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OXIDATIVE STRESS IN ASSOCIATION WITH MANY PATHOPHYSIOLOGICAL CONDITIONS AND THE ROLE OF THE NATURAL ANTIOXIDANTS IN LIVESTOCK: A REVIEW

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Abstract

Oxidative stress is a current subject of research in veterinary medicine and is the basis of many disease states. Understanding the pathophysiology of oxidative stress in ruminants will allow the design of specific antioxidant therapies. The present review aims to examine the role of oxidative stress in pathophysiological conditions and ways to prevent and overcome it by using natural antioxidants. The properties of polyphenols encourage the research and use of various biologically active components as a natural tool to improve animal performance and the quality of animal production. Currently, the development and use of effective antioxidants of natural origin is a priority. They have the ability to protect animals from free radicals and prevent the subsequent oxidative damage that leads to degenerative and pathological processes.

***Key words**: Oxidative stress, antioxidants, polyphenols, livestock.*

INTRODUCTION

In veterinary medicine, oxidative stress is an important issue associated with numerous pathological conditions like enteritis, pneumonia, sepsis, mastitis, acidosis, ketosis, respiratory and joint diseases (Celi, 2011). Studies in cattle are sporadic and largely concerning the conditions of mastitis, pneumonia and retained placenta. In recent years, research has been focused on metabolic diseases in dairy cows in the peripartum period. The methodologies assessing oxidative stress are numerous and rapidly developed and they have their benefits and drawbacks. Namely these differences in the methodologies render the comparisons difficult, even for studies that appear quite similar. A clear understanding of the nature oxidative stress and its causes in ruminants will afford therapeutic antioxidant strategies. The focus should fall on development of biomarkers of oxidative stress to be used in veterinary medicine (Celi, 2011). Oxidants are categorised in reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS are the most common free radicals in organisms (Miller et al., 1993). Reactive oxygen species are by-products of the metabolism of the cell and are playing role in differentiation or proliferation (Halliwell and Gutteridge, 2007). Most importantly, they are essential for the immune response, as ROS take part in the destruction and phagocytosis of pathogens and also in the expression of signalling molecules such as cytokines, eicosanoids and other substances of the immune response; furthermore, ROS have a key role in the inflammatory response (Kvietys and Granger, 2012). Excess amounts of ROS are destructive to cells disturbing their function and hence leading to tissue damage (Sordillo and Aitken, 2009). There are several antioxidant substances in the organism known to counteract excess production and accumulation of ROS. Nevertheless, oxidative stress (OS) can occur in case production of ROS prevails over the neutralizing effect of antioxidants. This can lead to tissue damage resulting from the oxidation of DNA, cellular lipids and proteins. In the transition period a cow has increasing demands (foetal growth, act of calving and early, peak lactation), metabolic stress occurs, which, in broad sense, is a hypermetabolic and catabolic response to the disrupted homeostasis, usually caused by low level of glucose in blood. Hypoglycaemia is a natural condition after parturition because major portion of the glucose undergoes lactose synthesis and the misbalanced insulin response works in favour of mammary glucose utilization (De Koster & Opsomer, 2013). Since the energy needs of increasing galactopoiesis are not sufficiently ensured by the diet in the first weeks postpartum, the own energy reserves of the organism are used. Thus, this state, called negative energy balance (NEB), typically involves considerable lipid mobilization. As a result, energy comes from the non-esterified fatty acids (NEFA) that are released into the blood stream. NEB can be successfully overcome when the concentrations of NEFA are so low that can be metabolized completely for the needs of the milk production (Sordillo & Raphael, 2013). If NEFA levels are higher during excess lipid mobilization, there occurs liver malfunction due to accumulation of triglycerides (fatty liver) and overproduction of ketone bodies, such as β-hydroxybutyrate (BHB). Elevated concentrations of NEFAs in the blood influence the inflammatory responses of the fresh bodies (Sordillo and Raphael, 2013), and when used as an energy source in peripheral tissues, the production of ROS during β-oxidation increases (Schönfeld & Wojtczak, 2008). The additional lipolysis as a result of oxidative stress contributes to higher NEFA levels in the transition period (Sordillo & Raphael, 2013), thereby closing the vicious circle of lipolysis and ROS production. Except being highly associated with metabolic stress, NEFA levels and ROS production are considered diagnostic symptoms for pathological conditions like retained placentas, mastitis, ketosis and fatty liver (Abuelo et al., 2014).

Various endogenous regulatory mechanisms are dependent on external supply of antioxidants to the body. Excessive administration of antioxidants might upset body antioxidant capacity (Rizzo et al., 2013), as low ROS suppress expression of antioxidant enzymes in this way suppressing also Nrf2. Therefore, further studies along these lines could afford useful information to establish the "success control" of exogenous antioxidants. Vitamins and some trace minerals (e.g., selenium), are good against OS counteracting against mastitis and metritis (Spears & Weiss, 2008; Bouwstra et al., 2009; Sordillo & Aitken, 2009), both via antioxidant action and immune response. Vitamin-mineral supplementation requirements have traditionally been used to prevent deficiency-related diseases, as it was shown that hyper supplementation can improve health status and the production quality. Animal health status is complex, and oxidative stress is only a part of the whole issue, which explains the inconsistency of the results of among supplementation trials. Therefore, analytical overview on literature evidences is necessary for the application of antioxidants as supplementation in practice (Abuelo et al., 2014).

In this context, the present review aims to treat the role of oxidative stress in pathophysiological conditions and the ways of its prevention and overcoming via usage of natural antioxidants.

MATERIALS AND METHODS

A profound comprehensive search of scientific literature was conducted in order to study the problem in focus. In the present review was used information from publications obtained on the Internet - exclusively Google Scholar but mostly Research Gate, PubMed, Scopus and Web of Science - as well as journal editions worldwide and also editions in Bulgaria. More specifically, the expertise and achievements with stevia of the team of plant breeders at Agricultural Institute - Shumen and also the research experience and experimental results of our animal breeding team were taken in consideration, as well.

RESULTS AND DISCUSSIONS

Various stress factors, including management (nutrition, weaning, etc.) and environment, affect animal productivity and health at different life stages (Dowarah, 2017). They can lead to an imbalance in the intestinal microbiota and create predisposition to pathogenic infections. In any case, animal health is essential for farm economy. The attention of scientists has been drawn to natural products of plant origin in recent years. Prebiotics are non-digestible but fermentable oligosaccharides that nourish the gut microbiota, stimulating its proliferation (especially bifidobacteria and lactobacilli), with subsequent effects on the welfare of the host, at the same time reducing the number of pathogenic bacteria both in animal and in human experiments (Proceedings of the International Conference on Distributed Multimedia Systems DMS 2012). Its composition is closely connected with the hosts' health status, and alteration can cause not only intestinal problems, but also a great number of metabolic diseases. Hence, the introduction of new prophylactic and therapeutic systems against intestinal dysbiosis is important (Allaw et al., 2020; Lalouckova & Skrivanova, 2021). Studying the antimicrobial activity of different plant extracts is very promising, as they are applicable as an alternative to antimicrobial substances, which are found to induce resistance in the pathogens after long periods of administration (Abdel-Rahman et al., 2015; Lemus-Mondaca et al., 2012). Furthermore, beneficial medicinal plant extracts do not invoke harmful side effects as many antibiotics do (Das et al., 2009).

Oxidative stress in animals is linked to numerous disorders of health, productivity and welfare (Herve et al., 2023). It is expressed in the prevalence of the production of free radicals over the antioxidant function that neutralizes them (Corino & Rossi, 2021). Antioxidant therapy is based on the idea that oxidative stress is linked to a number of diseases. (Sies, 1991a). Oxidants are a normal product of aerobic metabolism, but can be excessively produced in some pathological conditions (Sies, 1997). Oxidative stress is a normal phenomenon in the body, in which ROS are controlled by various enzymes involved in in vivo redox homeostasis. Therefore, pro-oxidants and antioxidants are not balanced in the organism, and this results in oxidative stress. (Rahal et al., 2014). They include enzymatic antioxidants (tocopherols, carotenoids, polyphenols and glutathione) and antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) (Sies, 1986). ROS can seriously damage macromolecules and in turn stimulate more ROS production (Bešlo et al., 2023). Reactive oxygen species are a typical byproduct of oxygen metabolism and are involved in several vital physiological functions, including cell differentiation and phagocytosis. They are byproducts of normal of metabolism of cells and are normally important for many physiological processes – transcription factor activation, protein phosphorylation, cell differentiation, oocyte maturation, apoptosis, steroidogenesis, immunity and resistance against microorganisms. When their concentrations increase in excess, it causes oxidative stress with its negative effects (Goncalves et al., 2010). Reproduction is negatively impacted by oxidative stress (Desai et al., 2009). Mitochondrial damage and the apoptosis caused by ROS damage the structures that take part in reproduction, thus contributing to reduced breeding capacity in dairy cows (Wathes et al., 2013). Therefore, the assessment of blood redox homeostasis contributes to the comprehension of the processes of the metabolic disorders and hence reproductive efficiency, affordinge health and metabolic diagnostics (Castillo et al., 2005; Bernabucci et al., 2005). It is necessary to determine their level as a means of preventing pathological changes. One of the greatest issues in the diagnostics of oxidative stress is the silent clinical symptoms (Nenova et al., 2023).

Many diseases are on the basis of the misbalance between antioxidants and free radicals. This disturbed balance is due to an array of factors, such as the cellular inability to produce antioxidants in adequate amounts, low mineral or vitamin diet, and excess ROS production (Abd, 2010).

In animals, there is a well-defined dependence of the incidence of certain diseases and the control over antioxidant status. Important diseases like pneumonia and enteritis are attributed oxidative stress. Many studies on the topic indicate that numerous researchers view oxidative stress mechanisms as crucial initial occurrences in the development of diseases. In theory, oxidative stress should be successfully treated with antioxidants, but, according to some authors, such a therapy is controversial (Lykkesfeldt & Svendsen, 2006). In 2006, the EU placed a ban on antibiotics and some other substances in view of the harmful residues in end food products. Control over oxidative stress and inflammation is known to have impact productivity. The awareness against pharmaceuticals and some other synthetic substances in food chain safety directed the interest towards phytocompounds. The use of polyphenols as animal supplementation has gained attention in animal husbandry. Polyphenols are essential secondary plant metabolites in plants, taking part in important functions such as growth, pigmentation and resistance against pathogens. As exogenous antioxidants, polyphenols are involved in cellular defence. Therefore, studies on the polyphenol's supplementation on the antioxidant activity in the organism of contribute to animal health reducing the free radicals. The bioactive compounds in polyphenols are beneficial for animal health status. Plants rely on them for growth, development, and reproduction, as well as for protection against pathogens. (Bravo, 1998). The interest in these phytochemicals and especially their association with normal health status is increasing (Lipiński et al., 2017; Abdel-Moneim et al., 2020). For the control over new free radicals' production, antioxidants are vital, polyphenols being the compounds that interact with free radicals. Free radicals lead to oxidative stress and the production of ROS can be reduced by antioxidant added to the diet. In addition, in vivo experiments have demonstrated the benefits of the supplementation of polyphenols, as potentially powerful antioxidants (Sharma et al., 2012; Cadet & Wagner, 2013; Cadet et al., 2017). The content of secondary metabolites and their biological functionality in the plant organism depend on maturity, soil status, water and light availability and other environmental factors (Asfaw, 2022). According to the literature, chemical compounds in the medicinal plants are strongly dependent on range and climate, cultivation, vegetation phase and gene modifications (Miliauskas et al., 2004). Dinev et al. (2021) investigated the antibacterial activity of extracts from different parts of the Stevia plant using the agar well diffusion method described by Velichkova et al. (2018). They found that menthol extracts of flowers and leaves had the highest antimicrobial and antioxidant activity against *S. aureus*. Abdel-Rahman et al. (2015), Mali et al. (2015), Tadhani and Subhash (2006), Debnath (2008) reported a higher activity of leaf extracts. On the other hand, Sunitha et al. (2015) did not find antibacterial activity leaf extracts of stevia against S. aureus, but the stem extracts had such activity, though not high. Nilson et al. (2023) investigated the effect of stevia extract as a substitute for antimicrobial drugs in broiler chickens. They found improved immunological maturity in primary lymphoid organs and a balanced gut microbiota.

For improvement of animal welfare, stress control, mitigation of the need of medication uses and for enhancement of state of foodstuffs of animal origin, the inclusion of polyphenols might be a justified approach in animal nutrition (Bešlo et al., 2023).

Over the last few years, for cancer and cardiovascular prophylaxis are recommended fresh fruits, vegetables or teas rich in natural antioxidants. The protective effects of herbal products are associated with mechanisms of action of several components - enzymes and proteins or molecular-weight compounds such as carotenoids, flavonoids, vitamins, anthocyanins and other phenolic compounds. Phenol compounds can be found in both edible and non-edible plants. Growth and protection against infection are controlled by them (Kefeli & Kutacek, 1977). They have important role in maintaining oxidative and microbial stability (Shalaby & Horwitz, 2015). Although phenolic compounds have special nutritional properties, their antioxidant activity is essential for human health. The importance of antioxidant ingredients in maintaining health and protecting against cardiovascular diseases and cancer (Kris-Etherton et al., 2002; Reboredo-Rodríguez et al., 2018) has also drawn interest of researchers, food manufacturers and consumers as the future trend is towards functional foods with health benefits. Consumers are concerned about the presence of phenols (especially in large amounts) in their diet and they associate them with antioxidant properties. Antioxidants like α-tocopherol and L-ascorbic acid are widely used as they are considered safer with fewer side effects, but they do not possess such a strong functional activity like the synthetic antioxidants butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) - promoters of carcinogenesis (Gülçin, 2007). Therefore, there is a need for safe, economical, highly active

antioxidants of natural origin to compete the synthetic antioxidants. Antioxidant from edible plants show to have little or no toxic side effects, for which they are promoted as supplements (Tadhani et al., 2007).
The compounds with anti-inflammatory, immunomodulatory and antimutagenic properties are over 10,000, and these properties are attributed to their antioxidant capacity (Heim et al., 2002). The benefits from such antioxidants is equally strong to the well-known antioxidants like vitamins E and C. On the other hand, the bioavailability of polyphenols is low and future studies are needed to test their efficacy in livestock (Lipiński et al., 2017). Phenolic compounds, or polyphenols, exist in many plants species and consist of one or more aromatic rings with one or two hydroxyl groups in them. They are classified in three main groups – namely, flavonoids, nonflavonoids, and tannins – functioning in dependence on their chemical structure (Serra et al., 2021). In this connection inflammatory processes should be associated, for the prophylaxis of oxidative stress. Oxidative stress provokes many ephemeral or chronic diseases, e.g. pneumonia (Lauridsen et al., 1999) and sepsis (Basu & Eriksson, 1998) in pigs. It is also observed in weaning piglets (Campbell et al., 2013) because the digestive tract and the whole organism are still immature, leading to lower appetite and growth (Wijtten et al., 2011). The organism of animals exposed to stress (starvation, transport, low and high temperatures) reacts with the release of glucocorticoids (CTC), and hence to increased free radicals and hence to increased oxidation of microfibrillar proteins, leading to suppressed muscle growth and loss of muscle tissue (Ohtsuka et al., 1998; Tanigucha et al., 1999).
It is possible to categorize antioxidants as secondary or processing antioxidants as well as primary or long-term antioxidants. Secondary laminas and hindered phenols are examples of primary antioxidants, while organophosphates and thioesters are examples of secondary antioxidants (Dopico-García et al., 2007). The primary antioxidants are active radical scavengers or hydrogen donors or breakers of chain reaction while secondary are peroxide decomposers.
According to FAO, saturated fatty acids (SFA) in the consumers' diet should provide less than 10% of the calories (FAO/WHO, 2003). Studies have proved limiting of the possibility of cardiovascular and cancer diseases with the consumption of milk delivers the beneficial conjugated linoleic acid (Parodi, 2004). A major policy objective of the World Health Organization (FAO/WHO, 2003) is to stimulate producers to enhance the lipid composition of foods of ruminant origin through farming based on pasture, because of the low consumption of CLA as required for cancer prevention (Dhiman et al., 1999). This feeding strategy is associated with increased peroxidation of fats, expressed in removal of electrons from membrane lipids by free radicals, causing cellular damage (Valko et al., 2006; Gutowski & Kowalczyk, 2013). For meat and dairy quality, it is important to prevent oxidative degradation, which can be achieved by antioxidant added to food. Recently, there has been an interest in replacing synthetic with natural antioxidants for environmental and economic reasons, and most importantly they are considered safer for the consumer (Serra et al., 2021).
There is an increasing interest in the application of plant-based prebiotics in animal nutrition, as they consist of high proportion of polyunsaturated fatty acids (PUFA) in addition to high levels of polyphenols (Chamorro et al., 2015). Such diet can make poultry meat less susceptible to fatty acid oxidation (Rymer & Given, 2010; Aziza et al., 2010). In pigs, the feeding grape pomace characterised by high PUFA (60-64%) and high PUFA/SFA ratio (2.8-3.0) improved growth rate, fatty-acid profile of adipose tissue and meat quality (Brenes et al., 2008; Pascual et al., 2007).
A literature review on the supplementation of polyphenols to animals was performed with the objective to study the changes (metabolism and biotransformation) of polyphenols in the digestive tract of livestock. Analysis was conducted on biological activities as antioxidant and pro-oxidant activities, as well as on the impact of polyphenols on animal development and immune system by modulating the diversity of intestinal microbiota. The results of the addition of polyphenols on animal health and the quality of

food produced are also analysed. Polyphenols are found practically in all plants. It has been confirmed that they are present in their different parts such as leaves, roots, flowers, fruits and seeds, which, in addition to their other properties, protect the plants against various pests and UV radiation (Di Ferdinandoa et al., 2014). Their distribution is different in the different tissues. So, higher levels of polyphenols are found in the outer layers of plants, and the insoluble polyphenolic compounds are in the cellular wall, while the soluble compounds are in the vacuoles (Amrit et al., 2023). Particularly, prolonged burning of the fruits of the plant reduces the polyphenol concentration, especially in high temperatures, which is due to their sensitivity to oxidation. The typical sources of polyphenols that are fed to animals are vegetables, fruits, nuts, legumes and herbs (Scalbert et al., 2002; Duda-Chodak & Tar, 2023). Polyphenols can act as chain breakers or radical scavengers for which reason antioxidant properties are attributed to them (Wink, 1997; Tsao, 2010).

For animal high productivity, the closely related oxidative stress and inflammatory processes should be controlled. Oxidative stress has turned into a significant challenge to farm management as it affects animal growth. It can reduce plasma globulin and hence reduce the immune response in poultry (Abdel-Moneim et al., 2020; Qui & Thu, 2022). A lot of research has been done to find that polyphenols are the safest solution. The finding of the antioxidant activity of polyphenols as a feed supplement has brought progress to improving animal antioxidant status, as they act against cellular damage scavenge free radicals (Rice-Evans, 2001). Understanding of such processes is crucial for determining their potential as bioactive compounds in vivo as well as their role in the prophylaxis of diseases associated with oxidative stress (Chen et al., 2022; Eseberri et al., 2022). The bioabsorption of polyphenols was found to have low bioavailability after high doses intake. A significant challenge associated with their pharmacological application is the low bioavailability, which arises from the interactions of polyphenols during various stages of digestion, absorption, and distribution. These interactions can modify their molecular structure, particularly through interactions with food and enzymes (Rice-Evans et al., 2000). More interest is focused on polyphenols due to their anti-damage and scavenging role (Bešlo et al., 2023).

The connection of diseases in dairy cattle and oxidative stress needs to be viewed on further studies on biomarkers of oxidative stress. Haematological and biochemical factors are essential for establishing biological markers of health status (Tufarelli et al., 2023).

Oxidative stress can be controlled via biomarkers like antioxidants and prooxidants that can be tested in whole blood or plasma. In recent years, significant advancements have been made in understanding the beneficial impact of exercise routines and dietary choices on oxidative stress. Oxidative stress in the body is a continuous process in which oxygen and oxygen-containing molecules - i.e. reactive oxygen species (ROS) - “steal” electrons from proteins, lipids, and nucleic acids, hence making them inactive or malfunctional. Oxidative stress transforms into oxidative damage of cells. Prolonged oxidative damage is linked to chronic conditions, including cancer, diabetes, Alzheimer's disease, and so on. As a consequence of excess of free radicals and ROS and malfunctioning antioxidant defence, oxidative stress results in damaged biological macromolecules and upset metabolism (Trevisan et al., 2001). Oxidative stress occurs when ROS production is faster than their neutralization by antioxidant mechanisms (Sies, 1991b). The incidence of health disorders in cattle are associated with such conditions. It has been noted that cows may experience oxidative stress during pregnancy, potentially resulting in peripartum disorders and metabolic diseases (Bernabucci et al., 2002).

There is a lack of studies regarding the effect of heat stress on oxidative status except the preliminary reports. Harmon et al. (1997) observed a reduction in plasma antioxidant activity in Holstein cows experiencing heat stress during mid-lactation. Trout et al. (1998) found no effect of heat stress on the levels of vitamin E and β-carotene in serum or thiobarbituric acid reactive substances in muscle. Calamari et al. (1999) observed weak diversely affected plasma markers of oxidative status by heat stress in mid-lactation cows.

Currently, there is a lack of studies examining the impact of heat exposure on the oxidative status of dairy cows during transition. We hypothesized that the oxidative status of transition dairy cows is affected by heat stress. There are several biomarkers (antioxidants and prooxidants) of oxidative stress and they can be assessed in plasma and in whole blood (Passi et al., 2001). To test this hypothesis, Bernabucci et al. (2002) analysed the alterations in some markers of oxidative status in plasma as well as in erythrocytes of Holstein cows in the summer and in a thermoneutral season (spring). Heat stress (HS) a serious welfare destroying factor with great economic impact, as it was found to deteriorate milk yield and protein in milk. Recent studies have shown that heat stress is provoking oxidative stress in tissues, as cows subjected to heat were found to have increased ROS concentrations and mitochondrial dysfunction. Oxidative stress induced by heat stress probably leads to diminished milk protein, since it results in higher insulin resistance and apoptosis, being in adverse relation to protein synthesis. Mammary apoptosis directly leads to reduced number of epithelial cells, while insulin resistance is responsible for insulin regulation of mTOR pathways. Strategies involving antioxidant supplementation have been adopted to alleviate OS damage (Guo et al., 2021).

Buffalo milk has good milk properties that allow it to be turned into excellent cheeses, especially mozzarella. The diet is what impacts the properties and quality of buffalo milk; for this reason, Khan et al. (2017) aimed to test the effect of antioxidants supplementation (SOD, Zn and Se) in lactating buffaloes on milk productivity and quality. Their results indicate that feed intake, feeding behaviour and feed efficiency weren't affected, while milk yield and milk coagulation are improved. This research assessed the impact of antioxidant supplementation on the quality of buffalo milk. Antioxidants neutralize free radicals and they should present in foods in sufficient amounts to prevent oxidative stress (Khan et al., 2017). Oxidative stress is expressed in prevalence of free radical production over antioxidant defence which is strongly associated with the immune and inflammatory status. Analysing other studies, Evangelista et al. (2022) discuss that raw buffalo milk is marked with greater antioxidant capacity compared to cow milk in view of the higher concentration of antioxidants – double higher vitamin E, triple higher catalase, triple higher vitamin C, Se, Zn, tyrosine and cysteine. In the study (Khan et al., 2017), adding antioxidants (SOD, Zn and Se) improved daily milk yield. These results are consistent with the findings of Singh et al. (2021) who found that milk production in buffaloes was improved supplementation by antioxidants (Cu, Zn and vitamins A and E) supplementation. Additionally, Tanwar et al. (2019) and Kantwa et al. (2021) chelated mineral mixture was also found to increase milk yield in buffaloes significantly. Other studies have established increased milk yield in dairy cows supplemented with organic mineral mixtures (Kellogg et al., 2004; Riad et al., 2018) and area-specific mineral mixtures (Kumar et al., 2020).

In alignment with other research (Kantwa et al., 2021; Gupta et al., 2017), the higher milk yield in the experimental group (compared to the control) may be attributed to the effect of the supplementation of minerals responsible for stimulating basket cells or udder myoepithelial cells and especially to Zn beneficial effect on udder health (Kellogg et al., 2004). Furthermore, according to Miranda et al. (2009) low concentrations of antioxidants adversely affect oxidative status in the mammary gland, which is associated with a reduced number of epithelial cells. Other authors also found that antioxidants supplementation reduces the number apoptotic epithelial cells (Wang et al., 2021; Evangelista et al., 2022).

Hussain et al. (2023) studied the effect of feeding betaine (Bet) to lactating Nili-Ravi buffaloes on the productivity in the hot and humid climate. The results showed that it improved milk yield ($p < 0.05$) and nutrient conversion regardless of the level of supplementation; however, the composition of the milk remains unaffected. An enhancement in performance, although not statistically significant ($p > 0.05$), was observed at elevated levels of Bet. Superoxide dismutase levels were higher across all three concentrations, while glutathione peroxidase showed a significant increase ($p < 0.05$) at the 0.2% Bet level when compared to the control group. However, no effect was found on malondialdehyde. The supplementation of Bet in the concentrated feed of lactating buffaloes at a level of 0.2% (dry matter basis) is recommended for production and antioxidant improvement in summer season (Hussain et al., 2023).

The results of Gong and Xiao (2018) showed that supplementing cows with Se-yeast during late pregnancy increased Se in plasma, improved antioxidant status, and effectively alleviated oxidative stress observed in early postpartum.

Highly maintained antioxidant status in livestock can have positive effect also on meat quality - vitamin E and lipid peroxidation. There are studies on supplements of plant origin used as alternatives of synthetic antioxidants. In fact, bioactive compounds as natural antioxidants are present in essential oils, natural extracts and plant by-products. There are evaluations concerning product quality, oxidative stability, and shelf life as influenced by natural extracts in pigs, ruminants, and rabbits. The researchers concluded that the herbal supplement effects were different but with some similarity to synthetic vitamin E, hence a natural alternative of it (Tsiplakou et al., 2021). The influence of plant supplements in poultry nutrition was also analysed based on selected literature from the recent 20 years (Righi et al., 2021; Pitino et al., 2021). Plant supplements were found to be a good instrument to reduce oxidative stress in poultry, also improving growth. However, in view of problems with digestibility and gut morphology, the right dosage essential (Corino and Rossi, 2021).

A favourable effect of plant extracts in the diet poultry on sensor characteristics, oxidative stability and fatty-acid profile of meat has been also observed, which allows partial replacement of synthetic antioxidants (Pitino et al., 2021; Pirgozliev et al., 2021; 2022; 2023).

In a study of our team (Nenova et al., 2023), in buffaloes during the breeding season, an increased oxidative stress was found, expressed in a significantly elevated ROS products in the blood serum and decreased activity of SOD, compared to the non-breeding season. The peak activity is observed in non-pregnant buffaloes throughout the summer. MDA levels were not significantly different between seasons, highest concentrations being reported in the buffaloes with established pregnancy during the breeding season. The lowest levels of glutathione (GSH-Px) were recorded in non-pregnant animals during both studied seasons. The values of total nitric oxide and protein carbonyl content were elevated in buffalo during the breeding season, with lowest levels recorded in non-pregnant animals. Fiesel et al. (2014) found that in weanling pigs supplementation with spent hops (source of natural polyphenols) significantly decreases protein and cellulose digestibility. No effect of the supplement was found on the performance, but on the feed conversion ratio increased in the experimental group by 10%.

A supplementation of *Moringa oleifera*, providing quercetin and kaempferol, afforded higher body weight and better feed conversion in 21-days chickens in comparison to the control group (Park et al., 2014). Plant extracts with concentration of 0.2% of *Lonicera japonica, Chelidonium majus* and *Saposhnikovia divaricata* (tannins, flavonoids, phenolic compounds, terpenoids, saponins and essential oils) increased finishing body weight and daily gain in chickens (Viveros et al., 2011; Surai, 2014).

A study of El-Iraqi et al. (2013) on the effect of diet enriched with mint and Ginkgo biloba in chickens under heat stress significantly improved finishing body weight and decreased utilization compared to chickens on individual herbs or vitamin C.

Viveros et al. (2011) observed that the 21-day-old chickens supplemented with grape seed extract (7.2 g/kg diet) had lower live weight in comparisson to the other groups (486 g vs. 553; 557; 542 g). They also had lower utilization of feed when fed grape pomace (60 g/kg) or antibiotic avoparcin (50 mg/kg feed). The feed conversion of pigs with polyphenols in the diet (grape seeds and grape marc) was higher than in the control group (652 vs. 624 g/kg; $p < 0.05$) (Gessner et al., 2013; Chedea et al., 2019). Similar are the results from the research of Nenova and Enchev (2022), where the addition of *Stevia rebaudiana Bertoni* to the compound feed during pregnancy and lactation had a positive effect on the health status of sows, expressed by some basic blood parameters and good health status of the suckling pigs. The inclusion of 20 g/head/day *S. rebaudiana Bertoni* in the compound feed of sows increased the daily growth of their suckling piglets significantly (p≤ 0.05). The study by Lipiński et al. (2015) with broilers showed that adding polyphenols (grape seed and onion) didn't affect growth, percentage of carcass weight loss, chest muscle yield and meat properties.

Flis et al. (2007) found no effect phenolic compounds in oat grains (45% of the diet) on growth of finisher pigs. A rich source of phenolic compounds like the cranberry extract in poultry did not affect body weight and feed utilization (Leusink et al., 2010). Simitzis et al. (2011) also did not find effect of hesperidin and tocopherol acetate on growth and slaughter weight in broilers. Supplementation of grape by-products did not affect performance, while flavonoid-rich herbs had favourable effect, especially under heat stress (Serra et al., 2021). Singh R. et al. (2017) conducted a study showing the beneficial effect of herbal vitamin E-selenium powder on oxidative stress, plasma mineral profile and biochemical parameters in pregnant buffaloes. Several parameters of oxidative stress were investigated - superoxidase dismutase (SOD), lipid peroxidation (LPO) and reduced glutathione (GSH), plasma mineral profile and various haemato-biochemical parameters. The level of LPO in buffalo increased significantly, while the levels of SOD and GSH decreased significantly throughout the period. There was significant decrease in albumin, total plasma protein, and glucose, as well as significant increase in beta hydroxyl butyric acid, plasma urea nitrogen, and nonesterified fatty acids (NEFA) after calving. A therapeutic study found significant reduction in LPO and NEFA and a significantly improved milk fat after supplementation with vitamin E-selenium powder conducted in 12 buffaloes. The conclusion is that LPO, SOD and GSH are reliable oxidative stress indicators in pregnant buffaloes and that the vitamin E-selenium powder ameliorates oxidative stress (Singh et al. 2017). Koujalagi et al. (2018) recommend herbal choline supplement (*1Biocholine) t a dose of 20 g/100 kg body weight/day + herbal liver tonic (*2LivoLiv250) at 10 g/100 kg body weight/day during pregnancy to reduce oxidative stress in cows.

Increased n-3 PUFA in the diet has been established to make fats in animal products more valuable. However, a diet with high PUFA renders the animal production susceptible to lipoperoxidation. Hence, it is recommended to use antioxidants to prevent peroxidation, improve animal healthcare and food safety (Rodríguez et al., 2019). Thus, vitamin E is used in a synthetic form. However, it was established that high doses of vitamin E have pro-oxidant effects. For this reason, for the optimization of the antioxidant defence in case of feeding PUFA-rich diets, it is recommended to use natural antioxidants. Polyphenols are found abundant in various herbs and plant residues and can be used against lipid oxidation. Some studies in poultry, have confirmed that lipoperoxidation can be mitigated by hesperidin plant extracts as a supplement (Qui & Thu, 2022; Simitzis et al., 2011; Shimizu, 2017).

Stevia (*Stevia rebaudiana B.*) is a plant species characterized by a variety of health benefits in humans and animals – antiviral, antiasthmatic, anti-inflammatory, antibacterial, antimalarial, antifungal, gastroprotective, hypoglycaemic, anti-cholesterol and antioxidant (Marcinek & Krejpcio 2016; Zangeneh et al., 2016). An experiment by Shivanna et al. (2012) shows that rats fed stevia had a decrease in blood glucose, ALT and AST and an increase in blood insulin levels. It lowers the concentration of MDA (malondialdehyde) in the liver and improves its antioxidant status. Glucose tolerance and insulin sensitivity are optimized. A study by Pirgozliev et al. (2021) showed that stevia in the diet improved the antioxidant status of liver in broilers by increasing hepatic levels of vitamin E and carotenoid content. Other scientific experiments found that the stevia inclusion to the feed of poultry can improve their antioxidant status (Pirgozliev et al., 2021), lead to a more saturated colour of the yolks and to an increased content of carotenoids in the eggs (Pirgozliev et al., 2022). Lalouckova and Skrivanova (2021) found that *Staphylococcus aureus* presence on the skin is the reason for most bacterial skin infections – from boils to sepsis and mastitis. On the other hand, administration of antibiotics in such cases might provoke resistance of the bacterial strains, even multidrug resistance (Lalouckova & Skrivanova, 2021). The activity of stevia extracts against *Bacillus cereus, Staphylococcus aureus* and *Escherichia coli* was studied by Pól et al. (2007). They found that highest was the antibacterial activity against *S. aureus*. Active compounds such as steviol, glycosides, phenols, tannins, flavonoids, and essential oils are credited with this attribution. (Debnath, 2008; Abou-Arab & Abu-Salem 2010; Lemus-Mondaca et al., 2012; Mali et al., 2015; Abdel- Rahman et al., 2015). Tadhani et al. (2007) found in a DPPH assay that the callus of stevia had higher antioxidant capacity than the leaves. The great amounts of antioxidants in stevia leaves and callus have strong functional activity that can be used against oxidative stress.

The detailed review of Serra et al. (2021) suggests that supplementation of polyphenols in the diet improves meat and milk without affecting animal health. The polyphenols from food are not subjected to significant metabolic transformations, in this way rendering meat (Corrêa et al., 2019; Iqbal et al., 2020) and dairy products (Scislowski et al., 2005; Gladine et al., 2007; Todaro et al., 2017) of higher quality. The 12-day supplementation of 5% dried GP, rich in PUFA, to the diet of pigs resulted in higher n-3 PUFA (especially α-linolenic acid) also in muscle (Habeanu et al., 2015). Polyphenols have been established to take part in the regeneration of tocopherol in the plasma of broiler thanks to its one-electron reduction potential, as well as to act against the oxidation of vitamin E, hence against the oxidation of fats (Muñoz-González et al., 2019).

CONCLUSIONS

In the future, it is essential to design more precise studies feeding polyphenols in parallel to the partial freedom afforded to animals in intensive farming systems to choose their feed – what type and how much quantity (Meier et al., 2012). This will bring animal produce with better quality to the market. Hence, to benefit the healthcare of animals and the foodstuffs for human consumption thereof, the use the functional effects of antioxidants as a unique natural tool is an advanced strategy. Further experimental work with polyphenols supplemented to livestock should be envisaged to support the relatively few proofs for the benefits for animal health. Moreover, to establish the most suitable ratio between polyphenol extracts and plants from which they can be used best, in dependence on the characteristics aimed to be improved, the quality of polyphenol preparations is also essential topic of research, in view of their efficacy of application. For better animal healthcare, lifestyle and food safety, the supplementation of polyphenols can be tested experimentally and in practice with a free-choice approach in feeding.

These properties encourage the research and use of various biologically active components as natural tool to improve animal productivity and the quality of the production thereof. The application of scientifically developed, effective natural antioxidants is a priority nowadays. They are good scavengers of free radicals hence preventing oxidative stress that leads to pathological and degenerative processes.

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