AGRICULTURAL BIOLOGY,
2020, V. 55, № 6, pp. 1107-1125
(SEL'SKOKHOZYAISTVENNAYA BIOLOGIYA)

ISSN 2412-0324 (English ed. Online)
ISSN 0131-6397 (Russian ed. Print)
ISSN 2313-4836 (Russian ed. Online)

UDC 636.4:636.087.7

doi: 10.15389/agrobiology.2020.6.1107eng
doi: 10.15389/agrobiology.2020.6.1107rus

USE OF ANTIOXIDANTS AS ADAPTOGENS FED TO PIGS (*Sus scrofa domesticus* Erxleben, 1777) (META-ANALYSIS)

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The authors declare no conflict of interests
Acknowledgements:
Supported financially from Russian Science Foundation, project No. 19-16-00068
Received August 10, 2020

Abstract

Meat quality shaped by the affecting factors during an animal's lifetime is basically dependent on muscle tissue characteristics. Feeding disorders and stresses can cause myopathy, a destabilizing factor of farm animal meat quality. The muscle tissue injury preventing is of particular interest as it can improve lifetime meat quality formation. Dietary enrichment of farm animal nutrition with natural adaptogens and antioxidants offers potential to reduce myopathies of various etiologies. This paper is an overview of nutrition factors as protective agents under stress loads and myopathies in intensively growing pigs. Dietary adaptogens, e.g. selenium, tocopherol, quercetins, etc., inhibit peroxidation of lipids, generation of reactive oxygen species and are important for the control of glycolysis and oxidative stress. Most adaptogens are antioxidants, they have a beneficial effect on the cardiovascular system, including blood capillaries, prevent damage to cell membranes caused by free radicals and apoptosis. The beneficial effects of vitamin E-enriched diets (from 10 to 1000 mg/kg feed, approximately 200 mg/kg mainly) on porcine meat quality characteristics have been well studied in pig breeds and breed combinations during various periods of growing. However, no effect of dietary vitamin E on the growth rate of animals has also been reported. Feed enrichment with dietary tocopherol leads to its deposition in all tissues and organs, primarily in the blood, liver, heart, and in muscle and fat tissues. Vitamin E has a membrane-stabilizing effect, reduces oxidation of membrane lipids, increases the total amount of fatty acids in mitochondria, antioxidant capacity and muscle glycogen content. It has been shown that in pigs fed diets supplemented with vitamin E during fattening phase the vitamin E deposition level in meat is higher. This, in turn, improves meat taste and flavor, reduces the smell characteristic of reheated dishes, does not change the aldehyde profile of meat volatiles and reduces the accumulation of nitrogenous volatiles resulted from the breakdown of meat proteins during storage, including in a vacuum. Less attention is paid to administration of selenium as an adaptogen. It was shown that selenium combined with higher vitamin E level can neutralize the adverse consequences of hyperthermia in growing pigs and increase free fatty acid content in fat. The organic form of dietary selenium improves the antioxidant status of muscles in pigs. However, selenium has different effects on the oxidation of proteins and lipids during meat storage. In some studies, selenium reduced oxidation; in others, on the contrary, it was proved to be unable to inhibit the accumulation of products of oxidative damage. Two flavonoids quercetin and dihydroquercetin (Taxifolin) are well known for their antioxidant properties. The research articles are mainly deal with quercetin and dihydroquercetin bioavailability and deposition, the impact on antioxidant status and reproductive functions of sows, leveling transportation stress, and pork quality. Quercetin supplements have a pronounced effect at 25-50 mg/kg live weight, dihydroquercetin supplements at 1-3.5 mg/kg live weight. The flavonoids are effective when administered both during the fattening period and before slaughter or transportation. Despite the encouraging reports, little research has focused on the role of these flavonoids in the pork meat quality formation, so further study requires. Quercetin when fed up to 6 months at 2 % of the diet reduced damage to dystrophic skeletal muscle fibers in laboratory animals due to a decrease in reduced production of hydrogen peroxide in mitochondria. Adaptogens and directed muscle tissue development regulators are proposed as potentially key supplements ensuring meat quality under intensive animal husbandry, therefore, further search for and study of bioactive substances which can protect muscle tissues from damaging factors are required.

Keywords: pigs, stress, pork, myopathy, adaptogen, antioxidant, selenium, vitamin E, quercetin, dihydroquercetin

Muscle tissue, as the main tissue of the animal's body, is considered as the main component that determines the quality of meat formed during the lifetime [1]. In this regard, it is of particular interest to study the factors affecting the appearance of myopathic conditions in an animal, as well as conditions that contribute to the leveling of the manifestation of such physiological deviations.

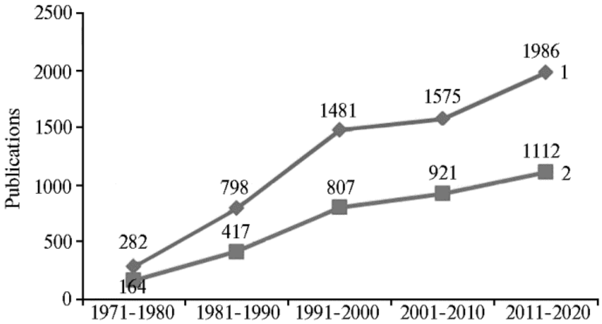

Fig. 1. Search results in ScienceDirect (https://www.sciencedirect.com) **for "myopathy", "stress"** (1), **and "food myopathy"** (2).

The initial information was collected in the ScienceDirect system using the main keywords: "myopathy", "food myopathy", "muscle fiber", "pig", "stress", "pork quality", and "pork PSE" (pale soft exudative). It was found that the number of scientific publications devoted to the study of the causes of the appearance and progression of myopathic states in humans, agricultural and wild animals and poultry, insects, fish, including ornamental ones, had been increasing since the beginning of the 1970s (Fig. 1). Thus, if in 1971-1980, the world published 282 works on the development of myopathies associated with the experienced stress and 164 works in the field of food myopathy, then in recent years (2011-2020), the search results revealed, respectively, 1986 and 1112 publications, that is, their number increased approximately 7-fold.

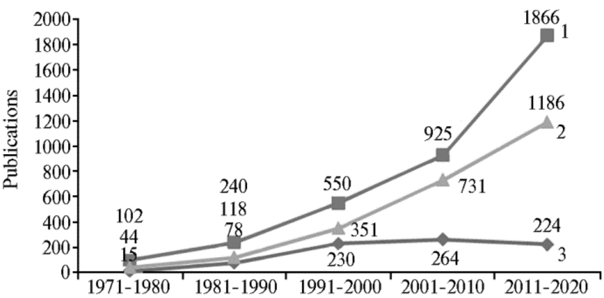

Fig. 2. Search results in ScienceDirect (https://www.sciencedirect.com) **for "pork quality, stress"** (1)**, "muscle fiber, pork quality"** (2)**, and "pork PSE"** (3, PSE — pale soft exudative).

Requirements for the consumer properties of pork have changed since the 1970s towards a decrease in the content of adipose tissue in carcasses and an increase in the mass fraction of muscle tissue, that is, the so-called leanness. The leanness of pork requires a certain quality of muscle tissue. In this regard, for half a century, there has been an exponential growth in the number of publications devoted to the study of the state of muscle fibers in terms of ensuring the quality of pork (Fig. 2).

It should be noted that until recently, when assessing the quality of pork, it was attributed to meat with a normal course of autolysis, or to the so-called PSE (pale soft exudative) meat, that is, having properties that make it dry and unattractive to the consumer. Interestingly, an analysis of the number of scientific publications devoted to this quality defect over the past 10 years has shown a tendency towards their reduction (see Fig. 2).

As it can be seen from Fig. 2, the maximum number of publications containing the words "pork" and "PSE" was in the 2001-2010 period. In the authors' opinion, the observed trend is explained not by the stabilization of the quality of pork, but rather by a change in the ideas of most specialists regarding the mechanisms and methods of ensuring its formation. This is evidenced by the increase in the number of publications devoted to the study of the quality of pork in relation to both the characteristics of muscle fibers and the influence of stress.

The development of methods for preventing myopathic conditions of various etiologies is based mainly on analyzing the possibility of using natural adaptogens and antioxidants in feeding productive animals. It is known that many drugs of natural (plant or animal) and synthetic origin have a stimulating effect on the nervous system and the organism as a whole. Such substances, possessing specific immune-stimulating and anabolic effects, stimulate the humoral response by sensitizing B-lymphocytes (synthesis of immunoglobulins), as well as T-lymphocytes (thymus-dependent cells), which provide a cellular immune response [2]. Vitamins (in particular, tocopherols), as well as microelements (primarily selenium), are the most common substances in pig breeding with antioxidant and adaptogen properties. The study of natural adaptogens – bioflavonoids contained in plants is one of the topical areas of research, therefore, to collect information, the authors searched for publications using additional keywords “vitamin E”, “tocopherol”, “selenium”, “dihydroquercetin”, and “quercetin”. For the analysis, the publications were selected that i) contained in the title or in the annotation (or in both), and in keywords (or in keywords) at least one of the specified main and additional keywords; ii) were original articles prepared by the authors based on the results of their own research on growing pigs; iii) included information on doses of vitamin E, selenium supplements and quercetins (dihydroquercetin), separately or in combination with each other, or in combination with other food components); iv) presented the data obtained after the slaughter of animals; v) dated no earlier than 1995.

The analyzed data set included the following information, presented in the form of tables: information regarding animals that were selected for feeding experiments (initial weight, age, pig breeds, breed combinations, etc.); the dose of adaptogen in the diet; the duration of feeding the adaptogen (adaptogens); achieved effects.

Vitamin E. The inclusion of adaptogens (selenium, tocopherol, and quercetins) in the diet allows controlling glycolysis and oxidative stress by inhibiting the formation of lipid peroxidation products and reactive oxygen species. Most adaptogens are antioxidants, they help to strengthen the cardiovascular system, including the capillary one, prevent the destruction of cells by free radicals, protecting them from apoptosis, and support the normal functioning of tissues and organs.

The use of vitamin E and its effect on the quality of meat has been well studied in growing pigs of different breeds and breed combinations. Out of 28 publications suitable for meta-analysis, 27 were devoted to the study of the role of vitamin E in pork production and one to the development of food myopathy in freshwater fish *Danio rerio* of the family Cyprinidae with vitamin E deficiency. The results were obtained in this study that are important for understanding the role of vitamin E in the development of food myopathies. In particular, it was shown that a lack of vitamin E in the diet caused sluggish behavior associated with multi-focal multiphase degenerative skeletal muscle myopathy. The manifestations of myopathy ranged from disseminated acute necrosis to advanced fibrosis. The addition of vitamin E to the diet of fish made it possible to maintain a 2-fold increase in the content of ascorbic acid ($p < 0.001$) in the muscles with a 3-fold decrease in the amount of malonic aldehyde ($p < 0.001$), which confirmed the high antioxidant status of the muscles. On the contrary, vitamin E deficiency caused an increase in oxidative stress and a secondary decrease in the content of ascorbic acid, which led to serious damage to muscle tissue and impaired muscle function [2].

In the studies on growing pigs and pigs on final feeding, different doses of vitamin E were compared, ranging from 10 to 1000 mg/kg of feed. The most commonly used dosage was 200 mg/kg of feed [4-12]. The authors compared different durations of feeding vitamin E, from the minimum (1 day before slaughter) to 70 days, as well as during the period of change in the weight of pigs from the initial one to the required one for sending to slaughter (from 105 to 135 kg). The study of the effect of vitamin E on the state of animals before slaughter and the quality of meat showed that tocopherol, even 1 day before slaughter, increased muscle glycogen stores by 10%, and also increased the moisture-binding capacity (MBC), especially when using a feed additive in combination with moderate physical activity in animals [13]. However, these findings were challenged in 2004 in a large-scale experiment ($n = 92$), in which it was found that supplementing the pig diet with vitamin E 5 days before slaughter did not increase its concentration in the muscles, did not contribute to the improvement of MBC and the color of meat. The authors concluded that under stress, the level of which is lower than in usual procedures associated with slaughter, the short-term introduction of additives to the diet does not seem to affect the quality of meat [14].

Overall, the meta-analysis revealed 16 expected effects from the use of vitamin E as a feed additive (Table 1). In four studies with a fairly large amount of experimental data, the authors came to the conclusion that vitamin E in the amount of 140-220 mg/kg of feed did not affect the growth parameters of pigs even with prolonged feeding, including in combination with vitamin C [14-17]. Such a conclusion, obviously, should be considered as ambiguous and not final or as corresponding only to the studied range of doses of tocopherol in feed: vitamin E is a biologically active and necessary supplement, its deficiency can cause food myopathies, and, consequently, reduce the growth rate of animals. In one work [17], it was noted that vitamin E in the amount of 220 mg/kg of feed reduced ($p < 0.36$) its effectiveness. At the same time, even the long-term introduction of tocopherol into the diet in the amount of 140 mg/kg of feed did not affect the slaughter indicators – the yield of slaughter products to the live weight of pigs [15], as well as the qualitative characteristics of pork carcasses [10]. In another study [17], long-term administration of vitamin E resulted in an increase in the mass fraction of muscle tissue in a carcass.

In 14 studies, the authors analyzed the accumulation of vitamin E in organs and tissues of pigs. The results clearly indicated that the introduction of tocopherol into the diet of pigs promoted its accumulation in all tissues, primarily in the blood, liver, heart, as well as in muscle and adipose tissues. The maximum increase in the amount of vitamin E in muscle tissue was achieved in 28 days at a dose of 200 mg/kg of feed. There was no further increase in the content of vitamin E in muscles. It was also reported that synthetic tocopherol (a mixture of eight compounds not found in nature) was able to replace natural tocopherol in the organism of animals [4, 7, 9, 14-16, 18-25].

The results of the analyzed studies also allowed concluding that vitamin E stabilizes the state of membranes, reduces membrane lipid oxidation, and increases the total amount of fatty acids in mitochondria [8, 19, 26].

The effect of vitamin E on the condition of muscle tissue of pigs has been little studied. The search revealed only two studies [13, 23], the results of which show that vitamin E increases the antioxidant capacity and glycogen content in muscles.

1. Meta-analysis of the data on the use of vitamin E as an adaptogen in pig production (ScienceDirect, 1995-2019)

Intended effect	Number of animals in experiments	Use of vitamin E		Conclusion	References
		doses, mg/kg of feed	period of time		
Growth indicators of pigs	246	140-220	From 25 to 110 kg live weight	Does not affect even with prolonged feeding and in combination with vitamin C	[10, 15-17]
Efficiency of assimilation of feed	48	220	From 54 to 113 kg live weight	Decreases ($p < 0.36$)	[17]
Slaughter parameters	Not reported	140	From 25 to 105 kg live weight	Does not affect even with prolonged feeding and in combination with vitamin C	[15]
Qualitative characteristics of carcasses	198	200-220	From 54 to 113 kg live weight	Does not affect. An increase in the mass fraction of muscle tissue in the carcass is possible	[10, 17]
Content of vitamin E in the blood, organs, muscle, and adipose tissue of the animal	154	100-1000	From 5 to 70 days	Increases depending on the dose with prolonged use. The maximum increase in muscle tissue on the 28th day	[4, 7, 9, 14-16, 18, 20-25]
Condition of cell membranes and mitochondria	Not reported	200-1000	From 46 days	Stabilizes the state of membranes, reduces membrane lipid oxidation, and increases the total amount of fatty acids in mitochondria	[4, 8, 19, 26]
Muscle tissue condition	56	500	From day 2 to the end of fattening	Increases antioxidant capacity, glycogen content in muscles. Vitamin E deficiency causes muscle tissue damage (degenerative myopathy)	[2, 13, 23]
Severity of the effects of transportation stress	288	200	28 days	Does not affect, as well as does not reduce the content of creatine kinase and cortisol in the blood serum, the expression of heat shock proteins in muscle tissue, damage to the intestinal epithelium	[12]
Accumulation of intramuscular fat and total chemical composition of muscle tissue	282	100-220	From 38 days; from 54 to 135 kg live weight	Overall, apparently, does not affect, although there are data that it increases the marbling score	[5, 17, 27]
Fatty acid composition of intramuscular fat	224	100-325	28 days and more	The data are contradictory: either does not affect or increases the content of polyunsaturated fatty acids	[5, 28]
pH, moisture-binding capacity, and the share of pale soft exudative meat	1060	80-1000	From 2 to 46 days; from 54 to 110 kg live weight and until the slaughter	There is no unambiguous understanding of the effect of vitamin E on pH, moisture-binding capacity, and pale soft exudative meat appearance	[5, 8, 11-14, 16, 17, 22, 25, 26, 28]
Accumulation of oxidative spoilage products	974	10-700	From 28 to 150 days, from 25 to 135 kg live weight	Secondary oxidation products (thiobarbituric value or hexanal): reduces the dynamics of their accumulation in meat; in some cases, vitamin E had no effect on the thiobarbituric value (two works out of 11). The peroxide number decreases (did not decrease in one case out of three)	[2, 5, 7, 10, 11, 15, 16, 20, 21, 25, 27, 29, 30]

Continued Table 1

General organoleptic score	84	100-500	During the fattening period until the slaughter	Does not affect	[5, 23]
Meat color	928	10-1000	From 5 to 70 days; from 51 to 113 kg live weight	There is no unambiguous understanding of the effect on color in general: if it improves it or does not affect. Redness: improves the indicator, in some cases has no effect; increases the redness of products with nitrite. Lightness: a significant positive effect if the meat is stored	[5, 7, 10, 11, 14, 17, 18, 21-23, 25, 27, 30]
Meat taste and smell	48	10-210	During the fattening period until the slaughter	It has a positive effect on smell and taste, enhances their intensity. Reduces the severity of the smell of reheated dishes. Does not affect the aldehyde profile of volatiles and reduces the accumulation of nitrogenous volatiles when stored under vacuum	[9, 16, 22]
Softness of meat	48	200-500	During the fattening period until the slaughter	The data is inconsistent: does not affect or increases	[16, 23]

The authors studied the possibility of mitigating the effects of transportation stress in pigs by adding vitamin E to their diet 28 days before transportation. However, the expected effect was not achieved. It turned out that vitamin E did not affect the clinical manifestations of this pathology, as well as did not reduce the content of creatine kinase and cortisol in the blood serum, the expression of heat shock proteins in muscle tissue, and damage to the intestinal epithelium [12].

The effect of vitamin E on intramuscular fat accumulation and the overall chemical composition of muscle tissue was examined. In general, it was concluded that there was no relationship between these factors, despite the data on an increase in the assessment of pork marbling [5, 17, 27]. The latter could be due to a change in color perception, and not to the accumulation of fat in the *longissimus dorsi* muscle.

The data obtained when assessing the effect of vitamin E on the fatty acid composition of intramuscular fat are contradictory: both the absence of a relationship [5] and an increase in the proportion of polyunsaturated fatty acids in the muscle tissue of pigs with the introduction of vitamin E into the diet were noted [28].

Twelve studies considered the possibility of reducing the proportion of PSE pork, increasing the pH and MBC of meat [5, 8, 11-14, 16, 17, 22, 25, 26, 28]. It was reported that in high doses (1000 mg/kg) vitamin E could stabilize cell membranes and regulate excess Ca^{2+} release, preventing the formation of meat with PSE defect and, at the same time, improving the MBC of muscle tissue [26]. Although an increase in MBC with different doses of vitamin E in the diet of animals was noted in a number of studies, it was not possible to draw an unambiguous conclusion, despite full-scale studies on a large sample of animals and with a significant duration of experiments. The opinions were divided approximately equally: in one part of the publications, it was concluded that there was no effect of vitamin E on pH and MBC, while in the other works, the introduction of vitamin E into the diet of pigs could reduce the proportion of PSE meat. As a reason, it can be assumed that, even with experimental slaughter, it is extremely difficult to create the same stress loads for all animals, as well as to take into account their individual characteristics of perceiving stressful situations.

In 13 works, the data on the dynamics of accumulating oxidative spoilage products during storage of both meat and finished meat products from animals in the diet of which vitamin E was introduced in an amount of 10 to 700 mg/kg of feed are presented [2, 5, 7, 10, 11, 15, 16, 20, 21, 25, 27, 29, 30]. The results of these studies testified to the inhibition of developing oxidative processes in meat and meat products with prolonged (from 28 days) use of tocopherol during the fattening period. Only under certain conditions (possibly, depending on the nutrient composition of the feed), such an effect was not achieved.

Two studies [5, 23] studied the effect of vitamin E in the diet of pigs on the overall organoleptic assessment of the resulting pork. The results showed no effect with long-term use during the fattening period at doses of 100-500 mg/kg of feed.

The possibility of stabilizing and improving the color and color characteristics of pork (L — lightness, a — redness, b — yellowness) was considered in 13 studies [5, 7, 10, 11, 14, 17, 18, 21-23, 25, 27, 30]. The results did not provide an unambiguous answer as to whether vitamin E affects the color of the pork. At least, it is clear that an increase in the amount of tocopherol in the diet and in meat did not lead to a deterioration in color indices even at the highest dosages of 1000 mg/kg feed. With regard to instrumentally measured color indicators (redness and lightness), the meta-analysis revealed their improvement in the case of meat sold in packaged form; in addition, vitamin E in meat raw materials effectively increases the redness of products made with nitrite.

The effect of vitamin E on taste and smell was identified as positive based on the results of three studies [9, 16, 22]. When vitamin E was used as an additive during the fattening period, its content in meat increased, which enhanced the intensity of taste and aroma, in addition, the smell of reheated dishes, which is considered undesirable, was less pronounced. The data that vitamin E does not change the aldehyde profile of volatile substances in meat and reduces the accumulation of nitrogenous volatiles formed as a result of the breakdown of protein substances during storage, including in a vacuum, can be considered as positive.

The study of the effect of vitamin E on the softness of meat [16, 23], as in the case of the effect on MBC, gave conflicting results (either does not affect or increases). These data are consistent with the results for MBC.

Thus, judging by the activity of research, most scientists continue to consider vitamin E as an important nutrient that can ensure the achievement of high consumer characteristics of slaughter products in pig breeding, be used to stabilize color, taste, aroma, and also to effectively suppress oxidative processes during production and storage of meat products.

S e l e n i u m. A search for publications on the use of selenium in pig feeding (from 1999 to 2020) identified 20 papers suitable for meta-analysis, that is, the research on selenium is conducted less intensively than on vitamin E. The total number (11) of tested hypotheses regarding the possible effects of selenium is also less (Table 2).

Selenium was fed in the inorganic (sodium selenite) and organic (Se-enriched yeast and selenomethionine) forms at a wide dosage range from 0.045 to 50 mg/kg of feed, as well as together with vitamin E and with the simultaneous introduction of fats into the feed, rich in unsaturated fatty acids. The most commonly used doses were 0.2-0.3 mg/kg of feed. The duration of the experiments reached 65 days. The mass of animals in the experiment was from an initial weight of 10 kg to a final weight of 160 kg.

The effect of introducing selenium into the diet of pigs on slaughter parameters was assessed in two studies [31, 32] on a total sample of 479 individuals. At high doses of selenium (up to 30 mg/kg of feed) and prolonged feeding (in one work from the initial weight of animals 20 kg to the final 105 kg, in another work for 30 days), no effect of both inorganic and organic selenium was found, except for selenomethionine. In animals that received it as a source of selenium, the yield of carcasses during slaughter was higher. Under similar experimental conditions, it was found that selenium (in organic and inorganic forms, as well as in combination with vitamin E) did not affect the qualitative characteristics of pork carcasses [31, 33].

Seven studies were devoted to the effect of selenium in feed on its content in the blood, organs, and muscle tissue of animals. The experiments were conducted on a representative sample of animals (n = 603) and at different dosages (0.045-50 mg/kg). The animals were selected according to their initial live weight (from 20 to 60 kg) or age (30 to 40 days), feeding of additional selenium was continued until slaughter.

The accumulation of selenium in tissues is faster in the case of organic selenium, especially selenomethionine, and promotes the accumulation of vitamin E. The most effective daily dose of selenium was found to be 0.4 mg/kg of feed. Interestingly, with such a daily intake, a young healthy organism stops storing selenium after 28 days [31, 32, 34-38].

Three studies [36, 39, 40] evaluated the effect of selenium on the condition of the muscle tissue of animals. The results of long-term experiments (26 days or more) made it possible to conclude that there was no such effect, including when selenium was combined with vitamin E. No changes in the microstructure of meat were revealed (regardless of the source of selenium). Nevertheless, during the maturation of meat, selenium (Se-yeast, selenium with vitamin E) intensified destructive changes on day 8, which is probably associated with a higher activity of tissue enzymes.

The possibility of leveling the effects of transportation stress in pigs due to the additional introduction of selenium into the diet was studied in one work [41] on 36 animals at a dose of 0.24 to 1 mg/kg and against the background of vitamin E consumption (17-100 mg/kg). The results clearly showed that selenium reduced the effects of hyperthermia in growing pigs.

The study of the fatty acid composition of intramuscular fat in animals that were given selenium against the background of basic and additional intake of vitamin E revealed an increase in the content of free fatty acids in fat under the influence of organic selenium. The effect is enhanced by vitamin E which increases the $C_{18:1}$ content and decreases the $C_{18:0}$ [38]. Eight large-scale studies in terms of the number of animals (n = 689) and duration of studies were devoted to the effect of selenium on pH, MBC, and the proportion of PSE meat. The results allow making an unambiguous conclusion that organic selenium increases MBC and pH [31, 32, 35, 38, 39, 42-44]. At the same time, it is unclear how to explain such a positive effect and why it does not agree with the data of studies on the state of muscle tissue.

The effect of additional selenium on oxidative processes during lifetime, as well as during storage of meat and meat products, is most studied. The unambiguous conclusion is that organic selenium increases the antioxidant status of muscles. However, the introduction of selenium into the diet had different effects on the oxidation of proteins and lipids during the storage of meat. The research results are ambiguous: in some studies, the data were obtained that allow concluding that oxidation decreases under the influence of selenium, in others, on the contrary, it was shown that selenium was not able to inhibit the accumulation of oxidative spoilage products [32, 34-36, 38, 39, 42, 44-48].

Two publications [33, 49] conclude that selenium and vitamin E do not affect the overall organoleptic assessment of pork. However, with regard to meat color, the results differed, which was explained by the form of administering adaptogens, as well as, possibly, the choice of the dosage and subjects of study. Thus, inorganic selenium did not affect or worsen the color indices, while organic selenium, on the contrary, either did not affect or improved the color indices. Only one study attempted to evaluate the effect of the combined introduction of selenium and vitamin E into the diet [50], in which such an effect was considered insignificant.

In general, in the authors' opinion, insufficient attention is paid to selenium as an adaptogen, important for the lifetime formation of meat quality.

Quercetin and dihydroquercetin. Quercetin and dihydroquercetin (taxifolin) are well-known and well-studied flavonoids. They are not toxic, have pronounced antioxidant and antimicrobial properties, as a result of which they are used both in the production of livestock products and during their processing and storage.

The number of publications on the required topics suitable for meta-analysis appeared to be limited, i.e., 23 articles (the sample was supplemented by Russian sources previously known to the authors of this meta-analysis), relating to the period from 1999 to the present (Table 3) and covering the results of the studies of the bioavailability of these flavonoids, their accumulation in animal tissues, the effect on the reproductive functions of sows, the antioxidant status of animals, a decrease in the effects of transportation stress, and meat quality.

2. Мета-анализ данных по применению селена в качестве адаптогена в свиноводстве (ScienceDirect, 1999-2019 годы)

Intended effect	Number of animals in experiments	Use of selenium		Conclusion	References
		doses, mg/kg of feed	period of time		
Slaughter parameters	479	0.05-30	From 20 to 105 kg; 30 days	No effect when using both inorganic and organic selenium (except selenomethionine, which increases carcass yield)	[31, 32]
Qualitative characteristics of carcasses	399	0.05-30	From 20 to 105 kg, 28 и 49 days	There is no effect when selenium is introduced into the diet in organic and inorganic forms, as well as in combination with vitamin E	[31, 33]
The content of selenium in the blood, organs, muscle tissue of the animal	603	0.045-50	From 20-60 kg until the slaughter; 30-40 days	The accumulation of selenium in animal tissues occurs faster when feeding with organic selenium, especially selenomethionine, and contributes to the accumulation of vitamin E. The most effective concentration is 0.4 mg/kg of feed	[31, 32, 34-37, 42]
Muscle tissue condition	Not reported	0.2-0.4	From 26 days; from 75 to 160 kg	Histological studies did not reveal the effect of selenium, including with vitamin E, on the condition of the pig's muscles (except that when the meat ripens, selenium as Se-yeast or selenium with vitamin E enhances destructive changes on day 8)	[36, 39, 40]
Severity of the effects of transportation stress	36	0.24-1 (with vitamin E, 17-100 mg/kg)	14 days	Reducing the effects of hyperthermia in growing pigs	[44]
Fatty acid composition of intramuscular fat	Not reported (meat was tested)	0.2-0.4 (with vitamin E)	Not reported (meat was tested)	Organic selenium helps to increase the content of free fatty acids in fat (the effect is enhanced by vitamin E). Se increases the content of $C_{18:1}$ and decreases the $C_{18:0}$ level.	[42]
pH, moisture-binding capacity, and the proportion of pale soft exudative meat	689	0.05-30	26-65 days; from 20-30 to 105-130 kg	Organic selenium raises moisture-binding capacity and pH	[31, 32, 35, 38, 42-44]
Accumulation of oxidative spoilage products	438	0.045-3	26-65 days	Organic selenium increases the antioxidant status of muscles, however, its effect on the oxidation of proteins and lipids during the storage of meat is not unambiguous, i.e., it reduces or does not affect it	[32, 34-36, 38, 39, 42, 44-47]
Total organoleptic assessment	107	Se (with vitamin E)	28-49 days	Does not affect	[33, 49]
Color of meat	380	0.045-0.5	30-65 days; from 20 to 105 kg	There is no clear understanding. Inorganic selenium does not affect or degrade color indicators, and organic selenium does not affect or improve color indicators	[48]
Taste and smell of meat	Not reported (meat was tested)	1 (with vitamin, 100 mg/kg feed)	Not reported (meat was tested))	Has an insignificant effect	[50]

3. Meta-analysis of data on the use of quercetin (QC) and dihydroquercetin (DHQ) as adaptogen in pig breeding (ScienceDirect, 1998-2019)

Intended effect	Number of animals in experiments	Use		Conclusions	References
		doses	period of time		
Growth indicators	10 340	DHQ (Ecostimul-2), 1 mg/kg of live weight per day); QC, 25 mg/kg of feed	DHQ during thermal stress; QC for 28 days	The survival rate and average daily weight gain of animals increases	[64, 66, 71]
Qualitative characteristics of carcasses	Not reported (meat was tested)	DHQ	Form 72 kg to the slaughter (45 days)	DHQ will not affect the morphological composition of carcasses	[67]
The content of QC in the blood, organs, muscle, and adipose tissue of the animal	10	QC (aglycone, quercetin-3-O-glucoside, rutin – quercetin-3-O-glucoramnoside), up to 65 g/day	Up to 10 days	Bioavailable. The bioavailability of QC depends on its type and the diet of pigs; it is higher for glucoside. The highest content of QC and its metabolites is in the liver, small intestine, kidneys, blood plasma; low in the brain, heart, and spleen. No tendency to accumulate (no difference between single and repeated use)	[51-55]
State of the muscle tissue (the results of studies on mice)	Not reported (meat was tested)	QC, 0.2% of the diet	From 14 days to 6 months	Long-term addition of QC reduces damage in dystrophic skeletal muscle, prevents muscle loss, and inhibits the development of muscle fiber atrophy by reducing the formation of hydrogen peroxide in mitochondria	[72, 73]
State of mitochondria	Not reported (meat was tested)	QC, 0.2% of the diet	14 days	Reduces the production of hydrogen peroxide in mitochondria	[73]
The severity of the effects of transportation stress	510	QC, 25 mg/kg of feed; 1.25-40 μg/ml (in cell culture)	28 days from 72 to 100 kg)	QC better than vitamin E mitigates the negative effect of transportation, affects the proliferation of epithelial cells, protects against oxidative stress, positively affects intestinal integrity, reduces the production of reactive oxygen species in the intestine and intestinal inflammation during transportation stress	[62, 68, 71]
pH, moisture-binding capacity, and the proportion of pale soft exudative meat	376	QC, 2.5-25.0 mg/kg of feed; DHQ, 3.5 and 7.5 mg/kg of live weight per day	28-45 days; from 60 to 110 kg; 4 h before transportation to the slaughter	The effect of QC and DHQ is ambiguous: they increase or do not change pH and moisture-binding capacity, storage losses decrease or do not change. It is assumed that QC and DHQ slow down the rate of autolysis, but the final pH does not depend on the diet of pigs.	[67-70]
Accumulation of oxidative spoilage products	816	QC, 25-900 mg/kg of feed, 10 mg/kg of live weight per day; DHQ, 1.0-7.5 mg/kg of live weight per day	17-45 days; 24 h	QC protects tissues and organs from oxidative stress, increases the accumulation of vitamin E. The effect on the antioxidant status of weaned piglets is controversial. Increases and stabilizes the antioxidant status of blood plasma, in serum, muscles, and liver reduces thiobarbituric and peroxide values (less primary and secondary lipid oxidation products during storage both in muscles and in fat). The effect is more obvious during long-term storage	[56, 61-66, 68, 70, 71]
Meat color	340	QC, 25 mg/kg of feed	From 74 kg to the slaughter weigh	QC has a positive effect on the color of meat 24 hours after slaughter, but the effect is considered insignificant	[68, 70]

The bioavailability of quercetin from quercetin glycosides is determined by a complex interdependence between the chemical forms of flavonoids and the composition of the diet (types of feed) [51, 52].

The accumulation of quercetin in pig tissues as a result of adding a flavonoid to the feed has been studied in sufficient detail in many studies. Conjugated quercetin is the main metabolite of quercetin detected in blood plasma 24 hours after the intake of this supplement into the organism [52]. The highest content of quercetin and its metabolites is noted in the organs responsible for the excretion of metabolic products – in the liver and kidneys (5.87 and 2.51 nmol/g of tissue, respectively), significantly lower – in the brain, heart, and spleen. At the same time, in the blood plasma and in the heart of pigs, quercetin accumulates more slowly and in smaller quantities than in rats, while its accumulation in the kidneys, brain, and spleen does not differ in these animals. The content of quercetin in the blood plasma of pigs after 3 days of consuming high doses of quercetin (up to 500 mg/kg) did not exceed 1.25 mmol/l [53, 54]. Moreover, no differences were found between the results of long-term and repeated use of this flavonoid and a single use [55]. Thus, it has been proven that feeding quercetin is safe for animals due to the absence of its accumulation in tissues [53, 55].

Out of the dietary factors, fat in the diet (depending on its content) influenced the bioavailability of quercetin [52]. At the same time, the combination of vitamin E with quercetin leads to the best positive effect [56].

Scientists have been interested in studying the effect of quercetin on the reproductive function of pigs for more than 10 years [57-60]. It was found that quercetin did not affect the growth of granulosa cells, but (depending on the dose) inhibited the production of progesterone and modifies the production of 17β estradiol. A negative effect of quercetin on the physiological status of the ovaries is possible. In addition, the flavonoid interferes with the angiogenic process by inhibiting the production of vascular endothelial growth factor, as well as through changes in the oxidation-reduction status [57]. Exogenous flavonoids reduced the content of reactive oxygen species in oocytes, but at high concentrations (50 μg/ml) turned out to be toxic to oocytes [58]. Quercetin exhibits an inhibitory effect on the main functions of the ovaries, does not prevent or mitigate the effects of benzene on reproductive processes, and enhances the effect of benzene on the release of progesterone [60].

Quercetin did not affect the activity of glutathione peroxidase, glutathione reductase, and glutamate-cysteine ligase in the mucous membrane of the small intestine and liver of piglets after weaning, while the activity of hepatic glutathione transferase significantly increased on the 5^{th} day after weaning when quercetin was taken at doses of 100, 300, and 900 mg/kg. Evaluating the content of malonic aldehyde in blood plasma, liver, and small intestine shows that the data on the effect of quercetin on the kinetics of glutathione in weaned piglets are contradictory, and the issue requires further study [61]. Quercetin helps to protect pigs' intestinal enterocytes from oxidative stress [62]. It was found that when the feed was contaminated with mycotoxins in animals receiving quercetin (alone or in combination with vitamins and selenium), the oxidative status was partially restored [63].

The use of dihydroquercetin in feeding piglets blocks the process of lipid peroxidation during the entire period of rearing and fattening, especially when exposed to high temperatures. The acid, peroxide number, and the content of malondialdehyde in the blood serum of piglets decrease with the use of dihydroquercetin, and the antioxidant defense of the organism is enhanced, which is expressed in an increase in the antioxidant activity of blood plasma. The improvement of liver functions is noted. Taken together, this has a positive effect on the daily gain and safety of pigs [64-67].

Quercetins reduce the effect of transportation stress, contributing to a decrease in the serum concentration of endotoxin, the amount of reactive oxygen species and malondialdehyde in the intestinal tissues; in the jejunum of pigs, an increase in the height of the villi is noted with a simultaneous decrease in the expression of inflammatory cytokines [68].

The influence of quercetin and dihydroquercetin on the quality of meat has been studied in sufficient detail (in relation to various technological and consumer characteristics at different stages of production — from fresh carcasses to frozen meat with long-term storage). The addition of quercetin to the diet of piglets during the fattening period and even 4 hours before slaughter slowed down the rate of pH decrease in muscle tissue. However, the final pH value at 24 hours after slaughter was independent of diet. An increase in the MBC of meat and a decrease in weight loss during storage in retail conditions for 12 days were noted [69]. Adaptogens (dihydroquercetin at a dose of 3.5 mg/kg of live weight and rose petals at a dose of 0.255 mg/kg of live weight) contributed to a decrease in the accumulation of primary and secondary lipid oxidation products during storage both in muscles and in fat. A slight positive effect was noted for the pH and color of pork [67, 70]. The effective doses for pigs were established, the 25-50 mg/kg of animal weight for quercetinthe [55, 58], 1 mg/kg of animal weight [64-66] and 3.5 mg/kg of live weight [67, 70] for dihydroquercetin, as well as the fact that flavonoids were effective for feeding both during the growth of animals [55, 65] and right before slaughter and transportation [68, 69, 71].

The analysis of the published data shows that the role of quercetin and dihydroquercetin in the formation of meat quality still needs to be studied. In the last few years, there have been reports that long-term consumption of quercetin (up to 6 months, 0.2% in the diet) is able to reduce damage to muscle fibers in dystrophic skeletal muscle in laboratory animals [72]. In addition, its feeding prevents muscle loss and the development of muscle fiber atrophy by reducing the formation of hydrogen peroxide in mitochondria, even in cases where the atrophy is caused by injury to the nervous tissue of the muscles [73].

Thus, despite the small number of sources on quercetin and dihydroquercetin, the meta-analysis allows highlighting promising areas of research to identify the effect of quercetin (dihydroquercetin) on the lifetime formation of pork quality. Among them, there is the study of the role of these additives in preventing pork quality defects caused by myopathy (see Table 3).

Summing up the analysis of publications on the effect of antioxidants of various natures under stresses affecting the microstructure of muscle tissue, it should be noted that the use of such adaptogens in industrial animal breeding can become an important element of intensive technologies that ensure the lifetime formation of meat quality. An expert assessment of the degree of knowledge of the intended effects of each of the three adaptogens is presented in Table 4.

4. Expert assessment of the coverage of studies of the potential for using adaptogens in pig breeding (ScienceDirect, 1995-2019)

Intended effect of the adaptogen	Vitamin E	Selenium	Quercetin (dihydroquercetin)
Influence on the indicators of pig growth	4+	1+	3+
Influence on the efficiency of using feed	4+	1+	1+
Influence on slaughter parameters	4+	4+	1+
Impact on qualitative characteristics of pig carcasses	4+	3+	3+
Influence on the content of adaptogen in blood, organs, Muscle, and adipose tissue of the animal	4+	4+	3+
Influence on the state of cell membranes and mitochondria	4+	1+	3+
Influence on the condition of muscle tissue	3+	2+	2+

Continued Table 4

Influence on the severity of the effects of transportation stress in pigs	4+	4+	4+
Influence on intramuscular fat accumulation and the total chemical composition of muscle tissue	3+	1+	1+
Influence on the fatty acid composition of intramuscular fat	2+	3+	1+
Effect on pH, moisture-binding capacity, and the proportion of pale soft exudative meat	2+	3+	2+
Influence on the accumulation of oxidative spoilage products	4+	2+	2+
Influence on the overall organoleptic assessment	3+	3+	*
Influence on meat color	2+	2+	3+
Influence on the taste and smell of meat	3+	3+	1+
Influence on the softness of meat	2+	1+	1+

Note. 4+ — large-scale study, unambiguous conclusions, the likelihood of new knowledge is very low; 3+ — studied in a significant amount, the conclusions are agreed, but there is a possibility of obtaining new knowledge; 2+ — insufficiently studied or no unambiguous conclusions, the probability of obtaining new knowledge is high; 1+ — studied very little or not studied at all, requires further study.

Thus, the conducted meta-analysis led to the following conclusions. It is required to continue the study of two key aspects of the possible use of adaptogens in the production of pork – the effect of antioxidants on increasing the pH and MBC of meat, as well as on the stabilization of color and inhibition of oxidative processes. It should be noted that histological studies are rarely included in the programs of scientific work. This is probably due to the lack of highly qualified histology specialists. The accumulation of data on the effect of adaptogens on the functional and technological characteristics of pork indicates their relationship with the lifetime state of muscle tissue and the importance of studies to minimize the risk of myopathy in conditions of intensive pork production.

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