Aceh Journal of Animal Science

Journal homepage: www.jurnal.unsyiah.ac.id/AJAS

The effect of β-carotene supplementation above requirement on the production and reproduction performance of female sheep and goats - A mini review

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ARTICEL INFO

Keywords:
Beta-carotene
Small ruminants
Antioxidants
Oxidative stress

Received: 22 June 2023
Accepted: 1 June 2024

DOI: 10.13170/ajas.9.2.32734

ABSTRACT

The high rate of metabolic activity during breeding, pregnancy, parturition and lactation may lead to oxidative stress in sheep and goats. Antioxidant supplementation is proposed as a therapy for encountering resultant stress. In animals, β-carotene functions mainly as pro-vitamin A and as a scavenger of free radicals, especially against singlet-state oxygen. This raises the question of whether supplementing β-carotene as an antioxidant above the vitamin A requirement is beneficial. While a number of studies have been conducted on the effect of β-carotene supplementation as a tool to improve the production and reproduction performance of female goats and sheep, the findings are inconsistent. Some of the main reasons for this inconsistency could be attributed to the variation in the amount of β-carotene supplemented, the amount of β-carotene in the animal diet and the difference in the animal requirement for β-carotene. The objective of this review was to determine the effects of β-carotene supplementation on the production and reproductive performance of female sheep and goats fed on a diet deficient or not deficient in β-carotene. Data were extracted from peer-reviewed articles that were searched in the Web of Science, Google Scholar and Scopus databases. Thirteen peer-reviewed published articles were found on the subject under review. We estimated the animal requirement for β-carotene, the amount of β-carotene provided to the animal in the diet and the amount of β-carotene supplementation used in each study. These estimations were made to indicate whether the diet fulfilled the animal's requirement for β-carotene or not. The review revealed that β-carotene supplementation enhances the production and reproduction performance of the sheep when fed on a carotene-deficient diet. Additionally, β-carotene supplementation may increase the levels of some hormones such as progesterone in sheep and goats when fed on a diet that fulfils their requirements of β-carotene. However, the supplementation of β-carotene above the requirements seems to not affect the production and reproduction parameters such as body weight, milk production, estrus parameters, conception rate, pregnancy rate, and litter size. In conclusion, while β-carotene supplementation is essential for female sheep and goats fed β-carotene-deficient diets to attain optimal production and reproductive performance, supplementing β-carotene above the requirements does not appear to provide any further benefits to their overall performance.

Introduction

There is some evidence that key physiological events such as breeding, pregnancy, and lactation may lead to oxidative stress in ruminants, including cows (Drackley, 1999; Castillo *et al.*, 2005), goats (Di Trana *et al.*, 2006; Celi *et al.*, 2008; Jozwik *et al.*, 2010; Zobel *et al.*, 2015) and sheep (Kamiloğlu *et al.*, 2006; Ognik *et al.*, 2015; Lotfollahzadeh *et al.*, 2016). Oxidative stress occurs when reactive oxygen species (ROS) exceed the body's antioxidant capacity, leading to damage to cellular components like DNA, protein, and lipids (Sies, 1997, Fernando *et al.*, 2024). Therefore, it is thought that oxidative stress may result in impairing fertility and reproductive outcomes (Agarwal *et al.*, 2012; Stier *et al.*, 2012, Rehman and Azhar, 2024).

Antioxidant supplementation is proposed as a therapy for oxidative stress (Forman and Zhang, 2021). Beta-carotene functions as a pro-vitamin A source (Nagarajan *et al.*, 2017) but also as an

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Printed ISSN 2502-9568; Electronic ISSN 2622-8734
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antioxidant by scavenging singlet oxygen (Stahl and Sies, 2005). Beta-carotene scavenges peroxyl radicals in lipid compartments like cell membranes (Paiva and Russell, 1999; Niki *et al*., 1995; Noguchi *et al*., 2023).

Animals cannot synthesize carotenoids and obtain them from their diet (Desmarchelier and Borel, 2017). While a number of studies have been published on the effect of β-carotene supplementation as a tool to improve the production and reproduction performance of female goats and sheep, the findings are inconsistent. Some authors reported a positive impact for β-carotene supplementations (Peirce, 1954; Salem *et al*., 2015), while others reported no effect on production and reproduction performance (Brozos *et al*., 2007; Meza-Herrera *et al*., 2011; Köse *et al*., 2013; Meza-Herrera *et al*., 2014; Gore, 2016; Meza-Herrera *et al*., 2017). Such inconsistency, when usually reported is contributed to the variation in the amount of β-carotene supplemented, the amount of β-carotene in the animal diet and the difference in the animal requirement for β-carotene. Thus, for the reader to generate a definite conclusion we reviewed the literature on the effect of β-carotene supplementation on the production and reproduction performance of female sheep and goats considering these three factors. The objective of this study was to determine the effect of β-carotene supplementation on the production and reproduction performance of female sheep and goats fed on a diet deficient or not deficient in β-carotene.

Materials and Methods

Peer-reviewed articles for the subject under investigation were searched in "Web of Science", "Scopus" and "Google Scholar" databases. The full search strategy employed for Google Scholar was "intitle:carotene*space*intitle:sheep|goat|goats|ewe|ewes|does|doe|lamb|lambs|kid|kids" while for Web of Science and Scopus, the following search string was used: (ABS(carotene) AND ABS(sheep OR goat OR ewe OR doe OR lamb OR kid)). There was no time range or limitation on the publication date, and the last search was on April 11, 2022.

The online research resulted in 1945 published documents. Out of which thirteen peer-reviewed published articles were found relevant to the subject under review. We estimated the animal requirement for β-carotene, the amount of β-carotene provided to the animal in the diet and the amount of β-carotene supplementation used in each article. The requirement was calculated according to NRC (2007) as µg β-carotene per kg body weight per day (µg/kg BW/d). In case not mentioned in the relevant article, the amount of β-carotene provided to the animal in the basic diet was estimated (µg/kg BW/d) from the primary sources of β-carotene in that diet. The estimation was done to indicate whether the diet fulfils the animal requirement of β-carotene or not. In studies number six to thirteen (Table 1), the percentage of the different components in the diet was not mentioned. However, the diet was based on alfalfa hay, which indicates that alfalfa hay composes at least 50% of the diet and upon that, the calculation was done. The levels of β-carotene supplementation (µg/kg BW/d) were calculated by dividing the daily supplementation of β-carotene (µg) by the animal weight (kg).

Oxidative stress

Oxidants such as reactive oxygen species (ROS) are involved in enzymatic reactions, cell energy production, signal transduction, gene expression, and the antimicrobial action of neutrophils and macrophages (Bayr, 2005; Valko *et al*. 2007; Forman and Zhang, 2021). Nevertheless, when the oxidants exceed the antioxidant capacity of the body, ROS can damage DNA, protein, lipid and cell components as well as alter the reduction-oxidation state, and interfere with metabolic processes (Miller *et al*., 1993; Ames *et al*., 1993; Bayr, 2005; Juan *et al*., 2021). The oxidants exceed the antioxidants during pathophysiological conditions (Rahal *et al*., 2014). However, there is some evidence that physiological stages such as breeding, pregnancy, parturition and lactation may lead to oxidative stress in cows (Drackley, 1999; Castillo *et al*., 2005), goats (Di Trana *et al*., 2006; Celi *et al*., 2008; Jozwik *et al*., 2010; Zobel *et al*., 2015) and sheep (Kamiloğlu *et al*., 2006, Ognik *et al*., 2015; Lotfollahzadeh *et al*., 2016). Oxidative stress reduces litter size (Stier *et al*., 2012), leads to granulosa cell apoptosis (Yang *et al*., 2017), endometriosis, polycystic ovary syndrome, unexplained infertility, spontaneous abortion, recurrent pregnancy loss and preeclampsia (Agarwal *et al*., 2012).

Oxidants can add oxygen, remove hydrogen or an electron from the target molecule, leaving an unpaired electron in the molecule's outer orbit and thus making it unstable (Lykkesfeldt and Svendsen, 2007). Antioxidants are the only substances that can delay or inhibit the process of oxidation, e.g. by donating electrons to the oxidants (Agena *et al*., 2023). Thus, antioxidant supplementation can prevent ROS-mediated damage (Bayr, 2005), optimize animal performance and maintain proper oxidant/antioxidant balance (Miller *et al*., 1993; Celi, 2011). Antioxidant supplementation can involve enzymes and low molecular mass substances such as tocopherols and carotenes in the lipid phase and ascorbate, glutathione and others in the aqueous phase (Sies, 1997; Sies *et al*., 2017).

Beta-carotene

Beta-carotene functions

Beta-carotene is a red-orange pigment and one of a large group called carotenoids (Smith, 1998). Carotenoids with one or two beta-ionone rings at the end of their structure are called provitamin A carotenoids such as β-carotene, which has two rings (Nagarajan *et al.*, 2017). In animals, β-carotene functions mainly as pro-vitamin A (Smith, 1998; Nagarajan *et al.*, 2017) and as a scavenger of free radicals, especially against singlet-state oxygen (Stahl and Sies, 2005). While animals can obtain vitamin A as retinoids or in the form of provitamin A carotenoids such as β-carotene, using β-carotene as a source of vitamin A is considered safer than retinoids. This is because, under the condition of vitamin A adequacy, the retinoic acid suppresses the enzyme (β-carotene oxygenase) that converts β-carotene into vitamin A, in the intestinal mucosa, liver, and corpus luteum (Nagarajan *et al.*, 2017; Combs Jr and McClung, 2017). The importance of β-carotene as a source of vitamin A in animal species is reviewed elsewhere by Green and Fascetti (2016). Beta-carotene scavenges peroxyl radicals and further decays to generate non-radical products and may terminate radical reactions by binding to the attacking free radicals (Paiva and Russell, 1999; Noguchi *et al.*, 2023). Beta-carotene is lipophilic and scavenges radicals within the lipophilic compartment such as the cell membrane even more effective than vitamin E (Niki *et al.*, 1995; Singh and Sambyal, 2022). However, some authors consider the β-carotene's effects to come from its impact on biochemical systems and not necessarily from its antioxidant properties (Pryor *et al.*, 2000). They argue that beta-carotene does not have a system that can donate a hydrogen atom or an electron to stabilize the oxidants. For example, both vitamins E and C have a hydroxyl group that is attached to an aromatic system, while beta-carotene has only a hydrocarbon chain without any functional group (Pryor *et al.*, 2000; Ribeiro *et al.*, 2018).

Beta-carotene requirement and toxicity

Animals are unable to synthesise carotenoids and obtain them from their diet (Kopsell and Kopsell, 2010; Desmarchelier and Borel, 2017). According to the National Research Council (NRC, 2007), the requirements for vitamin A in goats and sheep during breeding and early gestation are equivalent to 157 µg of β-carotene per kilogram of body weight per day. These requirements increase to 227.5 µg of β-carotene/kg BW/day during late gestation and further to 267.5 µg of β-carotene/kg BW/day during lactation. The subtropical grasses meet the requirements of grazing livestock for β-carotene except for a few months throughout the year (Arizmendi-Maldonado *et al.*, 2003). To our knowledge, there is no study on the toxicity of β-carotene in ruminants. Nevertheless, the treatment at high doses (approximately 180 mg of β-carotene/day) had no side effects in humans (Bendich, 2001), except for hypercarotenemia in some subjects (Diplock, 1995). Supplementation of experimental animals with about 17 times their requirements of β-carotene (Fiorelli *et al.*, 2014) and up to 1000 mg/day of β-carotene per kg body weight showed no signs of toxicity (Woutersen *et al.*, 1999). However, at the cellular level, β-carotene at high concentrations acts as a prooxidant and may lead to the neoplastic transformation of healthy cells exposed to oxidative stress (Palozza *et al.*, 2001). Because of the oxidative attack, carotenoid breakdown into highly reactive aldehydes and epoxides that inhibit the respiration of the mitochondria, reduce protein sulfhydryl content, decrease GSH levels and redox state, and lead to the accumulation of malondialdehyde (Siems *et al.*, 2009; Ribeiro *et al.*, 2018).

The effect of β-carotene supplementation on the production and reproduction performance of sheep and goats fed on a diet deficient or not deficient in β-carotene

Peirce (1954) conducted two experiments to examine the effect of feeding a β-carotene deficient diet on the performance of sheep ewes. In the first experiment, the ewes fed on a ß-carotene deficient diet (7-17 µg/kg BW/day) before and during the mating period. Subsequently, during the gestation period, the sheep received diets with different levels of ß-carotene (50, 100 and 150 µg/kg BW/day). According to the NRC (2007), those diets are ß-carotene deficient (Table 1). The study reported cases of night blindness, loss of appetite and some instances where ewes either died or became severely weakened when fed these β-carotene deficient diets. In the second experiment (Peirce, 1954) the sheep fed on diets with different levels of ß-carotene (≈7, 25, 50, 75 and 100 µg/kg BW/day) before and during mating and gestation periods. The study reported lambing performance for each diet group at least during two reproductive cycles. Survival rates of the lambs calculated from the study for the different diets were 50, 48, 65, 66.7 and 62.2 % respectively during the first week of lambs' age (Table 2). Although the diets used in this second experiment are considered β-carotene deficient the results appear to indicate higher survival rates for the lambs as the level of β-carotene supplementation increases. Salem *et al*. (2015) reported that injection of lambs with 100 µg β-carotene/kg BW twice per week increases estrus cases and estradiol-17β concentrations at puberty and post-puberty. No green forages were offered, which indicates that the diet did not fulfil the lamb's requirement of β-carotene. From the above, it seems that β-carotene supplementation enhances the production and reproduction performance of sheep fed on a carotene-deficient diet.

Brozos *et al.* (2007) found that supplementation of ewes with 1644 µg β-carotene/kg BW/day did not affect their body weight, luteinizing hormone (LH) concentration and milk yield when fed on diet fulfils their requirements of vitamin A and β-carotene (Table 1). Köse *et al.* (2013) reported that injection of ewes with 1000 µg β-carotene/kg BW/day on the day of sponge withdrawal did not affect their estrus response, pregnancy rate, lambing rate and litter size. However, no details were given regarding the diet of the ewes. Moreover, Gore (2016) supplemented goats with 2000 µg β-carotene/kg BW/day for 60 days starting 28 days before estrus synchronization and with 1000 µg β-carotene/kg BW/day from drying off until kidding (≈ 60 days). The diet provided in the study met the goat requirement of β-carotene. Gore's results showed that the supplementation had no impact on milk production, body weight, estrus parameters, oestradiol-17β concentration, number of follicles, size of largest follicle and CL, gestation length, litter size and birth weight of the kids. However, the supplementation increased plasma progesterone (P4) concentration and glutathione peroxidase activity. Additionally, a group of researchers supplemented goats with approximately 1116 µg β-carotene/kg BW/day (Arellano-Rodriguez *et al.*, 2007; Arellano-Rodriguez *et al.*, 2009). The diet used by the researchers fulfilled the goat requirement of β-carotene. The findings

Table 1. Summary of β-carotene (βC) supplementation studies done in sheep and goats.

No	References	Species	Physiological condition during βC supplementation	Diet fulfilment to βC requirement#	βC supplementation (µg/kg BW/day)
1	(Peirce, 1954)	Sheep	Pregnancy	Not fulfilling	25, 50, 75 and 100
2	(Salem *et al.*, 2015)	Sheep	Breeding	Not fulfilling	100 (twice/ week)
3	(Brozos *et al.*, 2007)	Sheep	Lactation	Fulfilling	1644.74
4	(Köse *et al.*, 2013)	Sheep	Breeding	NA	1000
5	(Gore, 2016)	Goats	Breeding &	Fulfilling	2000
			Pregnancy	Fulfilling	1000
6	(Arellano-Rodriguez *et al.*, 2007)	Goats	Breeding	Fulfilling	1116
7	(Arellano-Rodriguez *et al.*, 2009)	Goats	Breeding	Fulfilling	1116
8	(Meza-Herrera *et al.*, 2013a)	Goats	Breeding	Fulfilling	1089
9	(López-Flores *et al.*, 2018)	Goats	Breeding	Fulfilling	1089
10	(Meza-Herrera *et al.*, 2013b)	Goats	Breeding	Fulfilling	1089
11	(Meza-Herrera *et al.*, 2011)	Goats	Prepubertal	Fulfilling	2890
12	(Meza-Herrera *et al.*, 2014)	Goats	Prepubertal	Fulfilling	2890
13	(Meza-Herrera *et al.*, 2017)	Goats	Prepubertal	Fulfilling	2890

The requirements were calculated according to the NRC (2007), NA: not applicable

Table 2. Responses of female sheep and goats to β-carotene supplementation for the studies listed in Table 1.

No	β-carotene supplementation outcomes
1	Lambs survival rates were: 48.3, 65, 66.7 and 62.2 %, respectively.
2	Estrus cases (↑) & oestrogen concentrations (↑)
3	BW (=), LH concentration (=), milk yield (=) & litter size (=).
4	Estrus response (=), pregnancy rate (=), lambing rate (=) & litter size (=).
5	Plasma P4 concentration (↑), GSH-Px activity (↑) milk yield (=), BW (=), estrus parameters (=), oestrogen concentration (=), follicles number (=), largest follicle and corpus luteum size (=), gestation length (=), litter size (=) kids' birthweight (=).
6	BW (=), total follicles (=), corpus luteum number (=), total ovarian activity (=).
7	Serum P4 concentration (↑), BW (=), total follicles number (=), corpus luteum number (=), total ovarian activity (=).
8	Total follicles number (=), corpus luteum number (=), total ovarian activity (=), insulin hormone (=).
9	Total follicles number (=), corpus luteum number (=), total ovarian activity (=), growth hormone (↓) and IGF-1 (=).
10	Ovulation rate (↑) LH concentrations (↓).
11	Goats reaching puberty % (=), BW (=), serum insulin concentration (↑)
12	BW (=), goats reaching puberty % (=).
13	BW (=).

(=): statistically non-significant difference ($p > 0.05$), (↑): statistically significant increase ($p < 0.05$), (↓): statistically significant decrease, BW: bodyweight, P4: progesterone hormone, GSH-Px: glutathione peroxidase, IGF-1: insulin-like growth factors revealed a non-significant increasing trend in total follicles, corpus luteum number, total ovarian activity (Arellano-Rodriguez *et al.*, 2007; Arellano-Rodriguez *et al.*, 2009), and serum progesterone (P4) concentration (Arellano-Rodriguez *et al.*, 2009). Again, when goats were fed a diet fulfilling their requirements and supplemented with approximately 1089 µg β-carotene/kg BW/day, a similar non-significant increasing trend was reported in total follicles number, total corpus luteum number and total ovarian activity (Meza-Herrera *et al.*, 2013a; López-Flores *et al.*, 2018) in addition to a decrease in growth hormone (López-Flores *et al.*, 2018). It is also reported (Meza-Herrera *et al.*, 2011; Meza-Herrera *et al.*, 2014; Meza-Herrera *et al.*, 2017) that supplementation of 2890 µg β-carotene/kg BW/day to goats fed on a diet fulfilling their requirement of β-carotene did not affect their live weight or percentage of goats depicting puberty. Nevertheless, the supplementation increased serum insulin concentration (Meza-Herrera *et al.*, 2011). On the basis there of β-carotene supplementation may increase the levels of some hormones such as progesterone in the blood of sheep and goats fed on diets that fulfil their requirements of β-carotene. However, such supplementation above their β-carotene requirements does not affect their production and reproduction parameters such as body weight, milk production, estrus parameters, conception rate, pregnancy rate, and litter size.

Conclusions:

In conclusion, β-carotene supplementation enhances the production and reproduction performance of female sheep and goats fed on a carotene-deficient diet. Supplemental β-carotene may increase the levels of some hormones such as progesterone in the blood of sheep and goats fed on diets that fulfil their requirements of β-carotene. However, such supplementation above their β-carotene requirements does not significantly affect their production and reproduction parameters such as body weight, milk production, estrus parameters, conception rate, pregnancy rate, and litter size. In future studies, researchers are advised to determine the diet β-carotene content and to plan experiments using either a β-carotene deficient diet or a diet that fulfils the animal requirements of β-carotene.

Conflict of interest

We certify that there is no conflict of interest with any financial, personal, or other relationships with other people or organization related to the material discussed in the manuscript.

Acknowledgment:

The University of Pretoria is acknowledged for the allocation of a PhD research bursary award and postdoctoral fellowship to the first author.

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