



# Revisiting the Effects of Different Dietary Sources of Selenium on the Health and Performance of Dairy Animals: a Review

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## Abstract

Selenium (Se) is one of the most important essential trace elements in livestock production. It is a structural component in at least 25 selenoproteins such as the iodothyronine deiodinases and thioredoxin reductases as selenocysteine at critical positions in the active sites of these enzymes. It is also involved in the synthesis of the thyroid hormone and influences overall body metabolism. Selenium being a component of the glutathione peroxidase enzyme also plays a key role in the antioxidant defense system of animals. Dietary requirements of Se in dairy animals depend on physiological status, endogenous Se content, Se source, and route of administration. Most of the dietary Se is absorbed through the duodenum in ruminants and also some portion through the rumen wall. Inorganic Se salts such as Na-selenate and Na-selenite have shown lower bioavailability than organic and nano-Se. Selenium deficiency has been associated with reproductive disorders such as retained placenta, abortion, early embryonic death, and infertility, together with muscular diseases (like white muscle disease and skeletal and cardiac muscle necrosis). The deficiency of Se can also affect the udder health particularly favoring clinical and subclinical mastitis, along with an increase of milk somatic cell counts in dairy animals. However, excessive Se supplementation (5 to 8 mg/kg DM) can lead to acute toxicity including chronic and acute selenosis. Se is the most vital trace element for the optimum performance of dairy animals. This review focuses to provide insights into the comparative efficacy of different forms of dietary Se (inorganic, organic, and nano-Se) on the health and production of dairy animals and milk Se content.

**Keywords** Selenium · Antioxidant · Nanoparticles · Health · Production · Dairy animals

## Introduction

Trace elements or minerals are classified as micronutrients that have nutritional relevance for livestock generally (ruminants or non-ruminants), and they are considered in their diets [1]. These microelements are divided into essential (Fe, Cu, Co, Se, I, Mn, Zn, and B) and non-essential (toxic elements

such as Pb and Cd) elements. The essential microminerals act as co-factors of various metalloenzymes playing key roles in the body metabolism and immune system, which make them vital for animals [2]. Because of the physiological importance of essential trace minerals, their deficiency, due to either low supply or some mineral antagonism, negatively affects the health, reproductive, and productive performances of dairy animals [3].

Selenium (Se) is one of the most important essential trace minerals in livestock production owing to its diverse physiological roles. Se is a structural component of at least 25 selenoproteins as selenocysteine (Se-Cys) in their active catalytic site [4]. The majority of selenoproteins play a vital role in enzymatic redox reactions at the cellular level via Se-Cys, which convene their catalytic or antioxidant capabilities. The key physiological processes which essentially require selenoproteins include DNA synthesis (biosynthesis of dNTPs), scavenging of toxic or signaling peroxides, reduction of oxidized proteins and membranes, redox signaling, metabolism of thyroid hormone, transport, and storage of Se [5]. Three major groups of selenoproteins concerning key

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physiological functions in mammals include thioredoxin reductases (TrxR), iodothyronine deiodinases, and glutathione peroxidases (GSH-Px) [6]. The thyroxin system (constituting TrxR, thioredoxin (Trx), and NADPH) is a major cellular redox system that effectively regulates many essential cellular processes including DNA synthesis [7, 8], body defense against oxidative stress [9], and integrity of endoplasmic reticulum [10] through reduction of protein disulfides in ribonucleotide reductase, thioredoxin peroxidase, and protein disulfide-isomerase, respectively.

Moreover, this system also regulates the synthesis of the thyroid hormone and mediates the conversion of T4 (thyroxin inactive form) into T3 (active form) leading to influence overall body metabolism and development [11]. Additionally, the T3 hormone regulates the metabolism of the adipose tissue in association with a seleno-dependent hormone. Moreover, the thioredoxin system also regulates the gene expression through mediating transcription factors including NF- $\kappa$ B, Ref-1, AP-1, P53, glucocorticoid receptor, and apoptosis-regulating kinase (ASK1). Thus, it indirectly influences key cellular activities like cell cycle, apoptosis, and activation of the immune response [12].

The second most important group of selenoproteins as GSH-Px regulates the concentration of free radicals of reactive oxygen species (ROS) at cellular levels [13, 14]. Owing to the abovementioned physiologically diverse role of selenoproteins, an optimum quantity of Se is required in livestock feed to ensure proper immune functions, production performance, and fertility [15]. Previously, several studies have suggested that the therapeutic level of Se reduces the chances of several diseases, including oxidative stress, muscular dystrophy, cardiovascular disease, cystic fibrosis, and arthritis [16]. Selenium is extensively used as a feed supplement due to its direct connection with immunity and tumorigenesis [17, 18].

Due to the structural role as a co-factor in selenoproteins, Se performs key physiological functions or roles in reproduction, antioxidant defense system, metabolism of thyroid hormone, anti-apoptosis, and muscle functioning and development [19–21]. Owing to its major role in thyroid metabolism, optimum levels of Se is also required for body development and metabolism in growing animals [22]. Moreover, major physiological effects of Se are attributed to the functional role of selenoenzymes to mediate oxidative stress for normal cellular homeostasis and functioning. Studies have shown that alleviation of oxidative stress through improving the antioxidant system directly improves the reproductive physiology in different farm animals [23, 24]. So the dietary supplementation of Se is envisaged as crucial for the maintenance of normal reproductive physiology and fertility in dairy animals. The effects of Se supplementation in dairy cattle depend on physiological status (fertility, the incidence of mastitis, etc.) [25, 26], Se status of animals [27], Se type and content, and Se administration types [28]. Generally, two different forms (inorganic and organic) of Se are used, and both have different

bioavailabilities in the gastrointestinal tract. Many previous studies have shown that Se yeast has higher bioavailability and is associated with increased milk and blood Se content [29–31] with better antioxidant status [32, 33]. As a trace element, Se is used in very minute quantity in animal diets, but issues like low bioavailability, antagonism, and higher excretion from intestine limit its efficacy. Nanotechnology offers the opportunity to mediate these issues as bioavailability can be increased by enhancing the surface area of the Se by making its nanoparticles [34].

Keeping in view the importance of Se in health and production of dairy animals, the present review aims to provide insights into the key physiological role of Se and the potential benefits of its supplementation in dairy animals. Moreover, the comparative efficiency of different forms of Se is discussed with a special focus on nano-selenium (nano-Se).

## History of Selenium Discovery

The discovery and research on Se started in August 1817. Selenium was first isolated from Falun pyrite when the Swedish chemist Jacob Berzelius discovered a new element in 1818. Berzelius chose the name selenium (Greek: Selene, moon) for this new element [35]. The first report on the deficiency of Se in animals appeared in 1957 when deficient animals (in Se and vitamin E) showed white muscle disease in ruminants [36]. Other deficiency diseases like skeletal and cardiac muscle necrosis were observed by Smith et al. [37]. In 1973, Rotruck and his team [38] demonstrated the biochemical role of Se as a component of GSH-Px enzyme which functions as an antioxidant to protect cells against oxidative damage. In 1979, the Food and Drugs Administration (FDA) approved Se as a feed additive for dairy cattle, initially at an added level of 0.1 mg/kg of DM [39], and later on (since April 1987), at a concentration of 0.3 mg/kg of DM [40], which is equivalent to 0.7 mg/ewe/day [41]. In 2006, the European Commission authorized the use of Se yeast as a feed additive within the European Union [42]. Today we know that Se, as a trace element, has a wide range of important functions for humans (medicine), animals, and plants (biology) along with various industrial applications (in agriculture and environment).

## Sources of Selenium

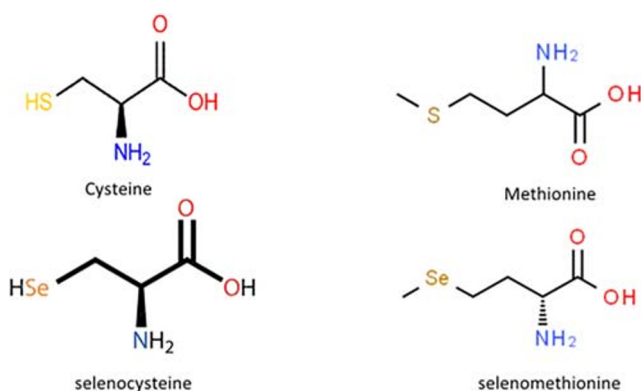
The major dietary sources of Se include inorganic and organic Se. The most common form of dietary Se includes inorganic Se salts, e.g., Na-selenate ( $\text{NaSeO}_4$ ) and Na-selenite ( $\text{NaSeO}_3$ ) which is usually provided in mineral premixes, injected or orally given in bolus forms. The chemical form of Se affects the absorption of Se, as sodium selenite (SS) when injected

subcutaneously showed more rapid absorbance than barium selenate. Moreover, inorganic salts are considered crucial to achieving optimum levels of Se in dietary supplements [43]. However, inorganic Se sources show poor bioavailability and antagonism with other minerals rendering in poor efficacy. Therefore, organic Se sources such as Se-enriched yeast, e.g., *Saccharomyces cerevisiae*, which contains Se amino acids (seleno-AA) such as hydroxy-selenomethionine (HMSeBA), selenomethionine (Se-Met), and selenocysteine (Se-Cys) in abundance (Fig. 1) [33, 44, 45]. Selenium is also found in animal fodders, but their Se contents vary with type, texture, and organic matter contents of the soil along with the extent of precipitation in the area. Recently, the nano form of Se is attracting the attention of nutritionists owing to its comparative advantages over conventional sources of Se. Nanotechnology utilizes matter at its dimensions from 1 to 100 nm with unique characteristics and novel applications. Such magnificent technologies have the potential to expand the bioavailability measures and other nutritional assessments. Bioavailability can be enhanced by increasing the surface area of respective minerals by making their nanoparticles [34]. It is one of the most innovative technologies to produce materials and different elements with change in structure, texture, and enhanced quality at the molecular level. This technology is contributing significantly in production, processing, storage, transportation, traceability, security, and safety of food [46]. Studies have shown that nano-Se has higher bioavailability, catalytic activity, enhanced adsorbing capability, lower acute toxicity, and no antagonistic effects in the gut [47, 48].

## Absorption, Bioavailability, and Metabolism of Selenium in Ruminants

### Absorption

Absorption in ruminants is through a rumen wall or in the small intestine. Most of the Se absorption site in both ruminants and



**Fig. 1** Chemical structure of amino acids, methionine and cysteine, and the comparable seleno-amino acids

non-ruminants cases is the duodenum. However, absorption of Se is different in the rumen and the intestine. Generally, the rumen receives Se in selenite form in the diet, while most of the selenate is reduced to selenite in the rumen before absorption, and part of the selenate bypasses from the rumen to the small intestine and absorbed as selenate. Another proposed mechanism of absorption in the rumen suggests that 30–40% of selenite is converted to low molecular weight insoluble forms of Se [49]. Moreover, 10–15% of the selenite is used to synthesize seleno-AA (predominantly Se-Cys) that is incorporated into the microbial protein by substitution of Se with a sulfur atom in the cysteine residue of the protein. However, 40–60% of the selenite leaves the rumen to the intestine where it is absorbed probably via a passive diffusion [50]. Studies have suggested that the true absorption of Se in the case of dietary inorganic form averages about 50% in dairy cows, goats, and sheep [51, 52]. Generally, the extent of absorption of selenite is quite low in ruminants (only 29%) as compared with monogastric animals and poultry (about 80–90%).

Several *in vitro* studies have suggested that Se-enriched yeast contains 90% of the Se in the form of Se-Met, and about 55% of which bypasses the rumen. The digestibility of Se from Se-enriched yeast is reported to be about 66%, so considering the digestibility of Se-Met as 80% (as average digestibility of ruminal microbial protein), it is about 30% higher than the true digestibility of Se from selenite. Many studies have reported this fact that absorption and bioavailability of organic Se are substantially higher than those of inorganic Se in ruminants [44, 53–55].

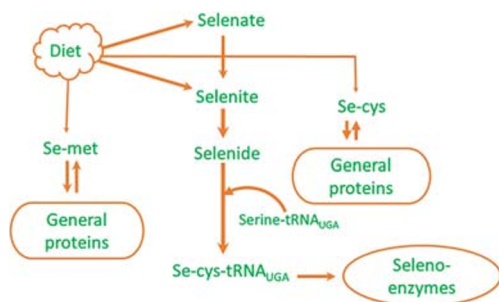
Numerous dietary factors affect the absorption of Se in ruminants owing to the antagonistic effects of other nutrients. The diets rich in carbohydrates or some salts such as nitrates, sulfates, calcium, arsenic, vitamin C, mercury, or hydrogen cyanide (clover, flax seeds) negatively influence the digestibility of Se in ruminants [56]. However, dietary proteins, vitamin E, and vitamin A have shown to enhance Se absorption.

### Bioavailability

As mentioned above, the availability of Se-Met (organic Se) is greater than that of selenite (inorganic Se). Further, Se-Met is rapidly incorporated into proteins. The inorganic Se is almost exclusively used to produce selenoenzymes, whereas organic Se can be used to produce both selenoenzymes and generally all proteins containing Met (Fig. 2). The only issue with organic forms of Se is their higher costs than inorganic Se sources.

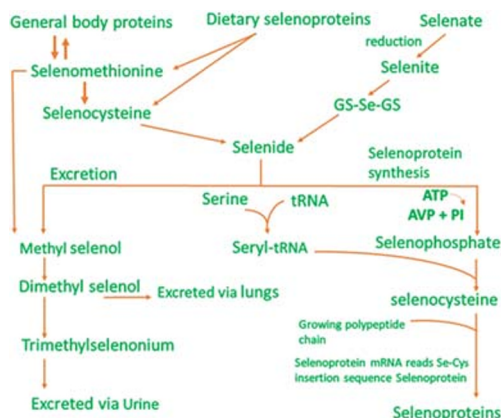
### Metabolism

The main utilization of dietary Se is its incorporation into selenoenzymes which constitute the cellular antioxidant system in the cytosol. Metabolic fates of dietary inorganic and



**Fig. 2** Simplified pathways of Se metabolism

organic Se forms differ, as organic Se (including dietary selenocysteine) must first be converted to the inorganic selenide (hydrogen selenide) before the process of forming and incorporating specific selenocysteine into the active site of one of the selenoproteins [57]. Selenate is reduced to selenite, and selenite is reduced via formation of selenodiglutathione to selenide [58, 59]. The putative mechanism of Se metabolism is presented in Fig. 3. Dietary Se sources (organic and inorganic) effectively provide two separate pools of Se in the body. Se-Met (organic) is incorporated into all proteins directly as a substitute for Met (nonspecifically) and reflects its concentration in the diet. While inorganic Se is only incorporated into a specific amino acid (cysteine) in the selenoproteins [60], excess absorbed Se is excreted as trimethylselenonium or exhaled as dimethyl selenide [61]. Studies have reported the putative metabolism and absorption of Se and its potential role in the immune system [62]. Ruminants generally excrete extra Se through urine and feces [63]. The intake of Se in the form of inorganic salts usually is utilized directly into the synthesis of selenoproteins and exhibits a short half-life as the excess amount is directly excreted and not stored in the body [64]. In contrast, Se in its organic Se forms like Se-Met and Se-Cys is efficiently stored in different tissues, thus preventing the deficiency of Se and increasing GSH-Px activity through mediating redox status and oxidative stress [65].



**Fig. 3** Metabolism and excretion of inorganic and organic Se in the body

## Dietary Requirements of Selenium in Ruminants

Selenium is beneficial within a narrow dose range for all farm animal species [66]. The daily requirements of Se depend on animal species (cows, buffaloes, camels, sheep, and goats), age of the animal (calves, kids, lambs, and adults), physiological stage (lactating or pregnant), and performance trait (meat or milk). Generally, the nutritional requirement of Se is met through animal diets supplemented with mineral salts and different sources and forms of Se [56]. The nutritional requirements of Se for animals are presented in Table 1. Generally, NRC [2] recommends the Se allowance for many livestock species to be about 0.1–0.3 mg/kg DM depending upon their growth performance.

## Deficiency and Toxicity of Selenium

The optimum level of dietary Se is required to maintain normal animal physiology; however, an excess or lower dietary Se can lead to toxicity or deficiency, respectively, with adverse consequences. The excessive amounts of Se can be very toxic to animals [69]. Different factors affecting Se toxicity usually include diet, sex, animal species, and chemical form of Se. It is suggested that inorganic Se is three times more toxic than organic Se [58, 70, 71]. In 1930, the first report on Se toxicity was received as hair loss, and lameness was observed in animals that grazed on forage with high Se levels. The signs of Se toxicity usually start to appear at Se levels of 5 to 8 mg/kg DM. The different forms of Se toxicity include chronic selenosis (alkali disease) and acute selenosis (blind staggers) in animals [72]. However, Schöne et al. [73] reported that Se toxicity is not considered as a life threat for animals or humans.

Generally, Se deficiency is observed in both animals and humans, when the dietary intake of Se is less than 0.05 mg/kg DM [74]. Selenium deficiency may affect the reproductive efficiency (retained placenta, abortions, early embryonic death, and infertility), growth performance (white muscle disease), and skeletal and cardiac muscle necrosis (stiffness and

**Table 1** Recommended levels of dietary Se for ruminants

Animal species	Dry matter ( $\mu\text{g}/\text{kg}$ )
Beef cattle [2]	100
Dairy cows [2]	300
Camels [67]	100
Calves [2]	100
Sheep [67]	400–500
Lambs	200
Goats [68]	200–400

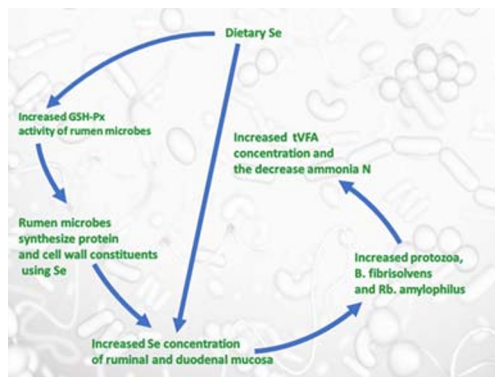
lameness) [49, 75]. Deficiency of Se can also affect the udder health, particularly mammary glands health, clinical and sub-clinical mastitis, and elevated somatic cell counts (SSC) [76]. Forages from Se-deprived soils can cause oxidative stress and pose a serious threat to the immune function of animals [75]. Additionally, the extent of Se toxicity and deficiency in animals vary in different animal species maintained on different forage, soil, and water resources [72, 77, 78]. It is generally accepted that Se deficiencies could be avoided by feeding animals with forages and diets containing sulfur amino acids.

## Dietary Supplementation of Se to Improve the Performance of Dairy Animals

As mentioned above, Se plays a significant role in cellular redox and antioxidant defense systems to maintain normal physiology. Ensuring a normal balance of ROS and antioxidant enzymes leads to normal animal physiology resulting in optimum productive and reproductive performance (Fig. 4). The major benefits of Se in dairy animals are summarized as below.

### Effects on Gestation, Colostrum, and Newborn

Selenium supplementation in dairy animals generally affects thyroid hormone metabolism, redox-active proteins to



**Fig. 4** Putative mechanism of action of Se to improve the rumen fermentation. Se has the potential to increase the antioxidant status of ruminal microbiome, subsequently leading to enhanced rumen fermentation and microbial growth. Microbial GSH-Px activity and Se concentration of rumen mucosa were also increased with the provision of dietary Se [79]. Besides, dietary Se supplementation can also stimulate digestive enzyme secretion and increase the GSH-Px activity of duodenal mucosa [80, 81]. Ruminal microbes utilize dietary Se to synthesize protein and cell wall constituents [82]. Fibrolytic bacteria concentration and degradation of structural carbohydrates were increased due to low rumen pH in response to Se supplementation [83]. Microbes in the rumen utilize different nutrients (like ammonia N, carbon-skeleton, and ATP) to synthesize microbial protein [84]. Enhanced microbial protein synthesis in response to Se supplementation may be attributed to the increased total VFA production and rumen bacterial populations together with lower ammonia-N.

regulate anti-oxidative status, and immune functions in dairy cows [85, 86]. Several studies have reported the negative relationship between Se concentration in blood and that in milk. The last 4 weeks of the gestation period in cows are very critical regarding Se availability, as Se is transported to the developing fetus via the placenta even when the dietary supply of Se is not optimum [49]. In pregnant female camel, the Se serum concentration was significantly higher post-partum than in the prepartum period [87]. It is attributed to the fact that Se levels (renal) in the fetus remain unchanged as compared with their dams [88].

Dietary supplementation of Se before parturition resulted in twofold higher Se levels (170 vs 87  $\mu\text{g/L}$ ) in the colostrum of dairy cows [89], while threefold higher in camels as compared with their unsupplemented counterparts [87]. Moreover, supplementation of organic Se (Se yeast) exhibited higher average Se levels in the colostrum (67 vs 35  $\mu\text{g/L}$ ) as compared with SS [28]. However, contrary findings were observed in Holstein cows, as no significant difference in Se contents of colostrum was observed in response to supplementation of both organic and inorganic sources of Se [27].

Selenium is transported from mother to fetus through the placenta, and after parturition, through colostrum and milk in ruminants. However, Se transfer through the placenta is more efficient than that found in milk because less quantity of Se is transferred from the blood into the milk [90, 91]. Hence, it is crucial to maintain adequate Se status in calves. Moreover, a dietary source also affects the extent of Se transfer from the blood to the milk. Many studies have reported better beneficial effects of dietary supplementation and efficiency of organic Se as compared with inorganic Se in calves [91, 92]. Studies have also shown that maternal dietary Se (Se-enriched yeast) resulted in higher birth weight and growth performance in Taihang black goats and male kids [66]. Recently, Żarczyńska et al. [93] reported that suckling dairy calves receiving intramuscular injections of 0.5 mg of Se/mL and 50 mg of vitamin E/mL showed better Se status and improved passive immunity than control. Similarly, dietary supplementation of a slow-release bolus (consisting of Zn, Se, and Co) in ewes 6 weeks prepartum revealed desirable effects on the antioxidant status of the dam and growth of lambs [94]. It substantially increased serum alkaline phosphatase and GSH-Px activity and plasma concentrations of Zn, Se, and vitamin B<sub>12</sub> in ewes and their lambs. Furthermore, ewes receiving Se bolus have shown better birth weights and average daily gain of lambs at weaning [95].

Dietary supplementation of organic Se has shown to improve the immune response of suckling dairy calves [96]. Similarly, feeding of Se-enriched alfalfa hay in beef calves improved immunity against J-5 *Escherichia coli* bacterin [97]. Moreover, dietary Se also improved serum Se levels (382.7  $\pm$  107.6 vs 176.3  $\pm$  18.0 ng/mL) of female camel calves as compared to their un-supplemented counterparts [87].

Dietary supplementation of HMSeBA in pregnant heifers improved the Se status of both the dam and calf compared with the SS [98]. Moreover, Se content of the maternal diet has shown to enhance testicular development and testosterone synthesis in goats kids through up regulating the testosterone-related genes [99]. Optimum serum Se levels are required to ensure proper immune response leading to normal health and growth performance in animals. For Se-deficient animals, injectable Se preparations can be used to readily establish Se status in calves, but it is usually temporary management, and other Se enriched supplements should be focused to sustain dietary Se intake [49].

### Effects on Milk Yield, Composition, and Milk Se Contents

Milk and milk products are considered a good source of micronutrients, including macro- and microminerals, that play important functions to ensure proper growth and health in humans [3]. For example, milk and its products contribute more than 4% of the total dietary Se consumed by humans in Belgium [100]. Owing to the direct association of dietary Se with milk Se contents, the level of Se in milk is considered as an easy and non-invasive way to evaluate herd Se status [49]. The Se contents of fodder/forages/feeds usually depend on the season and agro-ecological conditions which can subsequently influence the Se contents in milk. According to the FDA, bovine milk should contain an average Se level of about 0.14 mg/L [41]. However, milk Se contents of less than 0.12  $\mu\text{mol/L}$  indicate Se deficiency, while milk Se  $> 0.28 \mu\text{mol/L}$  shows adequate Se levels. Moreover, milk Se contents between 0.12 and 0.28  $\mu\text{mol/L}$  are considered marginal [101]. Many studies have been carried out in different regions of the world to document Se contents of milk in dairy cows which widely varied such as it was 30 g/kg in Belgium, 60 g/kg in South Korea, and 22 g/kg in Greece [5, 100, 102].

The amount of Se in plasma is three- to fivefold higher than in milk Se. Ivanis and Weiss [52] observed a positive correlation between plasma and milk Se content ( $y = 0.37x - 4.2$ , with  $x = \text{plasma Se } (\mu\text{g/L})$  and  $y = \text{milk Se } (\mu\text{g/L})$  content). Generally, seleno-AA are transported to liver and other tissues such as muscle and the mammary gland through systemic circulation. Mammary gland cells can incorporate Se-Met in place of Met during casein synthesis [92]. Various studies have shown that Se administration has the ability to increase serum albumin, insulin, and total protein contents in dairy cows [103–105]. Selenium supplementation can also potentially affect thyroid hormone metabolism and redox-active proteins to regulate anti-oxidative status and immune functions in dairy cows [85, 86]. The effect of dietary supplementation of Se on milk yield and composition has shown variable results. Several studies reported that milk yield and components did not change under a different conditions such as type

of animal, parity, age, stage of lactation, and Se source (organic and inorganic) [28, 106–108]. Contrarily, Moeini et al. [109] reported that Se supplementation at 0.5 mg/kg DM significantly increased daily milk production during the first 8 weeks of lactation in Holstein cows. Similarly, dietary supplementation of Se and vitamin E increased milk protein, non-fat solids, and lactose contents [25]. Supplementation of HMSeBA in Holstein dairy cows under heat stress conditions tended to increase the milk yield and decrease the fat percentage as compared with SS [110].

Dietary Se has no direct influence on lactogenesis, but it can indirectly affect milk production through diverse pathways particularly under stress conditions. The increase in milk yield in response to Se supplementation may be attributed to enhanced energy availability in lieu of alleviation of oxidative stress and/or maintaining redox homeostasis, because, both eliciting an antioxidant response and repairing free radical-induced damages require energy, which can be saved by maintaining redox balance with appropriate Se plasma levels [111]. In addition, milk yield increase might be attributed to the reduced free radical-induced damage within the mammary gland which can likely enhance milk synthesis [112].

Milk is a terminal pool for Se-Met as the mammary gland can extract an immense quantity of Met to produce milk proteins. Regarding milk fat, supplementation of organic Se increased the milk fat percentage (4.15% vs 3.96%) compared with the inorganic form in dairy cows [113]. This increase may be due to the lower enzymatic action of lipases of leukocytes resulting from lower SCC [114]. Neutrophils exhibited better ability against mastitis-causing pathogens when organic Se was supplied to animals [115]. It has also been reported that cows with lower incidence of mastitis exhibit higher milk fat percentage [116]. On the other hand, a recent study reported that supplementation of HMSeBA in cows tended to decrease the milk fat percentage compared with SS [110]. A possible underlying mechanism might be a negative relationship observed between blood Se and milk fat contents for herds at first season of Se supplementation [82], as increased Se might upregulate oxidative reactions within the tricarboxylic cycle and fatty acid [117]. However, Wang et al. [118] did not observe any negative relationship between blood Se and milk fat contents. Possibly, these contrasting results might be due to differences in the composition of the diet, dose of Se, and stage of lactation of dairy cows. However, these putative mechanism and contrary findings require further investigations.

Many studies have reported the effect of Se supplementation on milk Se contents. Generally, it is reported that milk whey contains a higher proportion (56.6%) of Se contents as compared with non-whey milk fat phase (10.1%) in dairy cows [119]. This is mainly attributed to the fact that 55–75% of milk Se is incorporated into casein, while 17–38% is contained in the whey and 7% in milk fat [120]. A survey of

Se contents in China revealed average Se contents in milk (0.13–0.44  $\mu\text{g/L}$ ), feed samples (0.11–0.38  $\mu\text{g/kg}$ ), and drinking water (0.09–0.29  $\mu\text{g/L}$ ) of dairy cows [3]. In camel, milk Se contents varied from 39.5 to 482.6 ng/mL [121].

Dietary supplementation of inorganic and organic Se in dairy cows showed an improvement in milk Se contents of up to 32.8 and 41.2%, respectively [32]. Similarly, milk Se contents linearly increased as 0.04, 0.31, 0.52, and 0.78  $\mu\text{g/mL}$  in goats fed in response to 0, 0.5, 2, and 4 mg Se/kg, respectively [66]. Moreover, Bagnicka et al. [107] reported an increase of over 300% in milk Se concentration in response to dietary supplementation of organic Se as compared with that of inorganic Se. Moreover, dietary Se also improved Se levels in the serum ( $305.9 \pm 103.3$  vs  $109.3 \pm 33.1$  ng/mL) and camel milk ( $167.1 \pm 97.3$  vs  $86.4 \pm 39.1$  ng/mL) as compared with unsupplemented groups [121]. The HMSeBA as an organic Se source has the potential to increase milk and plasma Se content and milk fat percentage with similar milk production parameters compared with SS [33].

Recently, Li et al. [122] reported that feeding HMSeBA (up to 0.5 mg/kg of DM) linearly increased Se content in milk and plasma and milk/plasma Se ratio in dairy cattle. Additionally, milk production, FCM, ECM, protein content, and lactose content of milk also increased in response to supplementation of HMSeBA. A comprehensive review has highlighted the effectiveness of organic Se to improve Se status in dairy animals as compared with SS or selenite [123]. Recently, Barbe et al. [124] evaluated the comparative efficacy of three levels (0.1, 0.2, or 0.3 ppm) of different sources of organic Se including (S2)-2-amino-4-methylselenylbutanoic acid (SM1) or R,S-2-hydroxy-4-methylselenobutanoic acid (SM2) and *Saccharomyces cerevisiae* R397 (SY) in dairy cattle. They reported that feed intake, milk yield, and milk composition were similar among different sources of organic Se. However, milk Se content was higher in the SY group at a higher level (0.3 ppm), while serum Se and Se bioavailability were higher at 0.3 ppm for all Se sources. In addition, supplementation of coated SS has been shown to increase milk yield, milk fat, and protein contents together with feed efficiency and digestibility of DM and OM in dairy cows [125]. The Se yeast (0.3 mg Se/kg) has shown a quite reasonable increase in milk production (up to 24.8%) than the control group [126]. These findings revealed that dietary supplementation of Se can increase serum and milk Se contents, but effects on milk production of dairy animals are not consistent. Moreover, organic Se is more effective in the enrichment of milk with Se in dairy animals.

### Effects on Rumen Microbiome, Rumen Fermentation, and Feed Digestibility

The Se has the potential to increase the antioxidant status of ruminal microbiome subsequently leading to enhanced rumen fermentation and microbial growth. Microbial GSH-Px

activity and Se concentration of rumen mucosa were also increased with the provision of dietary Se [79]. Besides, dietary Se supplementation can also stimulate digestive enzyme secretion and increase the GSH-Px activity of duodenal mucosa [80, 81]. Ruminal microbes utilize dietary Se to synthesize protein and cell wall constituents [82]. Fibrolytic bacteria concentration and degradation of structural carbohydrates were increased due to low rumen pH in response to Se supplementation [83]. Microbes in the rumen utilize different nutrients (like ammonia N, carbon-skeleton, and ATP) to synthesize microbial protein [84]. Enhanced microbial protein synthesis in response to Se supplementation may be attributed to the increased total VFA production and rumen bacterial populations together with lower ammonia-N. The putative mechanism of action of Se to modulate rumen microbiome, rumen fermentation, and feed digestion is presented in Fig. 4.

Dietary supplementation of Se has also shown to affect rumen microbiome, rumen fermentation, and feed digestibility (Table 2). Recently, supplementation of HMSeBA has been shown to increase the nutrient digestibility (CP, NDF, and ADF), ruminal propionate concentration, and Se bioavailability compared with SS [127]. A comparison of simple and coated SS showed better DM intake, ADG, and feed efficiency in dairy bulls supplemented with protected SS [17]. Nutrient digestibility (DM, OM, and CP) was also improved in the coated SS group; however, EE, ADF, and NDF digestibilities were similar in both Se groups. An increased ruminal total volatile fatty acids (VFA) and propionate concentration with lower rumen pH, acetate, and acetate to propionate ratio (A:P) concentration were observed in coated SS group. The improvement in nutrient digestibility and animal performance in response to dietary Se supplementation is likely a consequence of the enhanced antioxidant status of ruminal microbes [80]. Moreover, supplementation of coated SS has shown to increase milk production, the ruminal activity of pectinase and  $\alpha$ -amylase, concentration of ruminal total VFA, bacteria (*Ruminococcus flavefaciens* and *Butyrivibrio fibrisolvens*), protozoa, and fungi population in dairy cows [128]. Similarly, Zhang et al. [125] reported that both SS or coated SS substantially enhanced the activities of cellobiase, carboxymethylcellulase, xylanase, and protease while increasing the population of total bacteria, *Ruminococcus flavefaciens*, *Fibrobacter succinogenes*, *Ruminococcus amylophilus*, and total fungi in dairy cows. Similarly, dietary SS (at 0.3 mg/kg DM) improved xylanase, pectinase,  $\alpha$ -amylase, and protease activities as well as total tract digestibility of CP. Notably, populations of total bacteria (*R. albus*, *R. flavefaciens*, *Fibrobacter succinogenes*, and *Butyrivibrio fibrisolvens*), protozoa, and methanogens as well as urinary total purine derivatives excretion were also enhanced [132]. Lipid microencapsulation of SS enables Se to escape from complete rumen reduction and subsequently more efficiently incorporated into milk than its free form [147].

**Table 2** Effects of dietary Se on performance, feed digestibility, and milk yield parameters of dairy cattle

Species	Source and dose of Se	Major findings	Reference
Cows	HMSeBA 0.1, 0.3, or 0.5 mg of Se/kg of DM for 10 weeks	Linearly increased total VFA, butyrate and propionate concentration, and apparent digestibility of Se	[127]
Cows	HMSeBA 0.1, 0.3, or 0.5 mg of Se/kg of DM for 13 weeks	Milk yield, content, and feed efficiency increased with 0.3 mg/kg of Se	[122]
Dairy bulls	0.3 mg/kg DM of SS and coated SS for 80 days	Coated SS improved digestibility, blood Se level, and feed efficiency	[17]
Dairy cows	rumen-protected SS at 4.8 mg/day for 105 days	Increased milk and milk fat yields and increased ruminal enzyme activity	[128]
Lambs	0.3, 0.6, and 0.9 mg SS/kg DM for 56 days	Improved absorption and availability of Se as a result of 0.9 mg/kg DM	[129]
Sheep	0, 0.3, 3, and 6 g of nano-Se/kg DM for 80 days	Increased rumen fermentation and feed utilization linearly; 3 g nano-Se is optimum dose	[130]
Sheep	310 µg/kg DM SS and Se yeast for 5 months	Mainly increased population of <i>Ophryoscolex</i> and <i>Diploplastron</i>	[131]
Dairy cows	Se yeast 0, 150, 300, and 450 mg/kg DM for 45 days	Linearly increased the digestibility of DM, OM, CP, NDF, and ADF and milk Se content	[118]
Dairy cows	0.1, 0.2, and 0.3 mg Se/kg DM coated Se and 0.3 mg/kg as SS for 110 days	Increased feed efficiency as a result of 0.2 and 0.3 mg coated Se	[125]
Dairy calves	3.0 mg/kg DM SS	Increased total tract digestibility of DM, OM, NDF, and ruminal total VFA	[132]
Goats and their kids	Injection of 5 mL of selenite 45% per animal, 15 and 30 days prior to the expected day of birth and then at kidding and 15 days after kidding	Increased birth and weaning weight of kids with no effect on dam's body weight	[133]
Goat	0.3 mg/kg diet Se yeast for 8 weeks	Increased ruminal propionate concentration and density of papillae in the atrium ruminis, ventral rumen, and ventral blind sac of the rumen	[134]
Nellore cattle	0.3, 0.9, and 2.7 mg Se/kg DM SS or Se yeast for 84 days	BW, ADG, DM intake and gain to feed ratio was similar at 2.7 mg Se/kg; significant increase in meat Se content	[135]
Pregnant ewes	slow-release bolus (Zn, Co, and Se) before 6-week prepartum	Improved mineral status of ewes and their lambs; improved BW of lambs at weaning	[94]
Lambs	Supplementation of 0.4 mg Se in basal diet for 90 days	Increased final BW, DWG, thyroxin, and growth hormone	[136]
Lambs	0.30 mg/kg DM SS, Se yeast, and nano-Se for	Digestibility of OM, CP, CF, EE, NFE was higher for Se yeast and nano-Se, abd GSH-Px activity and testosterone levels were increased all Se source	[137]
Sheep	Se yeast at 0.2, 0.4, and 0.8 mg Se/kg DM during late gestation and early lactation	Increased DM intake, FCR and nutrient digestibility at an optimum level of 0.4 mg/kg DM	[138]
Lambs	Nano-Se and SS for 63 days	Observed similar weight gain for both sources of Se	[139]
Neonatal lambs	0.1 mg/kg Nano-Se orally for 1 month	Increased growth and antioxidant status	[140]
Cannulated steers	5 g Se/day per animal in soybean oi diet for 21 days	Increased ruminal total VFA concentration	[141]
Pregnant ewes	Se (bolus) at 0.3 mg/day for 30 days before parturition and 90 days after parturition	Increased daily gain of lambs and immunity	[95]
Pregnant goats	Se bolus at 0.25 mg/day for 4 weeks before parturition	Increased ADG and milk production	[142]
Pregnant ewes	SS and Se yeast 0.3 mg/kg DM for late pregnancy and early lactation	Increased milk yield in Se yeast, similar milk fat, and total solid for both groups; increased BW of lambs at birth and weaning in Se yeast group	[143]
Sheep	SS and Se yeast at 0.4 mg Se/kg of DM for 12 weeks	Increased Se concentration in blood and rumen fluid	[144]
Sika deer	0.2, 0.3, and 0.4 mg of Se	Optimum level is 0.3 mg of Se, increased final BW and ADG and apparent digestibility of CP, ADF and EE	[145]
Beef cattle	SS and Se yeast at 0.32 mg/kg DM	Increased growth performance with Se yeast	[146]

HMSeBA hydroxy selenomethionine, VFA volatile fatty acid, SS sodium selenite, DM dry matter, OM organic matter, CP crude protein, CF crude fiber, EE ether extract, NFE nitrogen free extract, ADF acid detergent fiber, DWG daily weight gain, ADG average daily gain, FCR feed conversion ratio

Similar to protected SS, organic Se has shown more pronounced effects on the promotion of specific microbes in the rumen as compared with SS. Supplementation of Se yeast enhanced the population of rumen protozoa, *Ophryoscolex*

*caudatus f. tricornatus* (up to 136%) and *Diploplastron* population (up to 63%), in sheep as compared with SS. However, relative abundance of *Dasytricha ruminantium* and *Polyplastron multivesiculatum* was similar in both groups



[131]. Wang et al. [118] also reported an increase in milk yield, fat-corrected milk (4%), ruminal total VFA concentration, and apparent total tract nutrient digestibility in response to Se yeast supplementation in dairy cows. These findings reveal that both protected SS and organic Se can positively influence rumen microbiome, rumen fermentation parameters, and nutrient digestibility leading to overall improvement in performance of dairy animals.

### Effects on Blood Metabolites

The blood metabolites are considered as a quick and effective tool to evaluate the health status of dairy herds. The serum is highly correlated to dietary intake of Se within 2 to 6 days after supplementation in diets [148, 149]. The Se in the blood is associated with different proteins including globulins ( $\alpha$  and  $\beta$ ), lipoproteins (both low- and high-density lipoproteins), and albumin [58]. Ten Se atoms as Se-Cys are included in the selenoprotein-P which is a selenoprotein supplier of Se to different body tissues. Studies have reported that the adequate Se level in the blood of cattle should be above 0.18  $\mu\text{g/mL}$  in whole blood and 0.08  $\mu\text{g/mL}$  in plasma. These concentrations could be achieved through dietary supplementation of Se at 0.3–0.5 mg/kg DM of diet in lactating cows [2, 54, 150].

Dietary supplementation of Se in goats has been shown to significantly affect the serum biochemical profiles in as serum ALT, total protein, globulin, total cholesterol, and glucose of kids improved in response to maternal dietary Se supplementation [66]. Recently, Liu et al. [17] reported that coated SS supplementation in dairy bulls have better blood glucose (29.1 vs 24.1 nmol/L), total protein (73.5 vs 68.5 g/L), and albumin (39.8 vs 34.6 g/L) contents compared with SS and control group; however, blood Se (0.17  $\mu\text{g/mL}$ ), insulin (29.4 mIU/L), and total cholesterol levels (8.58 mmol/L) were similar in both Se groups. Contrarily, supplementation of Se-Met in ewe's diet showed no effect on serum urea, cholesterol, total protein, albumin, A:G ratio, AST, and ALT, while decreasing serum glucose. Moreover, Se supplementation improved serum T3 and T4 levels and their ratio in dairy cows [151]. Similar results regarding serum ALT and AST in camel was observed [28]. Contrarily, higher serum cholesterol and  $\alpha$ -tocopherol/cholesterol ratios at calving were observed when dairy cows were fed diet supplemented with organic Se at 48 h compared with the control [97]. Supplementation of Se-Met has been shown to increase serum total protein and albumin concentrations in cows [105]. Moreover, dietary supplementation of Se in male buffalo calves exhibited no effects on serum glucose, total protein, urea, and creatinine contents; however, serum globulins significantly increased while decreasing albumin and A:G ratio [152]. Moreover, the level of different serum enzymes (ALT and AST) and hormones (T3, T4, testosterone, and insulin) did not differ among Se-supplemented and control groups.

### Effect on Immune Response and Antioxidant Status

The major effects of Se in dairy animals are attributed to the diverse functions mediated by selenoproteins. Cellular redox system and antioxidant defense of the body necessarily rely on selenoenzymes (GSH-Px, TrxR) and selenoprotein P, so optimum dietary Se is required to ensure proper supply of Se-Cys and Se-Met for the synthesis of selenoproteins. Dietary supplementation of Se has been conceived as a potential strategy to improve the immune response and alleviate metabolic/oxidative burden in dairy animals particularly during stress and disease periods (Table 3). Many studies have reported significant effects of dietary Se sources and their levels on antioxidant and immune status in dairy cattle with a major focus on GSH-Px activity in the blood [32, 62, 167]. Many studies involving dietary supplementation of Se in the diets of calves, heifers, fattening bulls, dairy cows, camels, buffaloes, goats, ewes, kids, and lambs reported increased Se contents and GPx activity in the blood [87, 107, 151, 168]. Recently, Wang et al. [169] revealed a positive correlation of serum Se level with GSH-Px activity and a negative correlation with SCC and Interleukin 6. They showed that the risk of subclinical mastitis increases when serum GSH-Px is less than 148 U/L and Interleukin 6 is less than 451 ng/mL in dairy cattle.

The ROS are naturally produced during cellular metabolic processes and are neutralized by the antioxidant defense system of the body. In stressful conditions, ROS overproduction negatively affects animal performance, health, and well-being [170]. The enhanced Se concentration or GSH-Px activity in the plasma/serum of dairy cows during early lactation (as compared with dry and peak lactation) has revealed the importance of Se to alleviate oxidative stress state in early lactation [167]. The comparative effect of coated SS on plasma GSH-Px activity (189 vs 161 U/mL) was substantially higher than that of SS in dairy cattle bulls [17]. Organic Se is considered a potential source for alleviating oxidative stress compared with its inorganic form, as Se-Met has 1.4 times higher blood GSH-Px activity than SS [171]. Recently, Sun et al. [154] reported that organic sources of Se (HMSeBA and Se-Met) resulted in higher GSH-Px activity and mRNA abundance of GPX3 with decreased SOD and ROS activities compared with SS in bovine mammary epithelial cells. However, HMSeBA and Se-Met have similar effects on bovine mammary epithelial cells. Gong and Xiao, [161] have shown a positive effect of the inclusion of Se yeast in the diets of dairy cows as increased plasma Se content and antioxidant status while reduced oxidative stress during early lactation. Improvement in blood parameters (RBC, WBC, and hemoglobin) has also been observed in response to the supplementation of HMSeBA in early lactating cows. However, neutrophils, lymphocytes, and monocytes were unaffected [122]. Higher levels of WBC and RBC indicate improved immunity status of animals.

**Table 3** Effects of Se on serum and milk Se levels, antioxidant status, and immunity-related parameters of farm animals

Animal species	Source and dose of Se	Major findings	Reference
Cows	0.30 mg Se/kg of DM as SS or Nano-Se for 30 days	Increased milk Se levels and GSH-Px activities through nano-Se	[153]
Cows	0.1, 0.3, or 0.5 mg Se/kg of DM as HMSeBA for 10 weeks	Higher serum activity of GSH-Px, total antioxidant capacity, and SOD with 0.3 mg Se	[33]
Bovine mammary epithelial cells	100 nM SS, 100 nM Se-Met, and 0.20, 50, 100, and 150 nM HMSeBA	100 nM of Se-Met and HMSeBA was comparable in terms of alleviation of oxidative stress	[154]
Pregnant dairy heifers and their calves after parturition	HMSeBA and SS at 2.74 mg of Se/heifer per day	Both HMSeBA and SS showed higher GSH-Px activity in heifers as compared with the control group; however, the plasma Se of calves was higher in HMSeBA group	[98]
Sheep	0.4 mg Se/kg DM of SS and Se yeast for 90 days	Increased GSH-Px activity and Se level in blood and tissue in result of Se yeast	[80]
Dairy cows	0.3 and 0.5 mg/kg DM of coated SS and Se yeast for 56 days	Comparable plasma and milk Se concentration with 0.3 mg/kg DM in both groups. Coated SS at 0.5 mg/kg DM showed higher plasma and milk Se content than Se yeast	[147]
Dairy cows	0.1, 0.2, and 0.3 ppm for three different organic Se (SY, SM1, SM2) for 34 days	Milk Se content was higher for Se yeast group at 0.3 ppm	[124]
Transition dairy cows	0.50 mg of Se kg/ DM from different source (SS, Se yeast, and Se-Met)	Se concentrations increased in Se yeast and Se-Met group	[105]
Dairy cows	0.1, 0.2 and 0.3 mg Se/kg DM coated Se and 0.3 mg/kg as SS for 110 days	Increased milk yield, fat and protein contents as a result of 0.2 and 0.3 mg coated Se supplementation	[125]
Transition ewes	0.3 mg/kg DM SS and Se yeast for 4 months	Increased blood Se levels during pregnancy and lactation and triiodothyronine in response to Se supplementation	[155]
Dairy goats	0.7 mg/day SS and 0.6 mg/day Se yeast for 180 days	Increased milk, fat and protein yield while decreased SCC in response to Se yeast	[156]
Simulated heat stress sheep	0.3 mg/kg Se yeast	Increased plasma GPSx by 10.62%, however, tri-iodothyronine, thyroxine, glutamic oxaloacetic transaminase were unaffected	[157]
Goat	0.3 mg/kg diet Se yeast for 8 weeks	Higher blood Se and GSH-Px activity and increased weight of colon and colonic mucosa	[158]
Pregnant dairy cows	0.3 and 0.4 mg/kg DM from 8 months of pregnancy to parturition	Higher serum progesterone concentration and reduced serum cortisol levels	[126]
Lambs	0.5, 1.5 or 4.5 ppm Se yeast for 90 days	Increased <i>Peste des petits ruminants</i> antibody titers and hepatic total antioxidant capacity with 1.5 or 4.5 ppm	[159]
Transition dairy cows	Se biofortified hay at 1 kg/100 kg of BW for 54 days	Greater Se level in blood and GSH-Px activity, increased Se content in colostrum but not in milk	[160]
Transition dairy cows	0.3 mg/kg DM Se yeast for 4 weeks before parturition	Increased plasma Se status, GSH-Px activities, superoxide dismutase and catalase, and the total antioxidant capacity	[161]
Periparturient cows	Intramuscular injection 0.5 of SS/mL and 50 mg of tocopherol acetate/mL in a single dose of 30 mL	Better lysozyme, gamma-glutamyl transferase activity, and IgG concentration in Se suckling calves	[95]
Pregnant ewes	0.150 and 0.300 mg/kg and 0.450 mg/kg Se yeast for 57 days prepartum and 7 days postpartum	Increased Ig concentration in placenta, serum, and colostrum in ewes and lambs	[162]
Ewes	0.25 mg Se/kg DM SS, 0.27 mg Se/kg DM Se product having 29% SS and 71% amorphous elemental	Increased plasma Se concentration and GSH-Px activity regardless of the Se source	[163]
Lambs	Nano-Se and SS for 63 days	Similar GSH-Px content in both sources of Se	[139]
Sheep	Se yeast at 0.2, 0.4, and 0.8 mg Se/kg DM during late gestation and early lactation	Increased antioxidant capacity at an optimum level of 0.4 mg/kg DM	[138]
Lambs	SS and nano-Se at 0.055 mg/kg BW compared with control without additionally Se for 90 days	Se concentrations in blood, erythrocytes, and platelets and GSH-Px activity was increased and comparable in both Se group than control	[164]
Pregnant goats	Se bolus at 0.25 mg/day for 4 weeks before parturition	Increased serum Se, T <sub>3</sub> , and GSH-Px levels in kids	[142]
Pregnant goats	SS, Se-Met, and nano-Se at 0.6 mg Se/head/day for 4 weeks before parturition	Serum Se level was higher with nano-Se than Se-Met in goats; however, Se transfer efficacy of placenta and colostrum into kid was higher for Se-Met	[165]
Dairy sheep	Diphenyl diselenide as organoselenium as five doses 3 µmol/kg	Increased antioxidant and anti-inflammatory responses; improved milk fat content and reduced oxidant levels in milk	[166]
Pregnant goats	0.5, 2.0, and 4.0 mg of Se/kg DM Se yeast for late pregnancy and early lactation	Increased RBC, hemoglobin and hematocrit value of kids, decreased WBC, lymphocyte, and monocyte percentages	[66]

GSH-Px glutathione peroxidases, HMSeBA hydroxy selenomethionine, SS sodium selenite, DM dry matter

Many studies reported significant effects of Se supplementation on the immune system of calves [96]. Dietary supplementation of SS and organic Se increased the levels of serum immunoglobulins (Ig) and interleukin (IL)-1 in dairy cows [32]. However, dietary Se sources have shown no effects on the neutrophil function of cows, serum immunoglobulins (IgM and IgG) of growing heifers, and serum IL-1 and IL-2 contents in sheep [54, 55, 172]. These studies provided convincing evidence that dietary supplementation can potentially modulate an immune response at various physiological stages in different animals.

### Effect on Reproductive Physiology

Reproductive performance is one of the key determinants of livestock profitability and is significantly affected by dietary trace minerals. Most of the reproductive disorders such as retained placenta, metritis, ovarian cysts, embryonic death during the first month of gestation, and malfunction of reproductive organs are generally caused by microbial infections or metabolic disturbances. The metabolic disorders can be effectively improved by adequately meeting requirements of essential nutrients especially trace minerals in animal diets [173, 174]. The role of Se in animal health is essentially based on maintaining normal physiological functions mediated by Se-Cys containing proteins that effectively constitute the body's antioxidant defense [175–177]. Oxidative stress adversely affects the cellular and tissue redox system leading to poor reproductive functions. Studies have shown that alleviation of oxidative stress through improving the antioxidant system directly improves reproductive physiology in different farm animals [23, 24].

Dietary supplementation of Se in dairy animals has been shown to exhibit variable effects on reproduction (Table 4). However, many studies have provided convincing evidence that stated insufficient Se intake can predispose cows and calves to subclinical diseases, resulting in poor animal performance [11]. Moreover, dietary supplementation of Se can decrease infertility ratio, reduce the incidence of early embryonic mortality, endometritis, and ovarian cysts during the postpartum period [15, 106]. The decrease in the incidence of infertility in response to Se supplementation may be attributed to the reduction of embryonic death during the first month of gestation. Notably, GPx-1 increases in granulosa cells as a consequence of enhanced expression of selenoproteins in large healthy follicles [186]. Se supplementation can improve the success rate to the first service in Se-deficient dairy cows [187]. Moreover, nano-Se has shown an effective potential to promote the development of secondary follicles [188]. Besides, Se can also decrease the incidence of metritis and ovarian cysts during the postpartum period [189]. Studies have reported a substantial decrease in the frequency of retained placenta in dairy cows supplemented with Se [26]. Besides females, deficiency of Se has also been associated with male infertility together with adverse effects on testosterone and spermatozoa synthesis [190]. Furthermore, the morphology of testes, as well as scrotal length and circumference, was improved as a result of Se supplementation [185]. Recently, Lizarraga et al. [184] reported that the treatment of cumulus-oocyte complexes with Se increased cumulus cell viability and hatching rate in cattle. These studies provide practical insights into the potential role of Se in male and female reproductive health and fertility ratio. It is revealed that optimum dietary Se is required to ensure proper reproductive

**Table 4** Effects of Se on reproduction-related parameters of cattle

Animal species	Source and dose of Se	Major findings	Reference
Male lambs	Capsule of SS (0.5 mg /kg) given for 90 days	Improved serum testosterone and globulin levels	[178]
Synchronized ewes	Intramuscular injection (5 mL) ESE (0.5 mg/mL SS and 50 IU vitamin E once every 2 weeks	Improved antioxidant and progesterone status	[179]
Estrus-synchronized ewes	Injection of vitamin E 13.6 mg/kg BW of plus Se 0.045 mg/kg BW	Decreased pregnancy losses from 44.8 to 24.3% and increased pregnancy rate	[180]
Goat kids infected with <i>Eimeria</i> spp.	Intraruminal bolus containing 90 mg Se	Reduced oocysts number and coccidiosis	[181]
Rams	0.3 mg/kg Se yeast for 120 days	No effect on scrotal circumference and testosterone concentrations	[182]
Lambs	0.1 mg/kg DM SS and Se yeast for 5 months	Increased weight gain, testes diameters, and testosterone in blood with Se yeast	[183]
<i>In vitro</i> oocyte maturation	0, 10, 50, and 100 ng/ml Se	Increased hatching rate by 10 ng/mL Se	[184]
Rams	SS 0.1 ppm/kg DM	Increased scrotal circumference and scrotal length	[185]

SS sodium selenite

functions and reduce the incidence of calving-related disorders in dairy animals.

### Effect on Udder Health

Somatic cell count is considered as a primary indicator of udder health, mastitis, and milk quality in the dairy herd. The milk somatic cells usually constitute leukocytes and mammary epithelial cells [191]. The SSC results during inflammatory response and damage to mammary gland epithelium during mastitis as an immune response to mastitis-causing pathogens consequently leading to a decrease in milk synthesis [192, 193]. The role of Se in the health of dairy cows has been clearly demonstrated during the incidence of mastitis. Many studies conducted during the last two decades have reported a positive association of Se deficiency in dairy cows with a poor immune response (revealed by intracellular neutrophils), higher milk SCC, and lower resistance to clinical and subclinical mastitis during early lactation [108]. In this context, it is suggested that Se deficiency can reduce GPx1 activity, cause lower normal bactericidal capacity of bovine neutrophils, and inhibit lymphocyte (leucocytes in the udder) proliferation leading to the poor immune response in bovines [194]. Dietary supplementation of Se yeast in dairy goats has been shown to reduce the SSC while increasing  $\alpha$ S2-casein and batenecin 7.5 in milk SCC [156]. However, no expression of batenecin 5,  $\beta$ 2-defensin, hepcidin, chemokine 4, tumor necrosis factor  $\alpha$ , toll-like receptor 2, cathelicidin-7, and cathelicidin-6 genes was detected in somatic cells.

Stress periods like the post-partum period following parturition result in depletion of antioxidant enzymes leading to compromised immune status owing to the downregulation of mRNA expression of genes related to antioxidant defense mechanisms. This immunosuppression makes the animal more susceptible to oxidative stress and infections [195, 196]. The Se deficiency might mediate a slow influx of polymorphonuclear cells into affected quarters or decrease the ability to kill pathogens causing mastitis [191]. However, optimum Se induces a high production of chemotoxins by macrophages stimulated with opsonized *Staphylococcus aureus* to mediate infection [108].

The milk SCC and the incidence of clinical mastitis were significantly decreased in response to dietary Se supplementation at 8 weeks of lactation in dairy cows [106, 108, 109]. An intramammary infection (IMI) is common in high-producing dairy cows. An udder quarter is considered to have an IMI at calving when it harbors  $\geq 1$  CFU/0.05 mL (equivalent to  $\geq 20$  CFU/mL) of a pathogen like *Staphylococci* [197]. *Staphylococci* species, particularly *Staphylococcus aureus*, are the major etiological agents of ruminant IMI. The *Staphylococcus aureus* with coagulase negative species (CNS) is the most frequent isolate from subclinical and clinical cases of IMI. Studies have reported that analyses of the

quarter samples confirmed coagulase positive species, CNS, bacteria *Streptococcus uberis*, and *Streptococcus agalactiae*, which are most often associated with the incidence of sub-acute and acute mastitis. However, IMI due to non-aureus *staphylococci* has shown slight elevation in milk SCC after calving, which did not exhibit any adverse effects on subsequent milk production [198]. Non-aureus *staphylococci* are a heterogeneous group having more than 50 species and subspecies [199]. In dairy herds, clinical IMI may have an incidence at a rate of lower than 5%; however, it can go up to 30–50% in small herds, causing mortality (gangrenous mastitis) or culling of  $\geq 70\%$  of the herd [108]. Recently Wang et al. [169] reported that serum Se level was negatively correlated with milk SCC in dairy cattle. In addition, Se has also shown cytoprotective functions as Se-Met attenuated the extended spectrum of  $\beta$ -lactamase *E. coli*-induced inflammation through activated selenoprotein S-mediated TLR4/NF- $\kappa$ B signaling pathway in bovine mammary epithelial cell and macrophages [200]. However, the mechanism of inhibition of NF- $\kappa$ B expression due to Se-Met is unclear and needs further investigations. The putative role of Se in inflammatory signaling pathways highlights its potential beneficial effects in addition to the antioxidant role, particularly in IMI and udder immune status. Therefore, it is essentially required to manage optimum Se status in dairy herds to sustain the milk performance while ensuring better udder health and lower SCC.

### Future Prospects of Nano-Se in Dairy Animals

The transfer of inorganic dietary Se into milk is in a very minute quantity due to its poor bioavailability. Therefore, we need to use better bioavailable Se sources to increase milk Se content to address daily Se requirements of humans [201, 202]. Although organic sources of Se (Se yeast, Se-Met, and HMSeBA) are considered as efficient bioavailable sources compared with inorganic Se, nowadays, nano-Se is getting more attention due to its multiple health benefits compared with inorganic and organic Se sources for use in dairy animals [203]. The comparative advantage and efficacy of nanoparticles stem from their smaller particle size and larger surface area, enhanced mucosal permeability, and higher intestinal absorption as a result of nano-emulsion formation. In addition to enhanced bioavailability, nano-Se has also reduced toxicity and lower antagonism with other minerals compared with other sources of Se [204]. Moreover, higher bioavailability and better utilization of nano-Se shows a desirable effect on body metabolism while reducing their excretion in the environment [205].

The inclusion of nano-Se in sheep diet has been shown to improve the total VFA and propionate concentration while reducing ruminal pH,  $\text{NH}_3$  nitrogen, and acetate to propionate ratio [130]. Dietary nano-Se has been shown to increase the HDL concentration (37.33 vs 30.37 mg/dL), while decreasing LDL

(25.53 vs 32.27 mg/dL) in lambs. Additionally, the concentrations of T4 (1.59 vs 1.23 nmol/L) and GPx (447.39 vs 239.24 kat/L $\mu$ ) were also increased [206]. Recently, dietary nano-Se enhanced the antioxidant status in dairy cows by elevating plasma Se and GSH-Px activity together with stimulation of gene expression in the mammary gland of cows compared with SS. The total milk Se concentration and mammary gland mRNA expression levels of GSH-Px 1, 2, and 4; thioredoxin reductase 2 and 3; and selenoproteins W, T, K, and F were also improved with nano-Se [153]. However, milk yield and composition were similar in both groups (SS and nano-Se).

Oral treatment with nano-Se restored plasma Se and serum antioxidant indices in affected deer (*P. picticaudata*) after treating orally with nano-Se [207]. Oral nano-Se also has been shown to promote growth rate and also in thiobarbituric acid reactive substances, serum Se, copper and zinc levels in neonatal (1 month) lambs [140]. Recently, Shahin et al. [208] reported a positive effect of the inclusion of Se nanoparticles to semen extender for improving the cryotolerance of camel epididymal spermatozoa. They reported that Se nanoparticles could improve the progressive motility, sperm membrane integrity, and vitality and decrease the apoptosis of sperm when frozen and thawed. This positive effect may be a consequence of nanosize leading to increased bioavailability and subsequently reducing undesired liberation of toxic substances (particularly ROS). Nano-Se has also shown potential effects on cryopreservation of sperm, semen purification, and semen preservation processes [209]. Recently, Khalil et al. [210] reported that nano-Se (10  $\mu$ g/mL) added in semen extender not only improved post-thaw sperm quality of bull, but also enhanced the *in vivo* fertility rate by reducing apoptosis, lipid peroxidation and sperm damage during cryopreservation. Similarly, nano-Se at 0.5 and 1  $\mu$ g/mL concentrations in extender exhibited positive effects on motility, acrosome protection, and preservation of sperm membrane integrity [211]. However, there is a need to investigate Se concentrations, combinations of various novel cryoprotectants, and validation of post-thaw sperm fertility [212]. Owing to higher bioavailability and enhanced surface area, nano-Se has most promising future applications to harvest benefits from better antioxidant and immune response in dairy animals. Further investigations are required to explore optimum levels of nano-Se for dietary supplementation at different physiological stages for different dairy species. Moreover, further research work is required to elucidate the putative mechanism of action of nanoparticles of Se particularly regarding modulation of different signaling pathways.

## Future Implications

Based on our findings, we recommend Se at 0.3–0.5 mg/kg DM (300–500  $\mu$ g/kg DM) of the diet in dairy cattle. The exact

dose of Se supplementation in dairy animals depends on the physiological stage, Se status of animals, type and content of Se, and mode of administration. Dietary supplementation of Se has been shown to improve the ruminal VFA concentration, nutrients digestion, and utilization. Selenoproteins, not only function as antioxidant enzymes, but also influence thyroid hormone metabolism, redox signaling, and regulation of immune responses. Organic and nano-Se had exhibited more bioavailability than inorganic Se sources. Organic Se supplementation in the dairy animal's diets has shown to increase the whole blood and milk Se contents of dairy cows. Nano-Se is less toxic and more bioavailable and possesses less antagonism with other trace elements in the GI tract. However, nano-Se has shown more promising effects regarding the enrichment of milk and meat Se contents, subsequently leading to enhanced antioxidant status and improved shelf life. Besides, it also opens a horizon for the development of a variety of functional foods for humans with effective health-promoting potential. However, further investigations are warranted to explore the optimum level of supplementation of nano-Se, and its direct comparisons are required at equitable intakes of organic and inorganic Se sources in dairy animals.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

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