

## **THE MODERN ANTI-STRESS TECHNOLOGIES IN POULTRY: FROM ANTIOXIDANTS TO VITAGENES**

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Upon the last 10 years, the numerous studies have convincingly shown the oxidative stress caused by excessive production of free radicals was the basis of the most stresses. In this, a delicate balance between anti- and pro-oxidants in the diet, gastrointestinal tract and the cells of various organs and tissues is the important factor which determines the resistance to stress and provides for an adaptive capacity of the organism to stressors. The defense agents are both natural antioxidants (vitamins E and C, carotenoids) or minerals of prosthetic groups of the antioxidant enzymes (selenium, zinc, manganese and copper), consumed from fodder, and protective molecules with an antioxidant activity (glutathione, thioredoxin, coenzyme Q) or protective functions, complementary to antioxidants (heat shock proteins, sirtuins, etc.), which are newly synthesized in organism. It was established that the synthesis of the above substances is regulated by a group of genes, the vitagenes, which in fact are the most important factors of adaptive capacity. Their activity is regulated by external factors, the stressors, and a number of substances having anti-oxidant properties, in particular carnitine, vitamin E, selenium, zinc, manganese, etc. As a result of our research, the Feed-Food Magic Anti-Stress Mix (PerforMax), a new feed additive which improves the ability of animal adaptation under stress, has been developed. It helps to overcome stress at lower losses and thus increase the efficiency of animal husbandry and poultry farming. The composition consists of 28 components, including vitamins, minerals, amino acids, organic acids, electrolytes. Due to their optimized content and synergism, the efficient recycling of vitamin E is maintained to reduce the formation of free radicals in mitochondria, and a pronounced immunomodulating effect is expressed. Currently, the composition is successfully used at a number of poultry companies in Egypt, Turkey, Ukraine, Russia and in pig-producing companies in Russia and several other countries.

Keywords: stress, free radicals, antioxidant defense, vitagenes.

Stresses of poultry and related economical loss from reduced productivity and reproductive performance of the bird has been actively studied in recent years (1-7). The new data of scientific research suggest that negative consequences of stresses are much deeper than it was previously thought. For example, the concept of vitagenes significantly clarifies molecular mechanisms of natural anti-stress protection. According to this concept, adaptation to stress is a process associated with a chain of molecular events leading to activation of certain genes and "switching off" the others, which enables all available reserves of an organism in order to minimize effects of stress. At the molecular level, negative effects of stress are mediated by overproduction of free radicals which cause damage to all types of biological molecules. The control of overproduction of free radicals in the cell (and a whole body) is a way to reduce adverse effects of stresses of various etiologies. In recent years, negative consequences of protein oxidation of cellular structures are being increasingly studied, as well as oxidative modification of DNA. A special attention is paid to the development of effective medications with a comprehensive action minimizing adverse effects of stress. Most of these studies were

associated with medicine, while only a few of these achievements were implemented in poultry industry.

**Stresses in poultry production.** A bird faces stress already in an incubator. Early post-hatch isolation of chicks, as well as delaying them in an incubator can notably reduce their future productivity. This can cause significant changes in antioxidant system of chicks (8). Vaccination of chicks in a hatchery, transportation and housing (including non-aligned bedding, inadequate temperature and ventilation) can also cause a stress. For example, in winter the intensity of ventilation is often reduced by managers in order to save energy costs, which inevitably leads to accumulation in the air of excessive ammonia and other harmful substances inducing stress. In hot summer days, ventilation and cooling system can be inadequate in maintaining an optimal temperature, so the bird can experience heat stress. Stresses associated with nutrition can be caused by transition of chicks from yolk supply (in the last week of incubation) to dry feed, as well as by unbalanced diet in respect to nutrients, including various bioactive substances. Feed mycotoxins are another frequent reason of stress, sometimes multiplied with other stressful factors - vaccination, thermal stress, etc. Avian stress of various etiologies during the industrial production of broilers, laying hens, parental flocks, and replacement chickens are described in detail in the literature (1, 2, 5, 9). Such close attention reflects a significant role of stress in reduction of bird's productive and reproductive performance.

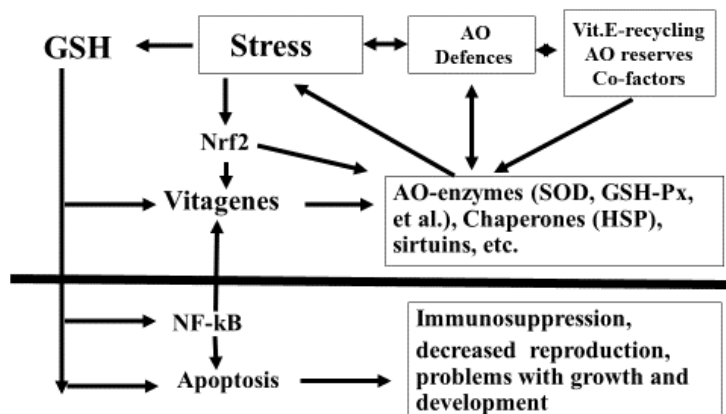
One of the major problems associated with stress is increased need for particular nutrients and bioactive substances necessary to combat stress but often insufficient due to a general reduction in feed consumption during stress (1-4, 9). At the same time, it was proved that such substances as carnitine, betaine, antioxidants and organic acids, consumed with feed can improve birds' adaptability to stress. Supply with important nutrients, including antioxidants, by administration them with drinking water can be the essential advance in anti-stress therapy of poultry. Today, many poultry farms are equipped with pumps dosatrons (medicators) for delivering various medicines, probiotics, and water disinfection.

**Molecular mechanisms of stress.** From a physiological point of view, stress is the response to deviation of environmental factors from their optimum, which includes external (housing, temperature) and internal (bacterial balance in the intestine) conditions, as well as nutrition (e.g., non-optimal composition of the diet). In general, there are three major types of stress in poultry industry: environmental, nutritional and internal stresses. All of them suppress reproductive performance of parental flocks (reduced fertility, hatching and viability of young chicks in the first few days of life), and productivity of broilers (impaired feed conversion, reduced average daily weight gain, high mortality). The immune system should be in focus, because it is the most sensitive to various stresses (10, 11). Dysfunction of the immune system weakens natural resistance to diseases, reduces beneficial effects of vaccination (4), which results in a significant loss in profits from meat and egg production. Once faced a stress, an organism overcomes it (adaptation), or dies depending on the intensity of stress. Adaptation has its cost, which in poultry farming is associated with reduced productive and reproductive performance. During the evolution, animals and humans have developed various adaptive mechanisms allowing to enable all body defenses to overcome stress. For years, scientists have tried to reveal the molecular mechanisms underlying various stresses (heat, nutrition, and internal ones). It was found that these states are accompanied by overproduction of free radicals and following disturbances in the structure of proteins, DNA, as well as oxidative degradation of lipids (3-7, 12-14). Free-radical theory of stress is the most intensely developed today. Free radicals, often called the reactive oxygen species (ROS, can damage all types of biological

molecules. It is known that about 20 billion ROS are normally produced in each cell per day. Under stress, ROS production increases by several times when antioxidant system becomes unable to neutralize this excess. This can cause disruptions of cell membranes and many other disturbances adversely affecting cellular metabolism, which, in turn, decreases productivity of poultry and its reproductive performance.

**Vitagenes and their importance for anti-stress defense** (15-17). Decrypting the genetic code of human and some animal species has helped to discover many regulatory mechanisms of genes' activity, such as gene activation, switching-off and modulated level of expression. Regulators of gene activity can be vitamins A, E, D, selenium, carnitine and other nutrients. Indeed, gene expression can be influenced by various dietary components (nutrigenomics) (18), some pharmaceuticals (pharmacogenomics), mycotoxins (mycotoxigenomics), environmental conditions (ecogenomics) and other factors.

The general scheme of adaptation to stress is shown on Figure 1. During stress, concentration of natural antioxidant glutathione (GSH) serves as one of specific sensors that determines cellular redox potential, and, accordingly, triggers the cascade of defensive reactions. For example, reduce in GSH content to a certain level provides activation of several so-called vitagenes - genes that promote the synthesis of substances responsible for restoration of the antioxidant-prooxidant (redox) balance in the cell. There should be also mentioned enzymes of antioxidant protection – glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD), heat shock proteins, sirtuins and other substances. Restoration of such balance in the cell is important for overcoming stress with minimal damage. However, when the intensity of stress is excessive and adaptive synthesis of protective substances cannot oppose to the excess of free radicals (“red line” is crossed), then irreversible changes including apoptosis can occur. This process is accompanied by reduce in birds' productivity, reproductive performance, and increased mortality. Additional supply with cofactors (selenium, zinc, manganese) can be very important for additional adaptive synthesis of antioxidant enzymes in such pathological states.



**Fig. 1. Scheme of cell responses to stress resulted by adaptation or death**

The cell responds to stress by activation of specific pathways aimed at survival, which involves the aforementioned extra synthesis of molecules with antioxidant and anti-apoptotic properties

promoted by vitagenes responsible for maintaining viability of the organism in critical conditions (Fig. 1). Resistance to stress and correction of damage at the molecular level depend on functional activity of vitagenes that restore cellular homeostasis during stress and, therefore, health and productive performance of an organism. The vitagenes' expression results in synthesis of the aforementioned antioxidant enzymes (SOD and GSH-Px), heat shock proteins (chaperones) and sirtuins (the family of deacetylase enzymes with protective effects preventing the damage from free radicals), as well as enzymes providing the second phase of detoxification of foreign substances, growth factors, proteins involved in regulation of energy metabolism and maintenance of cellular calcium balance. Changes in gene expression and apoptosis are the most important elements of adaptation to stress, and they should be primarily considered in the development of techniques for stress prevention. For example, the additional synthesis of SOD and GSH-Px significantly reduces the damage of biological molecules from free radicals which are being more strictly controlled by antioxidant enzymes.

**Heat shock proteins (HSP; 19-22).** For the first time HSP were discovered peculiar to heat shock (and named so), though later the increased synthesis of HSP was found to appear at any stress – oxidation, oxygen deficiency, toxicants, radiation etc., when they provide chaperone function. Chaperones – are a large group of proteins that perform evolutionarily important functions related to cell survival in stress. These unique proteins assist the assembly and disassembly, folding and unfolding of cellular proteins; the new synthesized proteins with HSP assistance form secondary and tertiary spatial structure necessary for adequate biological activity of proteins. For proteins intended to be eliminated, HSP, on the contrary, unwind their polypeptide  $\alpha$ - and  $\beta$ -chains, and control their subsequent degradation through activation of cytoplasmic proteasomes. It was shown that stress activates not only HSP expression, but it also stimulates formation and activation of proteasomes thereby increasing catabolism and structural correction of cellular proteins. Chaperones are involved in disaggregation of misfolded proteins, destruction of protein aggregates and unfolding of native target proteins before their trans-membrane transfer; HSP themselves suppress many biochemical reactions and induce the synthesis of other chaperones and specific proteins necessary for cell survival. At the same time, the most important functions of HSP is protection of receptors of immune cells from damaging by free radicals. Recently it has been suggested that the main problem of immune system during stress is a disruption of communications between immune cells due to the damage of receptors by free radicals (3). Thus, additional protection of these receptors ensures effective communication of immune cells, their immunocompetence, and prevents immunosuppression.

**Sirtuins, and their role in stress (23-27).** Sirtuins is another important element of anti-stress protection. These proteins provide regulation of cell metabolism by modification of gene expression and activity. It is known that all body cells have a similar set of genes, but certain genes are functionally active only in specific differentiated tissues. Activity of various genes is regulated, in particular, by compaction of the DNA molecule: high degree of compaction prevents transcription, and the gene is inactive (silent genes). In eukaryotic cells, the nucleus contains chromatin, which consists of nucleic acids and proteins. Among the latter histones have a special role: they are involved in formation of nucleosomes (the first level of chromatin compaction) as core octamers consisting of eight histone molecules (two copies of H2a, H2b, H3 and H4) around which the double-stranded DNA is winded. Histones indirectly influence DNA transcription: when histones are dense packaged (and, consequently, more dense compaction of the entire DNA owing to its high-dense core of histones in a nucleosome) it makes impossible the synthesis of RNA molecules and expression of genes. Sirtuins provide the properties of histone deacetylase and mono-ADP-ribosyltransferase, which allows

assuming them as enzymes affecting the compaction of chromatin. In this way, sirtuins prevent the expression of genes whose products are not needed in the cell at time or even harmful for it. Acetylation of proteins is the main mechanism that regulates transcription; it provides key phases in the control of physiological processes such as cell life cycle, response to DNA damage, metabolism, apoptosis and autophagy. Deacetylase activity class III of histone deacetylases (sirtuins) depends on the presence of NAD<sup>+</sup>, so, their function is quite important for cellular energy metabolism. Sirtuins' activity is a connection link between the modulation of chromatin dynamics and transcriptional regulation during the oxidative stress, on one side, and the lifecycle of cells, glucose homeostasis, inflammation and various diseases, on the other. Therefore, sirtuins perform coordination of cellular response to stress of various origin including inflammation, hypoxia and heat shock; doing so, sirtuins regulate survival or cell death (apoptosis), differentiation, and endocrine signaling. In particular, sirtuins control transcription of such critical factors as NF- $\kappa$ B, p53, HIF-1, HIF-2, FOXOs, E2F1 and heat shock factor (HSF1), which are involved in regulation of cellular aging and development of various diseases.

Sirtuins are the members of antioxidant protection systems which control different phases of ROS formation and detoxification. For example, sirtuin-3 (SIRT3) provides elimination of free radicals through deacetylation of SOD (the key enzyme for elimination of superoxide radical), isocitrate dehydrogenase (the key enzyme in glucose metabolism), and major components of the electron-transfer chain (the main source of free radicals). Sirtuins are also involved in restoration of DNA damage caused by free radicals. However, migration of sirtuins to repaired DNA sites weakens their main function – chromatin compaction, which then cannot exclude accidental activation of genes leading to various metabolic disturbances. It was shown (28, 29) that during low stress cellular level of free radicals is controlled by the antioxidant system, and in this case the amount of DNA damage doesn't hinder sirtuins from functioning in both directions – DNA repairing and regulation. However, when stress elevates, increasing damage to mitochondria – a source of cellular energy – produces the excess of free radicals, and sirtuins can perform mainly just repairing action. This results in cellular metabolic imbalance negatively affecting growth, development, productive and reproductive characteristics of an organism.

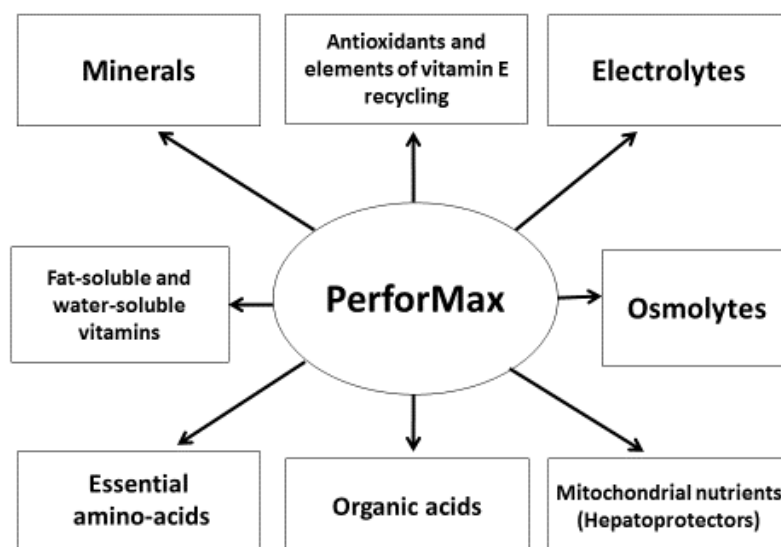
**The concept of anti-stress protection of poultry.** According to modern trends of molecular biology, adverse effects of stress can be reduced mainly by enabling all body reserves, particularly by activation of vitagenes and additional synthesis of antioxidants. In recent years, the understanding of antioxidant cell defense proceeded from a simple antioxidant dietary supplementation (mainly with vitamin E) to much more reasonable introduction to food or water of certain substances enhancing stress adaptability of an organism (carnitine, betaine, selenium, etc.). For example, it was shown that the efficacy of vitamin E antioxidant protection depends mainly on the efficiency of its recycling rather than on its content in an organism (12, 13). Therefore, supplementation with substances involved in the recycling of vitamin E (vitamin C, selenium, vitamins B1 and B2) helps to achieve high efficiency of antioxidant protection at relatively low concentrations of this vitamin.

Earlier, a number of premixes enriched with various antioxidants were developed for poultry and farm animals to use during stress (1-2, 30, 31). However, the large-scale use of such premixes appeared to be restricted due to certain problems. On the one hand, refilling the feed tank in a poultry house is technically difficult, because new feed (or supplements) can be provided to the bird only after complete spent of the previous one (sometimes it takes a few days), which complicates rapid response to a stressful situation. On the other hand, feed intake

during stress is usually reduced and supply with necessary extra vitamins, minerals and other substances with feed declines, which increases adverse effects of stress. Modern veterinary practice has adopted medication by pump medicators (dosatrons) widespread used for precise dosage and administration with water of antibiotics, probiotics, vitamins, and other preparations. The authors' concept of anti-stress treatment agrees with this common practice allowing rapid response to stress in poultry.

**Composition of the newly developed anti-stress product.** The key element of the proposed concept of anti-stress protection was choosing the components to be included in the new developed composition. Treatment of poultry is often limited by using a mixture of vitamins, minerals and amino acids, which give some positive effect. At the same time, there are many other substances (antioxidants, hepatoprotectors, osmolytes, electrolytes, organic acids, etc.) important for prevention of negative effects of stress and usually not included in compositions available in the market of various countries.

Advances of latest scientific researches and results of our own experiments have allowed to identify key components that regulate expression of vitagenes and maximize enabled anti-stress defences (Fig. 2).



**Fig. 2. Key components of the new generation anti-stress medication PerforMax (Feed-Food Magic Antistress Mix) providing the expression of vitagenes and mobilization of maximum body defences**

Composition of the new advanced anti-stress composition Feed-Food Magic Antistress Mix (PerforMax) includes the following groups of nutrients (by their properties):

- regulators of vitagenes (carnitine, betaine, vitamins A, E, D, C, selenium);
- antioxidant complex including optimum balanced doses of vitamins and minerals, necessary for efficient recycling of vitamin E in the cell;
- electrolytes, providing increased water consumption in stress and preventing damage from heat and other stresses;

- osmolytes (betaine);
- organic acids, maintaining the optimum pH in the intestine for normalizing its microflora, which in turn, protects the mucosa from damage and improves digestion;
- essential amino acids (lysine and methionine);
- mitochondrial nutrients with hepatoprotective properties (carnitine);
- substances optimizing the metabolism of mycotoxins in the liver (carnitine, betaine, vitamin E, vitamin C, selenium, lysine and methionine);
- immunomodulators (vitamins E and C, carnitine, betaine, lysine, methionine, selenium, zinc and manganese);
- fat-soluble and water-soluble vitamins, trace elements (zinc, manganese and magnum) (Fig. 2).

**Indications for use of the new anti-stress composition in commercial poultry production.**

The studies and experience with poultry industry (broiler production, rearing birds, parent stock, and commercial layers), suggest using the proposed concept of effective anti-stress protection with drinking water of the newly developed composition in the following critical periods of development:

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|--|---|
| <ul style="list-style-type: none"> <li>• First 2-5 days post-hatch</li> </ul>  | Anti-stress defence is necessary in this critical period to provide the optimal development of digestive and immune systems;                      |
| <ul style="list-style-type: none"> <li>• Vaccination</li> </ul>  | Anti-stress medication prior and post vaccination ensures the best efficiency of vaccination;   |
| <ul style="list-style-type: none"> <li>• Nutrition stresses (mycotoxicosis)</li> </ul>   | Normalization of the liver metabolism and fast metabolism of mycotoxins are key elements for health maintenance;                                  |
| <ul style="list-style-type: none"> <li>• Heat stress</li> </ul>  | Using the anti-stress supplement significantly reduces mortality, prevents decrease of growth and development, and helps to avoid production loss |
| <ul style="list-style-type: none"> <li>• Stressful technological activities (catching, thinning out, weighting, etc.)</li> </ul> | Anti-stress defence prevents decline in productive performance  |
| <ul style="list-style-type: none"> <li>• Sudden death syndrome and ascites</li> </ul>  | Using the anti-stress supplement reliefs stress load and notably decreases mortality  |

For replacement chickens, the additional stress is caused by transition to adult flock and aggressive pecking possible due to increased illumination. Under these conditions, anti-stress protection was found to be efficient as important technological approach used in many countries with developed poultry industry. In breeders and commercial layers, one of main stresses is associated with the peak of egg production, which necessitates the increased supply with a complex of biologically active substances. Protective effect of the presented anti-stress composition in mycotoxicosis was shown as well (32-35).

The presented new composition along with the proposed concept of anti-stress protection were

successfully tested in both experimental and industrial conditions. Today they are applied in many poultry companies that produce broilers, rearing birds, commercial layers and parent flocks. Along with it, beneficial anti-stress effects of this composition have been confirmed in turkey and waterfowl (36), as well as in pigs (37). So, the new anti-stress composition Feed-Food Magic Antistress Mix (PerforMax) contains the synergistic complex of substances that cooperate to provide the maximum mobilization of body defenses and to minimize negative consequences of stress. All components of Feed-Food Magic Antistress Mix (PerforMax) are provided in optimal doses ensuring the best protective effect. Development of the composition was based upon the long-term studies of molecular mechanisms of stress, as well as on knowledge of various biologically active substances and their effects on the regulation of homeostasis during stress. The proposed anti-stress composition is the new generation of products for efficient treatment of stresses and reducing their negative impact on productive and reproductive performance of poultry.

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### **S u m m a r y**

Upon the last 10 years, the numerous studies have convincingly shown the oxidative stress caused by excessive production of free radicals was the basis of the most stresses. In this, a delicate balance between anti- and pro-oxidants in the diet, gastrointestinal tract and the cells of various organs and tissues is the important factor determining the resistance to stress and provides for an adaptive capacity of the organism to stressors. The defense agents are both natural antioxidants (vitamins E and C, carotenoids) or minerals of prosthetic groups of the antioxidant enzymes (selenium, zinc, manganese and copper), consumed from fodder, and protective molecules with an antioxidant activity (glutathione, thioredoxin, coenzyme Q) or protective functions, complementary to antioxidants (heat shock proteins, sirtuins, etc.), which are newly synthesized in organism. It was established that the synthesis of the above substances is regulated by a group of genes, the vitagenes, which in fact are the most important factors of adaptive capacity. Their activity is regulated by external factors, the stressors, and a number of substances having anti-oxidant properties, in particular carnitine, vitamin E, selenium, zinc, manganese, etc. As a result of our research, the Feed-Food Magic Anti-Stress Mix (PerforMax), a new feed additive which improves the ability of animal adaptation under stress, has been developed. It helps to overcome stress at lower losses and thus increase the efficiency of animal husbandry and poultry farming. The composition consists of 28 components, including vitamins, minerals, amino acids, organic acids, electrolytes. Due to their optimized content and synergism, the efficient recycling of vitamin E is maintained to reduce the formation of free radicals in mitochondria, and a pronounced immunomodulating effect is expressed. Currently, the composition is successfully used at a number of poultry companies in Egypt, Turkey, Ukraine, Russia and in pig-producing companies in Russia and several other countries.

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