and presence of different bioactive compounds in the milk of these species can fluctuate due to several factors, such as animal breed, stage of lactation, season, management and nutrition. Many strategies have been implemented to enhance dairy ruminant product quality, one of which is to focus on the influence of dietary supplementation.

The enrichment of ruminant diets with agro-industrial by-products (for example, citrus pulp, grape pomace and pulp, molasses and olive leaves) that are rich in bioactive compounds such as polyphenols has been demonstrated to improve the nutritional and chemical composition of milk and dairy products (Křížová *et al*., 2021). Dietary supplementation has an important role regarding the presence of antioxidants in milk and dairy products. For example, supplementation with citrus pulp (9–18%) increased the polyphenol and flavonoid concentrations in Holstein milk (Santos *et al*., 2014). The identification of these types of compounds is important because they are thought to have health benefits, such as lowering blood pressure, stopping Gram-negative pathogens like *Escherichia coli* and *Salmonella typhi* (Murakami *et al*., 2004) and having anti-inflammatory and antioxidant effects (Marcone *et al*., 2017).

Fatty acids also play a significant role in the nutritional value of ruminant products and can be influenced by the enrichment of ruminant diets. The type and quantity of fatty acids in milk are influenced by the animal's breed, lactation stage, husbandry and diet (Tzamaloukas *et al*., 2021). Ianni *et al*., 2019 found that adding grape pomace to the diet of Friesian cows increased the concentration of polyphenols and linoleic (C18:3n-3), vaccenic (C18:1 *trans* 11) and rumenic (C18:2 *cis* 9, *trans* 11) acids in the cheese. It is known that polyunsaturated fatty acid (PUFA) content in milk plays an important role in consumer health (Chilliard and Ferlay, 2004). Thus, this review aimed to summarize evidence of the effects of dietary supplementation with antioxidants and phenolic compounds on the milk and dairy products of the main dairy animals.

Materials and methods

The present study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Page *et al.*, 2021). The study design required neither Institutional Review Board approval nor patient informed consent.

Search strategy

Two authors (AAN and IMV) performed the search strategy independently. The studies were identified through the online source MEDLINE/PubMed. The search was conducted for articles published until July 2022. We applied the description of the population, intervention, control and outcomes (PICO) strategy as described by Methley *et al.* (2014), where the population was dairy ruminants, the interventions were bioactive compounds and antioxidants in diets, a standard ruminant diet was the control and the outcomes were the fatty acid profile, bioactive compounds and antioxidant levels in the milk and dairy products of the population (online Supplementary Table S1).

Potential articles were searched using keywords by constructing blocks of descriptors in English. The Boolean operators AND (to add at least one word from each group) and OR (to list at least one word from each block), parentheses (to combine search terms by outcome categories) and quotation marks (to search for exact terms or expressions) were used. The groups of descriptors for the search strategy related to the outcome in dairy products were Ruminants AND bioactive compound AND dairy products NOT a review, Ruminants AND bioactive compound supplementation AND dairy product.

Selection of studies

After removing duplicates, the same authors (AAN and IMV) independently screened the titles and abstracts for eligibility evaluation based on the inclusion criteria. The title and abstract candidates to enter the review were evaluated in accordance with their eligibility criteria by all authors. Finally, data extraction of the full texts was carried out. Original studies were included if they met the following criteria:

(1) performed on ruminants (for this review, the search only focused on dairy goats, cows and sheep)
(2) reporting dietary interventions that included bioactive compounds and antioxidants in the diet of ruminants
(3) a design with a standard diet as a comparator
(4) reporting change or concentration of the fatty acid profile, bioactive compounds and antioxidants in milk and dairy products of the ruminants.

Exclusion criteria were:

(1) in vitro studies
(2) characterization of antioxidant concentrations in milk and dairy products without intervention studies
(3) studies where the intervention was focused on comparing feeding by different types of grazing and did not supplement.

Data extraction

Data extraction for all selected articles was performed independently by all authors. This information included the ruminant species, the bioactive compound(s), the description of the intervention, the comparator, the follow-up time, the type of product studied, the main findings about dairy products and finally the first author's name and year of publication. The process of identification and extraction is given at online Supplementary Fig. S1 and the complete list of references is at online Supplementary Table S2.

Results

According to the search, 94 articles were identified, and when duplicates were excluded 81 records were evaluated with title and abstract. In accordance with the eligibility criteria 66 articles were excluded (online Supplementary Table S2). The principal reasons to exclude articles by title and abstract were: no-intervention ($n = 17$), no-intervention in ruminants ($n = 14$), food characterization study ($n = 12$), *in vitro* study ($n = 8$), intervention different from the stated objective ($n = 6$), study of supplementation food or food creation ($n = 5$), review study ($n = 2$) and interventions that did not involve bioactive compounds ($n = 2$). Finally, 15 articles were included in the review (online Supplementary Fig. S1).

Animal models, study designs and dairy products

The studies included in the analysis showed a range of publications from 2014 to 2022 (Table 1). Animal models included were sheep (2 papers), cows (9 papers) and goats (4 papers). Some studies also reported the progeny of the animals such as primiparous (Safari *et al.*, 2018; Li *et al.*, 2021) and multiparous (Hausmann *et al.*, 2018; Safari *et al.*, 2018; Li *et al.*, 2021; Wang *et al.*, 2021) and included the period of lactation (Ianni *et al.*, 2019, 2021; Bonanno *et al.*, 2019b; Mapato *et al.*, 2021; Menci *et al.*, 2021) or specified mid-lactation (Scuderi *et al.*, 2019; Simitzis *et al.*, 2019). Design of the studies included randomized (Cais-Sokolińska *et al.*, 2015; Hausmann *et al.*, 2018; Safari *et al.*, 2018; Ianni *et al.*, 2019; Bonanno *et al.*, 2019a; Walkenhorst *et al.*, 2020; Li *et al.*, 2021; Wang *et al.*, 2021), stratified (Scuderi *et al.*, 2019; Walkenhorst *et al.*, 2020), allocated (Delgadillo-Puga *et al.*, 2019; Simitzis *et al.*, 2019) and 4×4 Latin square design with a 2×2 factorial arrangement (Mapato *et al.*, 2021). Dairy products evaluated in different studies included kefir (Cais-Sokolińska *et al.*, 2015), milk (all other papers) and, additionally, cheese (Ianni *et al.*, 2019; Bonanno *et al.*, 2019a, 2019b; Menci *et al.*, 2021).

Types of supplementation

Interventions with plants, herbs, seeds, grains and isolated bioactive compounds were used in the studies. Among the plants included in the interventions were *Acacia farnesiana* (Delgadillo-Puga *et al.*, 2019), bamboo grass (Mapato *et al.*, 2021), olive leaves (Ianni *et al.*, 2021), herbal feed additives

https://doi.org/10.1017/S0022029923000511 Published online by Cambridge University Press

Table 1. Bioactive compounds and nutritional interventions used in dairy cattle and its effect on milk and dairy products

Ruminant specie (P)	Bioactive compounds	Intervention (I)	Comparator (C)	Follow-up time	Type of product studied	Main findings (O)	Article
Holstein dairy cows (*n* = 36)	Pomegranate seeds (PS) Total phenolic compounds (1.61 *g*/kg) and Total tannins (1.31 *g*/kg) Pomegranate seed pulp and peels (PSP) Total phenolic compounds (25.5 *g*/kg) and Total tannins (21.9 *g*/kg)	Diet supplemented with PS (400 *g*/cow/d) Diet supplemented with PSP (400 *g* of seeds/cow per day + 1200 *g* of peels/cow/d)	Control diet no pomegranate by-products (CON)	From 25 d before the expected calving date to 25 d postpartum	Milk	In PS and PSP Yield (kg/d): ↑ 3.5% FCM ↑ ECM ↑ Fat There were no changes in milk composition. ↓ lipid oxidation ↓peroxidation	Safari *et al.* (2018)
Holstein dairy cows (*n* = 140)	Plant bioactive lipid compounds + biotin (PBLC + B) Timol, eugenol, limonene and vainilln	Diet supplemented with PBLC + B (2 *g*/d and 40 mg/d) Diet supplemented with monensin. (MON)	Non-supplemented control diet (CON)	*Phase1:* d-21 to d-1 prepartum *Phase 2:* d1-37 d postpartum Phase *3:* d38 to d58 postpartum	Milk	There was not difference in milk yield in PBLC and MON in d 21 and 37 after calving. On d 21 there was no difference in fat in PBLC and MON ↑ (trend) on milk protein in PBLC *vs.* MON On d 37 ↑ fat in PBLC + B vs. MON ↑ (trend) in ECM in PBLC *vs.* MON Phase 2 ↑ ECM in PLBLC + B *vs.* MON and CON Phase 3 ↑ ECM in PLBLC + B and MON *vs.* CON	Hausmann *et al.* (2018)
Holstein dairy cows (*n* = 14)	*Perilla frutescens* leaf (PFL) Clareolide (13.1%), betaine (8.26%), sucrose (7.48%), scutellarin (6.15%) and apigenin (5.24%)	Total mixed ration diet with dietary PFL at 300 *g*/d per cow	Total mixed ration diet (CON)	1-week adaptation and 8-week sampling period	Milk	PFL *vs.* CON ↑ oleanolic acid, DG (18:0/20:4 (5Z,8Z,11Z,14Z)/0:0), PE-NMe(18:1 (9Z)/18:1(9Z)), thymidine, thymine, 6-phospho-D-gluconate, 2-ketobutyric acid, 2-phenylacetamide, 1-phenylethylamine, N-acetyl-D-Glucosamine 6-Phosphate, 3- methyluridine, azelaic acid, deoxythymidine 5′ -phosphate, D-ribulose 1,5-bisphosphate, stearic acid, and palmitic acid ↓ LysoPC (18:1(9Z)), ononin, glyceric acid, acetylcholine, D-glucono-1,5-lactone, ribitol, 2-hydroxycaprylic acid, Leu-Ala, daidzin, and 3-methylhistidine	Wang *et al.* (2021)

Dairy sheep, Chio breed ($n = 36$)	Hesperidin Naringin α-tocopheryl acetate	H: Alfalfa hay and concentrate supplemented with Hesperidin (6000 mg/kg) Alfalfa hay and concentrate supplemented with Naringin (N) (6000 mg/kg) Alfalfa hay and concentrate supplemented with α-tocopheryl acetate (VE) (200 mg/kg)	Alfalfa hay and concentrate (CON)	1-week adaptation 4-week treatment	Milk	H, N and VE *vs.* C There was not difference in milk yield (mL) There was not difference in milk fat (%) There was not difference in milk protein (%) ↓ MDA ↑ Oxidative stability after 14d with H and N *vs.* VE and C	Simitzis *et al.* (2019)
Dairy goats, Polish White Improved ($n = 66$)	*Camelina sativa* cake Tocopherols (CS) (700 mg/kg)	Concentrate supplemented with CS (120 *g*/d)	Concentrate without supplementation (CON)	During lactation	Kefir	CS *vs.* CON ↑ proportion of PUFA in CS ↑ CLA ↑ n-3 fatty acids	Cais-Sokolińska *et al.* (2015)
Italian Red Pied dairy cows ($n = 36$)	Durum wheat bran at 0% (DWB0), 10%(DWB10) and 20% (DWB20) Ferulic acid	Total mixed ratio supplemented with DWB10 (1.5 kg/d per cow) Total mixed ratio supplemented with DWB20 (3 kg/d per cow)	Total mixed ratio without DWB0	100 d of lactation	Milk and cheese	DWB10 and DWB20 did not modify milk yield. DWB20 *vs.* DWB10 and DWB0 ↑ casein and curd firmness ↑ polyphenol content in chesses ↑ antioxidant capacity in cheeses ↓ peroxidation in cheeses	Bonanno *et al.* (2019a)
Dairy sheep, Valle del Belice ($n = 21$)	Mushroom myceliated grains at different percentages 0% (MMG0), 10% (MMG10) and 20% (MMG20) Total phenolic compounds (0.84 *g* GAE/kg DM)	Sulla hay and concentrate supplemented with MMG10 Sulla hay and concentrate supplemented with MMG20	Sulla hay and concentrate with MMG0	8 weeks	Milk and cheese	MMG20 *vs.* MMG10 and MMG0 ↑ milk casein content ↑ Trolox equivalent antioxidant capacity in cheese	Bonanno *et al.* (2019b)
Dairy goats, French Alpine ($n = 50$)	*Acacia farnesiana* (AF) Quercetin, gallic acid, catechin and epicatechin	Conventional diet + 10% of AF pods (AF10) Conventional diet + 20% AF (AF20) Conventional diet + 30% AF (AF30)	Grazing (G) without supplementation Conventional diet without AF (CD)	Lactation period of 150 d	Milk	AF20 and AF30 *vs.* AF10 and C ↑ antioxidant activity ↑ Polyphenols ↓ cholesterol content	Delgadillo-Puga *et al.* (2019)
Dairy goats ($n = 24$)	Fumaric acid (FUM) N-[2-(nitrooxy) ethyl]-3-pyridinecarboxamide (NPD)	Basal diet supplemented with FUM (34 *g*/d) Basal diet supplemented with NDP (0.5 *g*/d) Basal diet supplemented with both FUM (34 *g*/d) and NPD (0.5 *g*/d)	Basal diet without any additives (CON)	12 weeks	Milk	NPD ↑ Daily milk production ↑ (trend) fat corrected milk ↑ T-AOC ↑ SOD FUM ↓ Milk fat content ↓ (trend) daily far yield ↓ MDA ↑ T-AOC	Li *et al.* (2021)

(*Continued*)

Table 1. (*Continued.*)

Ruminant specie (P)	Bioactive compounds	Intervention (I)	Comparator (C)	Follow-up time	Type of product studied	Main findings (O)	Article
Dairy cows (*n* = 14)	Tannins (TAN)	Diet supplemented with TAN (150 *g* / head/d)	Diet without TAN supplementation (CON)	23 d	Milk and cheese	TAN *vs.* CON There was no difference in milk yield, milk fat. or milk protein (g/kg) There was no difference in cheese yield (g /100 *g*)	Menci *et al.* (2021)
Dairy cows (*n* = 4)	Bamboo grass (BP) Condensed Tannins (3.2 *g* / 100 *g* MS)	Rice straw (RS) and concentrate supplemented with BP (150 *g*/d) Sweet straw and concentrate supplemented with BP (150 *g*/d) (SG-150BP)	and concentrate supplemented without BP (RS-0BP) Sweet straw and concentrate supplemented without BP (SG-0BP)	14 d adaptation and 7 d sampling period	Milk	SG-150BP and SG-0BP *vs.* RS-150BP and RS-0BP ↑ Milk yield (kg/day) ↑ 3.5% FCM (kg/ day) ↑ UFA, MUFA and PUFA (g/100 *g* FA) SG-150BP *vs.* SG-0BP, RS-150BP and RS-0BP ↑ Fat (%) ↑ Protein (%) RS-150BP and RS-0BP *vs.* SG-150BP and SG-0BP ↑ MCFA (g/100 *g* FA)	Mapato *et al.* (2021)
Dairy goats, Saanen (*n* = 30)	Olive leaves (OL) Oleuropeosides, flavones, caffeic acid, tyrosol, and hydroxytyrosol	Polyphite hay and concentrate supplemented with 10% OL (EG)	Polyphite hay and concentrate without OL (CG)	30 d	Milk	EG *vs.* CG ↑ Total phenolic compounds ↑ Antioxidant activity ↑ Apigenin ↑ Kaempferol ↑ Luteolin ↑ Rutin	Ianni *et al.* (2021)
Friesian dairy cows (*n* = 18)	Grape pomace (GP) Phenolic acids, flavonoids, tannins and proanthocyanidins	Maize silage, alfalfa hay and concentrate supplemented with 5.1% of grape pomace. (GP +)	Maize silage, alfalfa hay and concentrate supplemented without grape pomace. (GP-)	60 d	Milk, cheese	GP + vs GP- ↑ linoleic, vaccenic, and rumenic acids in milk and cheese ↑ Antioxidant activity ↑ Total phenolic compounds	Ianni *et al.* (2019)
Dairy cows (*n* = 10)	Grape marc (GPM) Condensed tannins	Grass silage, corn silage and concentrate supplemented with GPM (1.5 kg dry matter/cow/d)	Grass silage, corn silage and concentrate supplemented without) (CON)	14 d adaptation and 7 d sampling period	Milk	GPM *vs.* CON There was no difference in milk yield or milk composition.	Scuderi *et al.* (2019)
Dairy cows (*n* = 81)	Multicomponent herbal feed additive (HFA) Phenolic acids and tannins	Diet supplemented with two multicomponent HFA (50 *g*/d) (HFA-50) Diet supplemented with two multicomponent HFA (100 *g*/d) (HFA-100)	Placebo (PL)	21 December 2012 to 22 July 2013	Milk	HFA-50 and HFA-100 *vs.* PL There was no difference in milk yield or major components. HFA-100 ↓ Milk Urea, ↓Milk acetone	Walkenhorst *et al.* (2020)

Abbreviations: d, days; FCM, Fat-corrected milk; ECM, Energy-corrected milk; PUFA, polyunsaturated fatty acids; CLA, conjugated linoleic acid; CON, Control.

(Walkenhorst *et al.*, 2020) and *Perilla frutescens* leaf (Wang *et al.*, 2021). Other studies included seeds such as false flax cake (Cais-Sokolińska *et al.*, 2015) and pomegranate seeds (Safari *et al.*, 2018). There were studies whose interventions were based on food components like durum wheat bran (Bonanno *et al.*, 2019b), grape pomace or marc (Ianni *et al.*, 2019; Scuderi *et al.*, 2019) and mushroom myceliated grains (Bonanno *et al.*, 2019a). Intervention with isolated bioactive compounds included plant bioactive lipid compounds plus biotin and monensin (Hausmann *et al.*, 2018), hesperidin or naringin or α-tocopheryl acetate (Simitzis *et al.*, 2019), tannin extract (Menci *et al.*, 2021), and finally N-[2-(nitrooxy) ethyl]-3-pyridinecarboxamide combined with fumaric acid (Li *et al.*, 2021). The main beneficial effects of the dairy interventions are summarized in Table 1.

Effects of supplementation on fatty acids profile of dairy products

Six studies investigated the impact of dietary intervention on the fat content of milk. Supplementation with plant bioactive lipid compounds and biotin (PBLC + B: Hausmann *et al.*, 2018), fumaric acid (FUM: Li *et al.*, 2021), rice straw and sweet grass (Mapato *et al.*, 2021) all promoted an increase in milk fat concentration. It has been reported that cattle diets have an important role in properties such as milk fat composition (Chen *et al.*, 2017), particularly grass feeding and grazing, which promote higher levels of PUFA in comparison with concentrate (Mohan *et al.*, 2021).

Due to its high phytochemical content, pomegranate has been widely studied for its health properties, and several products aimed at human health have been developed, causing an increase in agro-industrial residues (Varma *et al.*, 2018). Pomegranate peel extract and pomegranate pulp improve in vitro dry matter digestibility and volatile fatty acid production (Jami *et al.*, 2012; Shaani *et al.*, 2016). Thus, the use of pomegranate residues in ruminant feed might have an important role in milk production. However, interventions with pomegranate seeds or pomegranate seed pulp did not show differences in milk fat (Safari *et al.*, 2018).

There were seven instances of lipid profile being altered by supplementation. False flax cake increased the content of PUFA (by 1.5 times) and n-3 fatty acid levels (by 1.7 times) compared to the control group (Cais-Sokolińska *et al.*, 2015). Intervention with sweet grass increased the concentration of monounsaturated fatty acids (MUFA) and PUFA by modest but significant amounts compared with rice straw (Mapato *et al.*, 2021). It is important to increase the content of PUFA in dairy products because it has been established that PUFA, among other health benefits, regulates the inflammatory response (Bentsen, 2017). During this process, immune cells produce inflammatory mediators such as tumor necrosis factor-alpha, interleukin (IL)-1beta, IL-6, IL-12, interferon gamma, and IL-8. These mediators activate pro-inflammatory signaling cascades, including the nuclear factor-kB (NF-kB) signaling pathway, the Janus kinase/signal transducer and activator of transcription signaling pathway and the mitogen-activated protein kinase signaling pathway (Kahkhaie *et al.*, 2019). It has been demonstrated that PUFA, specifically n-3 PUFA, inhibits the synthesis of IL-1, IL-2, and IL-6 and the NF-kB signaling pathway (Oppedisano *et al.*, 2020). Thus, the increase in PUFA concentration observed in the evaluated supplementations indicates that it is possible to enhance the nutritional value of milk and, therefore, might improve the consumer health. It must be cautioned that there is no direct evidence for this, nevertheless, it is an exciting prospect.

Among the PUFA compounds that showed the most change through interventions were linolenic acid, linoleic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Intervention with *Acacia farnesiana* at 30% significantly increased the concentration in milk of linoleic acid and DHA compared with control (Delgadillo-Puga *et al.*, 2019). Similarly, dietary supplementation with dried grape pomace promoted an increase in the percentage of linoleic acid and linolenic acid (Ianni *et al.*, 2019). One of these studies showed that EPA was only detected in the milk of groups fed mushroom myceliated grains (MMG), but this intervention did not show an effect on other PUFA such as linoleic (C18:2 n-6), rumenic (CLA, C18:2 c9 t11), α-linolenic (C18:3 n-3) and arachidonic (C20:4 n-6) acids (Bonanno *et al.*, 2019b). Also, sweet grass increased the proportion of C18:1 *cis*-9, C18:2, C18:2 *cis*-9, *trans*-11 and C18:3 (Mapato *et al.*, 2021). PUFA have an important role as active dietary compounds, particularly CLA has shown different beneficial effects, such as antihypertensive and anti-carcinogenic activities (Koba and Yanagita, 2014). In this aspect, when compared to women who consumed 1 serving/d, those who consumed >4 servings of high-fat dairy foods and CLA per day (including whole milk, full-fat cultured milk, cheese, cream, sour cream and butter) had a tendency to decrease the incidence of colorectal cancer (rate ratio = 0.59 [95% CI: 0.44, 0.79; P for trend = 0.002]), and the increment of 2 servings of high-fat dairy foods/d decreased by 13% risk of colorectal cancer (multivariate rate ratio: 0.87, 95% CI: 0.78, 0.96). Thus, consuming high-fat dairy products rich in CLA may lower the risk of developing colorectal cancer (Larsson *et al.*, 2005). Once again, a caveat is needed since these effects are small and have not been confirmed in bigger studies.

A further note of caution is needed. Supplementation not only showed an effect on these potentially beneficial fatty acids but also promoted an effect on saturated fatty acids. Supplementation with MMG increased the amounts of saturated fatty acids (80.3 vs. 77.94*g*/100 *g* of fatty acid, $P < 0.01$: Bonanno *et al.*, 2019a). For several years, the consumption of saturated fatty acids was associated with the prevalence of cardiovascular disease (Siri-Tarino *et al.*, 2010) and metabolic diseases such as metabolic syndrome and type 2 diabetes (Warensjö *et al.*, 2005), however, recent evidence indicates that there is a clear difference between dietary and circulating saturated fatty acids, and multiple studies indicate that there is no association between the consumption of saturated fatty acids and the risk of chronic disease (Astrup *et al.*, 2020). It is important to note that milk and dairy products are food matrix foods rich in saturated fatty acids and beneficial compounds such as PUFA, and their consumption should not be associated with an increase in cardiovascular and metabolic risk.

Four studies showed the effect of the intervention on the fat composition of cheese. Supplementation with grape pomace resulted in a significant increase in the concentration of oleic acid, linoleic acid and rumenic acid (all $P < 0.01$) compared with the control group (Ianni *et al.*, 2019) and intervention with tannin extract during the dry season increased the concentration of conjugated linoleic acid (Menci *et al.*, 2021). However, durum wheat bran and MGG supplementation did not modify the chemical composition of the cheeses (Bonanno *et al.*, 2019a, 2019b) despite the latter's effect on milk composition.

Identification of bioactive compounds in dairy products altered by supplementation

One of the most important aspects of interventions with bioactive compounds in the feeding of dairy animals is that these compounds need to be bioavailable in the products obtained. Among the studies included, five reported the presence of bioactive compounds in milk (Delgadillo-Puga *et al*., 2019; Ianni *et al*., 2019, 2021; Bonanno *et al*., 2019a, 2019b) and three in the composition of cheese (Ianni *et al*., 2019; Bonanno *et al*., 2019a, 2019b). The inclusion of *Acacia farnesiana* at 20 and 30% in the diet of goats significantly increased the total phenolic content in the milk and bioactive compounds such as gallic, chlorogenic, ferulic acids and catechin were only detected in milk from supplemented goats (Delgadillo-Puga *et al*., 2019). The same group tested the impact of consuming goat milk supplemented with 30% *Acacia farnesiana* in conjunction with a high-fat diet to assess metabolic alterations in a mouse model, and decreased body weight and body fat mass, improved glucose tolerance, and prevention of hypertrophy of adipose tissue and hepatic steatosis. The effect of supplementation on body weight and body fat mass could be explained because a higher energy expenditure was documented, evidenced by a higher oxygen consumption in indirect calorimetry. Additionally, it has been documented that a lower amount of lipids in brown adipose tissue is related to an increased abundance of uncoupling protein 1. The effects demonstrated in this study might indicate that the consumption of goat's milk supplemented with *Acacia farnesiana* would be a dietary strategy to improve the metabolic alterations induced by the high-fat diet. However, human studies are required before any definitive conclusions can be drawn. According to the body surface area normalization method (FDA, 2005), the mouse dosage would equate to an equivalent daily human intake of 1.4–2.8 cups (250 ml per cup/d) of fresh goat's milk for a 60 kg adult, so this dose could be the reference to show its effectiveness in clinical studies.

Supplementation with grape pomace caused an increase in the total phenolic compounds in milk in comparison with the non-supplemented group (Ianni *et al*., 2019). Grape pomace is a product with prebiotic activity because it contains up to 75% dietary fiber (Yu and Ahmedna, 2013), however, the prebiotic effect in addition to the fiber could be given by the phenolic compounds, as they also have a significant effect on the composition and activity of the intestinal microbiota by stimulating or inhibiting specific bacterial groups (Seo *et al*., 2017). Phenolic compounds are poorly absorbed in the small intestine and do, therefore, reach the colon, where they are metabolized by the resident microbiota into biologically active metabolites (Ozdal *et al*., 2016). This results in the appearance of a wide range of phenolic metabolites (phenylacetic acids, phenylpropionic acids, valeric acids, cinnamic acids, benzoic acids, and phenols, among others: Mena *et al.*, 2019). Grape derivatives, such as phenolic compounds, can promote the growth of probiotic bacteria, including *Bifidobacterium teenageris*, *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, and *Lactobacillus rhamnosus* (Parkar *et al*., 2008; Gwiazdowska *et al*., 2015). This modulation in the intestinal microbiota has a positive effect on the health of the host because experimental studies have shown effects in decreasing weight, waist circumference and fat mass and also in decreasing insulin resistance after probiotic treatments, mainly *Lactobacillus* and *Bifidobacterium* (Ejtahed *et al*., 2019).

Unfortunately, phenolic compounds are not particularly stable in refrigerated milk. Dairy products that were enriched with polyphenolic compounds showed a decrease in the phenolic content after 28 d of refrigerated storage, which was attributed to their oxidation (Deolindo *et al*., 2019). One option to prevent oxidation would be the encapsulation of polyphenols, since encapsulation can protect the bioactive compounds from oxidation. However, encapsulation is more favorable for the enrichment of the dairy product than for the interventions to the diets of the ruminants.

Olive leaf supplementation is another intervention that significantly increases the concentration of phenolic compounds in milk. The main compounds detected in this milk were cinnamic acid, chlorogenic acid and tyrosol (Ianni *et al*., 2021). An interesting finding in the profile of bioactive compounds in milk was the content of chlorogenic acids (CGAs), since these are among the most common bioactive compounds in plant foods such as coffee, apples, tea and berries, as well as in beverages such as wine (Zanotti *et al*., 2015). These compounds are esters that are made when quinic acid and *trans*-cinnamic acids join together. They are usually partially absorbed in the small intestine and partially absorbed in the large intestine after being broken down by bacteria (Olthof *et al*., 2001, 2003). The concentration of CGAs in milk is relevant because, according to the literature, their consumption could have an important impact on the improvement of glucose and lipid metabolism. Various mechanisms have been proposed, including that they are involved in the inhibition of α-amylase, an enzyme responsible for the decomposition of starch present in saliva that inhibits the absorption of sugar from diet (Narita and Inouye, 2009). In addition, they could modulate gastrointestinal peptides such as gastric inhibitory polypeptide and glucagon-like peptide 1 (Johnston *et al*., 2003) as well as stimulating glucose transporter 4, thereby increasing glucose uptake by peripheral tissues (Song *et al*., 2014). All these mechanisms result in a significant reduction in blood glucose levels (Van Dam, 2006). On the other hand, for lipid metabolism it has been shown that CGAs could down-regulate sterol regulatory element-binding protein 1C (Murase *et al*., 2011) which is the main genetic switch that controls lipogenesis. Both CGA and caffeic acid stimulate the peroxisome expression of nuclear transcription receptor proliferator-activated receptor alpha in obese mice induced by a high-fat diet. This receptor, when activated, acts as a sensor of lipids, and regulates lipid metabolism. The liver is its main target tissue, and its key genes are enzymes involved in the β-oxidation of fatty acids (Cho *et al*., 2010). Although highly speculative, all of this together may result in improvements in lipid metabolism. However, not all supplementations have positive effects. Intervention with durum wheat bran (20%) only showed a tendency in phenolic compounds in milk with respect to the control group (Bonanno *et al*., 2019b), and none of the cheese studies yielded positive changes on total phenolic compounds.

Antioxidant compounds in dairy products affected by supplementation

An outcome of interest from supplementation is the antioxidant effect generated by dairy products. Of the fifteen selected studies, six of these reported an antioxidant effect in milk after the intervention of *Acacia farnesiana* (Delgadillo-Puga *et al*., 2019), hesperidin or naringin (Simitzis *et al*., 2019), durum wheat bran (Bonanno *et al*., 2019b), MMG (Bonanno *et al*., 2019a), grape pomace (Ianni *et al*., 2019), and olive leaves (Ianni *et al*., 2021).

https://doi.org/10.1017/S0022029923000511 Published online by Cambridge University Press

Intervention with *Acacia farnesiana* at different concentrations significantly increased antioxidant activity determined both by oxygen radical absorbance capacity assay and ferric reducing antioxidant power assay compared with conventional diet (Delgadillo-Puga *et al*., 2019). Similarly, supplementation with MMG at 20% showed a significant increase in total equivalent antioxidant capacity with respect to the control without interventions (Bonanno *et al*., 2019a), antioxidant activity in milk from animals that were fed grape pomace (Ianni *et al*., 2019) or olive leaf (Ianni *et al*., 2021) increased significantly compared with the control groups and 14 d of hesperidin, naringin or α-tocopheryl acetate dietary supplementation achieved the same effect (Simitzis *et al*., 2019).

The role of antioxidants is relevant because they can contribute to the reduction of reactive oxygen species (ROS). Where there is an abundance of ROS and a deficiency of antioxidants, oxidative stress is generated, which in turn causes oxidative damage to biomolecules such as DNA, proteins and lipids (Aranda-Rivera *et al*., 2022). Since lipid oxidation, also known as lipid peroxidation, produces oxidative biomarkers such as malondialdehyde (MDA) and oxidized LDL (ox-LDL), an increase in these biomarkers has been associated with metabolic alterations and cardiovascular complications (Lee *et al*., 2012).

Scientific evidence to support the use of antioxidants from food, such as dairy products, as a strategy to prevent pathologies and/or complications related to oxidative stress would be of considerable value, but simply showing their presence in the raw product is only a part of the solution. There are only a few studies that demonstrate the antioxidant effect of dairy products. One of these studies in a healthy population showed that after 21 d of consumption of goats' milk there was a small but significant increase in the percentage of total antioxidant activity and a decrease in the relationship of levels of the endogenous antioxidant glutathione (oxidized glutathione:reduced glutathione: Kullisaar *et al*., 2003). A second asked participants to consume, for 4 weeks, an experimental cheese that was made from the milk of cows fed a diet containing 5% linseed oil. In this case, serum ox-LDL decreased significantly (Intorre *et al*., 2011).

It is not only important to consider that antioxidant activity increases, but also that it is able to decrease levels of ROS. Excessive ROS oxidizes cell components, which produce alterations in their structure, causing interruption of signaling pathways or even generating dysfunction of metabolic pathways. Thus, the importance of antioxidants showing this effect on health is to promote benefits in populations with pathologies associated with oxidative stress such as obesity, type 2 diabetes, dyslipidemia and cardiovascular disease (Forrester *et al*., 2018). A study that included patients with a diagnosis of metabolic syndrome and a 12-week intervention with several serves of dairy per day (adequate dairy) or less than one (low dairy) showed that adequate dairy consumption significantly decreased levels of MDA and ox-LDL (Stancliffe *et al*., 2011). The decrease in these markers is potentially of great importance, however, it is an isolated example and more evidence about the consumption of dairy products in different types of populations is needed to demonstrate the antioxidant effect it may generate.

Discussion

In recent years, bioactive compounds and agro-industrial residues have been used as feed for dairy animals because they may have positive effects on animal production, such as regulating ruminal fermentation, stopping methane production and protein breakdown, boosting the immune response, and increasing antioxidant activities in animal tissues (Niderkorn and Jayanegara, 2021). There are a great variety of bioactive compounds that can be used in the nutrition of dairy animals. In this review, 19 different types of supplements were used. Only one of them, biotin, is an approved additive according to the EU Register on Nutrition Health Claims; pomegranate seed, alfalfa hay, hesperidin, naringin, mushroom myceliated grains, and tannins are not approved. Meanwhile, the remaining interventions do not appear on any list as authorized or non-authorized. To ensure food safety and animal welfare, it is essential to regulate the feeding of dairy animals with bioactive substances and agro-industrial residues.

Milk and milk products are important foods for human nutrition, constituting 25–30% of the diet. Their nutritional value is, in part, associated with the lipid content due to the inclusion of fatty acids, vitamins and minerals (Visioli and Strata, 2014). Epidemiological data have shown associations between health effects and dairy product intake (Givens, 2020). On the other hand, many other studies have linked the consumption of dairy products with the risk of developing pathologies, mainly because of their lipid content (Fontecha and Juárez, 2017). Thus, health policies have suggested the consumption of fat-free milk and milk-derived products to prevent the risk of cardiometabolic pathologies (You, 2015). More recent analysis employing systematic review has shown inconclusive or contradictory results about the health effects of dairy product consumption (Nieman *et al*., 2021). Epidemiological studies have shown an inverse association between the intake of dairy products and hypertension, stroke, and colorectal cancer, but there is no evidence of an association between the consumption of dairy products and breast cancer. There is some weak evidence of the protective capacity of dairy products for bone health (Alvarez-León *et al*., 2006). A meta-analysis showed that milk and total dairy products, but not cheese or other dairy products, are associated with a reduction in colorectal cancer risk. Inverse associations were observed in both men and women but were restricted to colon cancer, where there was evidence of a significant nonlinear association between milk and total dairy products and colorectal cancer risk, and the inverse associations appeared to be the strongest at the higher range of intake (Aune *et al*., 2012). The nutritional benefits of milk and dairy products are undeniable, but the intricacies of specific health or disease consequences are very difficult to establish.

Dairy products may contain antioxidants such as vitamins A and E, which may provide health benefits due to their ability to reduce oxidative stress and inflammation, but note the term 'may'. Depending on factors such as animal diet, breed and production methods, the antioxidant content of dairy products can vary. Some studies indicate that feeding dairy animal diets rich in antioxidants, such as those containing high levels of vitamin E or plant-based compounds, can increase the antioxidant content of their milk (Delgadillo-Puga *et al*., 2019, 2020), which is encouraging but we are far from understanding whether such increases actually achieve health benefits. Nevertheless, we can say that improving the diet of dairy animals could potentially increase the nutritional value of the milk they produce.

Efforts have been made to maximize the potential health benefits of dairy products and increase their clinical relevance. Studies have demonstrated that improved chemical composition or enrichment with bioactive compounds such as PUFA, peptides and antioxidants can contribute to the enhancement of the

https://doi.org/10.1017/S0022029923000511 Published online by Cambridge University Press

quality of these products by promoting positive effects. Recent evidence suggests that benefits from dairy products on health include regulation of carbohydrate and lipid metabolism through effects on abundance and composition of gut microbiota, cardiovascular diseases, type 2 diabetes, modulation of the immune response and decreased risk of different types of cancer (Tong *et al.*, 2011; Sharafedtinov *et al.*, 2013; Nilsen *et al.*, 2015; Brassard *et al.*, 2017; Santurino *et al.*, 2020).

Changes in these types of products brought about by the presence of bioactive compounds can also have positive outcomes for the production animal. For example, the increase in milk fat concentration due to plant bioactive lipid compounds and biotin can be explained by the prevention of postpartum weight loss and an increase in back fat thickness (Hausmann *et al.*, 2018). Fumaric acid had a negative impact on total fat content. The authors theorized that this was due to the decreased proportion of precursors for the de novo synthesis of milk fatty acids, such as butyrate and the acetate-to-propionate ratio (Li *et al.*, 2021). The higher production of fat in milk when sweet grass was supplemented was accompanied by an increase in digestibility and feed intake, thereby increasing the nutrients available for the rumen microbes and enhancing rumen fermentation, total milk production and milk composition (Mapato *et al.*, 2021). Also, sweet grass increases the concentration of MUFA in milk because fresh grass increases milk fatty acids that are ruminal biohydrogenation intermediates (C18:1, C18:2, C18:3). It has been demonstrated that MUFA can improve glycemic control and prevent the development of metabolic syndrome and its complications (Sheashea *et al.*, 2021). Similar results are shown in the intervention with *Acacia farmesiana*, dried grape pomace, and MMG that increased the long-chain fatty acids, like linoleic and alpha-linolenic acids. This effect can probably be related to ruminal kinetic modifications due to the rich bioactive compounds found in supplements (Delgadillo-Puga *et al.*, 2019). Enrichment in the content of PUFA in this study has an important role in consumer health because PUFA are associated with preservation of insulin sensitivity, regulation of blood pressure, adequate coagulation and enhanced endothelial function (Julibert *et al.*, 2019).

The use of tannin extract in the diet, by contrast, had a negative effect on C18:1 *trans*-10, which may affect the pathway of microbial conversion of C18:3 *cis*-9, *cis-12, and cis*-15 to C18:1 *trans*-10 in the rumen. However, these effects were not reflected on cheese-making parameters (Menci *et al.*, 2021). Mapato *et al.* (2021) found that adding bamboo grass with bioactive compounds like condensed tannins improved the rumen microbiome, which had a positive effect on total volatile fatty acids and propionic acid. The increment of saturated fatty acids due to the inclusion of MMG in the diet was explained by an increment in palmitic acid (C16:0) (Bonanno *et al.*, 2019a).

Variation in milk composition may also be accompanied by the presence of bioactive compounds such as phenols and ferulic acid in milk, with a subsequent presence in processed products. A positive effect on oxidative damage was observed in cheese, which was less prone to proteolysis during ripening without any changes in sensory characteristics (Ianni *et al.*, 2019). Another example of the antioxidant capacity was also described in cheeses induced by MMG in the diet due to the presence of phenolic acids, flavonoids, polysaccharides, carotenoids, ascorbic-acids, and tocopherols.

In conclusion, consumption of products with antioxidants and an adequate lipid profile can be considered a strategy to prevent the damage caused by oxidative stress (Rani *et al.*, 2016).

This systematic review compiles scientific studies about supplementation with bioactive compounds to improve the nutrition profile and composition of milk and dairy products. It was observed that supplementation with bioactive compounds in the diet of dairy animals had a positive impact on dairy products, which ranged from an increase in antioxidant capacity to a decrease in metabolites such as malondialdehyde. Future studies should focus on exploring the impact of consuming these products on human health.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0022029923000511

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