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CONFERENCE PROCEEDINGS

Autoregulation of Stress Response in Microorganisms

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Abstract—Examples are considered of the involvement of low-molecular-weight autoregulators in the development of resistance of proliferating microbial cultures to unfavorable environmental impacts of various intensity, including impacts programmed to occur in the developmental cycle ("new medium stress," starvation stress) and nonprogrammed impacts. It was shown that extracellular adaptation factors control the reversible adhesion of cells in submerged cultures and the processes of cell reactivation in the poststress period and are involved in the stabilization of cellular biopolymers (proteins and DNA) and subcellular structures (membranes); the adaptogens of the phenolic type also act as efficient scavengers of reactive oxygen species. The protective effect of the adaptogenic autoregulators is manifested in the increase of resistance of microbial cells to stressors of various nature and in the preservation of the cell proliferative ability.

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Key words: microorganisms, stress, adaptation, extracellular autoregulators

Microorganism adaptation to stress is among the most pertinent problems in microbiology. Molecular-biological studies of intracellular adaptation mechanisms have yielded much information on such events as switching on of DNA reparation systems [1, 2], operation of enzymes involved in antioxidant defense [3–6], and induction of the expression of shock proteins [7–9], including heat-shock proteins [10–12]. At the same time, in recent years, interest has increased in extracellular autoregulators that provide for cell-to-cell communication during the formation of stress response. A number of physiological processes have been described that are associated with the stationary phase of microbial cultures (determined by starvation stress or by the achievement of a critical cell population density) and are controlled by autoregulators of various nature and different mechanisms of action [13–17]. However, the role of interactions between cells and the role of exometabolites in the defense system of actively growing microbial cultures remain poorly studied.

Taking into account the aspect of this problem that is currently under consideration, attention should be given to the role of extracellular autoregulators in the development of the cell's defensive response, in the control of the processes of structural rearrangement and stabilization of subcellular structures, in reparation of damaged structures, and in cell reactivation. Autoregulators that have adaptogenic functions include proteinous protectants of *Escherichia coli* [18, 19], osmoprotectants contained in lysates of halobacteria [20], extracellular metabolites exhibiting protective and adaptogenic effects [21, 22], and microbial anabiosis autoinducers—d_1 factors, represented by alkylhydroxybenzenes (AHBs) in a number of bacteria and by tyrosol in yeasts [14]. The latter two groups of autoregulators will be discussed in greater detail later.

Propionic acid bacteria synthesize metabolites with antimutagenic properties and excrete them into the culture liquid (CL). The addition of these CLs to a *Salmonella typhimurium* test culture decreased or almost abolished the mutagenic effect of 4-nitroquinoline-1-oxide [23]. It was established that the active substance is represented by thermostable low-molecular-weight compounds of a nonpeptide nature. Apart from propionic acid bacteria, similar compounds are also produced by lactobacilli, streptococci, bifidobacteria, and *Escherichia coli. Luteococcus* representatives, which are related to propionic acid bacteria, constitutively produce, in the course of their normal developmental cycle, a thermostable low-molecular-weight extracellular protein that exhibits a reactivation effect (RF protein). The addition of RF protein to cultures subjected to lethal impacts of various stressors (heat, oxidants, UV light) increased the viable cell titer by one–two orders of magnitude. Importantly, the effect of the RF protein is inversely proportional to the number of cells surviving stress [26]. RF protein was shown to be synthesized by a number of bacteria and by the yeast *Saccharomyces cerevisiae*; it is not species-specific since it exerts influence both on its producers and other microorganisms [25, 26]. Thus, the adaptation system of propionic acid bacteria includes at least two extracellular

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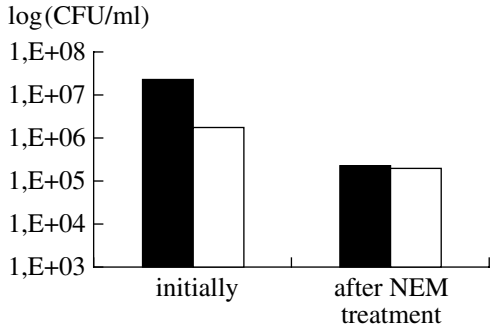

Fig. 1. Survival of adhered and free *B. licheniformis* cells after treatment with 200 μM *N*-ethylmaleimide (NEM). Filled columns, abundance of free cells; open columns, abundance of adhered cells.

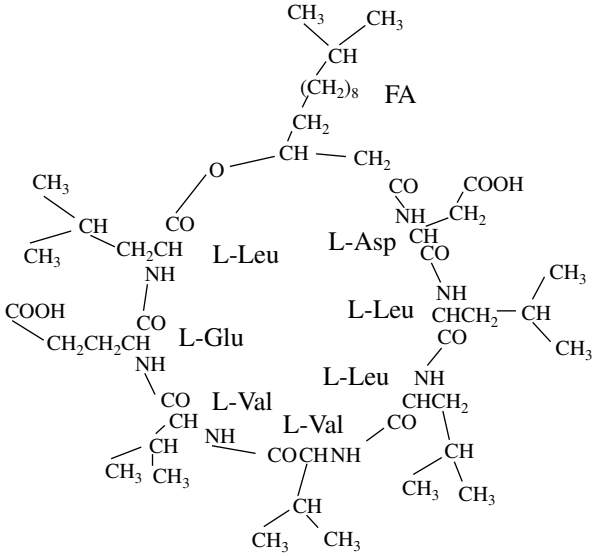

Fig. 2. Structure of the *B. licheniformis* antiadhesin. FA, fatty acid residue. Amino acid residues are designated by common abbreviations.

adaptogens: low-molecular-weight desmutagens and the RF protein, producing protective and reactivating effects.

Another group of extracellular autoregulators controls the adhesion of cell populations under conditions of stress. Cell adhesion to solid surfaces is a protective reaction of microorganisms. The involvement of reversible adhesion in the response to the "new medium stress" was shown for *Pseudomonas fluorescens* and *Bacillus licheniformis* [22, 27, 28]. Investigation of the growth parameters of *P. fluorescens* cultures developing in a medium that is new with respect to nutrient sources showed a statistically significant decrease in the number of free-swimming cells in the lag phase. The growth curve exhibited a characteristic drop within the first hour after inoculation [27].This decrease in the number of cells occurring in the liquid phase was accounted for by pseudomonad adhesion to flask walls. After that, a phase of rapid detachment of cells occurred. The protective effect of the reversible adhesion was manifested, e.g., in a tenfold increase in the resistance to the lethal action of *N*-ethylmaleimide, demonstrated for *B. licheniformis* (Fig. 1) [29].

The detachment of adhered cells is controlled by extracellular autoregulators. The bacterial antiadhesins were identified as a mixture of *n*-alkanes and extracellular protease in *P. fluorescens* [30, 31] and as a cyclic lipopeptide in *B. licheniformis* [32] (Fig. 2).

It should be noted that cyclic lipopeptides of similar (but not identical) structure were found in many gram-positive bacteria [33]. These compounds were described as biosurfactants; their biological function remained unknown. The description of the cyclic lipopeptide of *B. licheniformis* sheds light on at least one function of these cyclic lipopeptides—regulation of adhesion.

Evidently, reversible adhesion should be a widespread mechanism of microbial stress response in addition to other known mechanisms of stress responses. The arguments supporting this statement are as follows. The duration of the attachment–detachment cycles is much less than the generation time. Thus, this is a mechanism of rapid reaction of a cell population. As distinct from irreversible adhesion, this reaction does not imply change in the developmental strategy. A reversibly adhered cell has a possibility of choosing between returning to the nonadhered mode of existence (characterized by higher growth rate and greater amenability to adverse environmental factors) and continuing the attached mode of existence, with its decreased growth rate and increased resistance to adverse factors. The importance of this adaptive response is evidenced by the fine mechanism of its regulation (synthesis of several regulators of adhesion). If the stress impact persists, the reversible adhesion becomes irreversible and the population switches to development in the form of a biofilm.

The regulatory functions of the microbial extracellular d_1 factors, which were first described as anabiosis autoinducers, have been studied in greater detail [34–36]. In a number of bacteria and yeasts, the d_1 factors were shown to be represented by alkylhydroxybenzenes (AHBs) of the alkylresorcinol type [23, 36] and tyrosol [24]. Upon the increase in their concentration in a developing microbial culture, which occurs in parallel with the increase in cell number, AHBs induce the transition of the culture to the stationary growth phase; upon further increase in AHB concentration, they induce the formation of resting cystlike cells that exhibit an increased resistance to adverse impacts [37–39]. These biological effects of AHBs allowed us to assume that they contribute to increased resistance of vegetative microbial cells to stresses. To prove the adaptogenic function of AHBs, it was necessary to demonstrate an increase in their concentration during the development of stress response of a microbial pop-

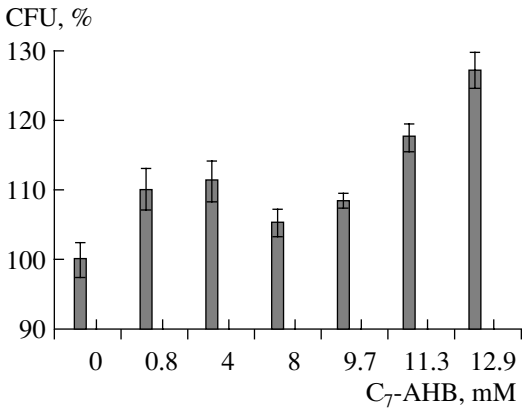

Fig. 3. Protective effect of C_7-AHB on the yeast *S. cerevisiae* subjected to oxidative stress (γ irradiation in a dose of 50 krad). Survival rate was determined 2 h after irradiation.

ulation. Such data were obtained by using as a model the bacterium *Micrococcus luteus*, in which the d_1 factor is represented by alkylresorcinol-type AHBs, whose concentration can be quantitatively determined in a specific reaction [36]. After a temperature shock, when, as a reaction, cessation of growth occurred, the amount of extracellular AHBs increased abruptly, whereas their concentration in the control culture did not change. The exit of the culture from the stressed state was associated with an increase in the intracellular AHB level and a concomitant decrease in the AHB content in the medium. In a culture exposed to shock, the total content of extra- and intracellular AHBs increased by 35% as compared to the control, which reflected the reaction of micrococcus cells to the stress impact [40]. Thus, the formation of the *M. luteus* stress response was associated with increased biosynthesis of AHBs, whose extracellular pool was redistributed between the cells of the population.

The results obtained allowed us to assume that increasing the concentration of extracellular AHBs in a microbial culture by their exogenous introduction should promote the defense of cells against subsequent

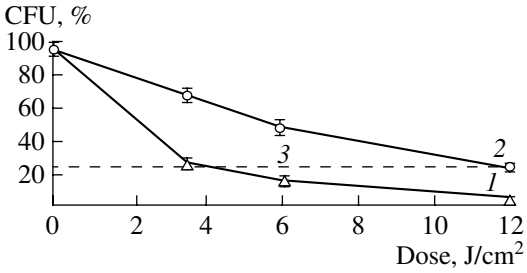

Fig. 4. Dose-dependence curves of the survival of the yeast *S. cerevisiae* treated, 30 min before irradiation, at λ = 662 nm, with (*1*) chlorine e_6 and (*2*) chlorine e_6 + 8 mM C_7-AHB. Dashed line (*3*) shows 34% survival level.

stress impacts. These adaptogenic functions of AHBs were proved by us in experiments that involved preincubation of linear-growth-phase micrococcal cells with C_7-AHB, a chemical analogue of the d_1 factor of these bacteria, which was introduced 30 min prior to heat shock. The protective effect of the AHB was concentration-dependent; the most pronounced effect was observed at 12 mM: in this case, the development of the culture after thermal treatment resumed without a lag (observed in the control culture), although at a lower rate.

It is known that the response of microorganisms to heat shock and other stress impacts is accompanied by excessive accumulation of reactive oxygen species and development of an oxidative stress [41, 42]. Therefore, the ability of AHBs to increase the thermotolerance of microbial cells allowed us to assume that they may have a wider adaptogenic effect, i.e., may protect cells from oxidative stresses of different origins. This assumption was confirmed in the experiments with the yeast *S. cerevisiae* stressed by irradiation with light or γ-rays. As a protective adaptogen, we used C_7-AHB, which was introduced into linear-growth-phase yeast cultures 30 min prior to irradiation at a dose of 50 krad. Most efficient was the concentration of 11–13 mM, the application of which resulted in a 20–45% increase in the viable cell number (as compared to the control not amended with AHB) (Fig. 3) [40].

In another model that we used, the damaging factor was singlet oxygen, which was generated upon irradiation with a laser at 662 nm in cells photosensitized with chlorine e_6. C_7-AHB was introduced into the experimental variants 30 min prior to irradiation. The optimal protective concentration was 8 mM: after its application, the dose killing 75% of cells was 3.5-fold higher than the dose producing the same effect on nonprotected cells (12 and 3.5 J/cm^2, respectively) (Fig. 4).

Thus, it was found that an increase in the AHB concentration in proliferating bacterial and yeast cultures protects their cells from stress impacts (heat shock, γ-radiation, photooxidation), which is manifested in increased resistance of cells and preservation of their proliferative ability.

What are the mechanisms of the protective effect of AHBs? The main reactions forming the stress response of cells are an increase in the stability of cellular structures, enzymes and DNA first of all, and in increase in the level of antioxidant defense. The function of stabilizers can be performed by molecular chaperones, which are proteins whose structure is complementary to the structure of the protected proteins [43]; chemical chaperones are also known, which are low-molecular-weight compounds able to form complexes with macromolecules at the expense of weak physicochemical interactions, stabilizing thereby their spatial structure and promoting the dissipation of energy [44]. Readily oxidizable compounds, along with the antioxidant defense enzymes, play an important role in scavenging

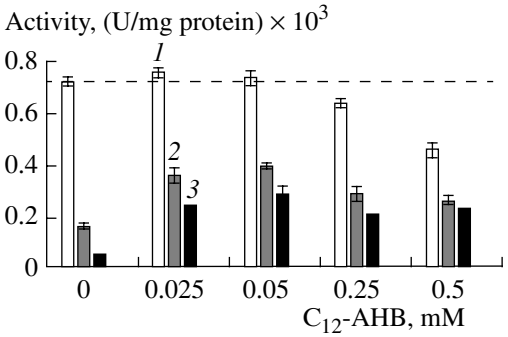

Fig. 5. Thermostability of trypsin in a complex with C_{12} AHB. The preincubation time was 40 min and the duration of heating at 60°C: (*1*) 0 min (control), (*2*) 10 min, and (*3*) 20 min.

reactive oxygen species (ROS). Specifically, we showed the capacity for ROS scavenging to be peculiar to some phenolic compounds. The in vitro experiments that demonstrated the above-described functions of AHB are considered below.

The experiments were conducted with C_{12}- and C_7-AHBs (alkylresorcinols, which are chemical analogues of bacterial d_1 factors) and tyrosol (d_1 factor of yeasts). These compounds differ in their hydrophobicity (determined by the length of the alkyl chain) and polarity (determined by the number and position of hydroxyl groups in the aromatic ring). These properties influence interactions of the AHBs with biopolymer molecules. The chaperone functions of AHBs were judged from their effect on the stability and catalytic activity of the enzymes trypsin and α- and β-amylases.

The effect of the complexation of the enzymes with C_{12}-AHB (the most hydrophobic homologue) depended on its concentration and the duration of interaction. In low concentrations, C_{12}-AHB somewhat increased the activity of trypsin, and, in a broad range of higher concentrations, it inhibited trypsin activity, with complete suppression at certain concentrations. In parallel with the alteration of activity of the modified enzymes, their resistance to denaturing impacts increased. For example, the activity of nonstabilized trypsin under thermal denaturation at 60°C for 10 or 20 min decreased to 20 and 5%, whereas, in a complex with C_{12}-AHB, trypsin retained 50% of its activity (Fig. 5).

The conjugation between the increase in stability of the enzymes modified by chaperones and the decrease in the enzymatic activity, observed in our experiments, has also been noted in most analogous enzymological works; however, it is not inevitable from the theoretical viewpoint. Our experiments with a less hydrophobic homologue, C_7-AHB, demonstrated a concomitant increase in the stability and activity of enzymes. Upon complexation with trypsin and α- and β-amylases, C_7-AHB increased their activity by 100% at a certain concentration [45]. In parallel with the increase in activity, the modified enzymes exhibited an increase in

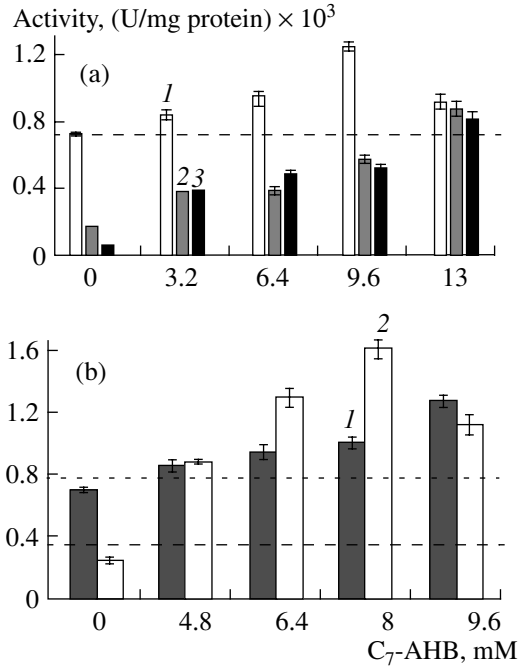

Fig. 6. (a) Thermostability and (b) radiostability of trypsin in a complex with C_7-AHB. (a) Preincubation time, 60 min; the duration of heating at 60°C: (*1*) 0 min (control), (*2*) 10 min, and (*3*) 20 min. (b) Preincubation time, 40 min; γ irradiation dose, 12.7 krad; *1*, activity of nonirradiated trypsin; *2*, activity of irradiated trypsin. Dashed line shows the activity of control after irradiation; dotted line shows the activity of control before irradiation.

thermo- and radiostability (Fig. 6). The temperature and pH ranges of the catalytic activities broadened significantly (Fig. 7). Tyrosol, which is the yeast d_1 factor, produced an action analogous to that of C_7-AHB, which was suggestive of similarity of the chaperone action of these bacterial and yeast autoregulators. These in vitro experiments were the first to demonstrate the ability of factor d_1 chemical analogues (C_7- and C_{12}-AHB and tyrosol) to perform targeted modification of the structure of enzymes, resulting in an increase in their stability and in alteration of their catalytic activity (either activation or inhibition).

The changes in the activity of the enzymes stabilized by AHBs correlated with changes in their kinetic characteristics. Upon trypsin complexation with C_{12}- or C_7-AHB, the Michaelis constant virtually did not change and was equal to the K_m in the control variant (100 mM). Thus, the interaction of trypsin with either of the homologues did not change the conformation of its active center, and the affinity to the substrate remained unaltered. However, the V_{max} value exhibited statistically significant changes as compared to the control (2.1 μmol/(min mg protein)): it decreased by 10–30% upon trypsin interaction with C_{12}-AHB (to 1.4–1.8 μmol/(min mg protein)) and increased by 15–75% upon its complexation with C_7-AHB (to 2.4–3.7 μmol/(min mg protein)). The direction of activity

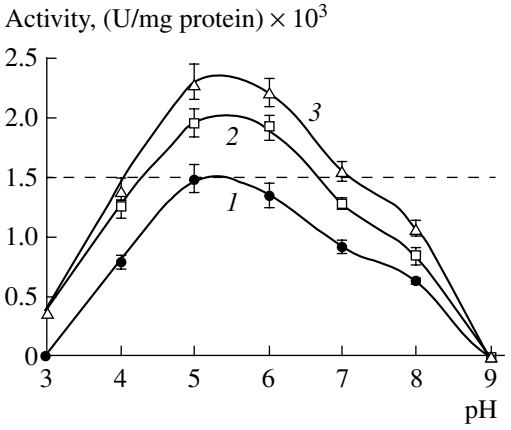

Fig. 7. Effect of C_7-AHB (preincubation time, 30 min) on the activity of β-amylase at various pH values: (*1*) control without AHB; (*2*) 0.64 mM AHB; (*3*) 5.6 mM AHB.

changes correlated with the direction of the changes in hydrophobicity. Upon trypsin interaction with C_7-AHB, its hydrophobicity index decreased and its catalytic activity increased, whereas after complexation with C_{12}-AHB, hydrophobicity increased and the activity decreased (Fig. 8).

Thus, AHBs differing in their hydrophobicity produce different changes in the physicochemical properties and functional activity of enzymes. The correlation that we revealed between the changes in the hydrophobicity index of enzymes, occurring upon complexation with structurally different AHBs, and the direction of changes in the enzymatic activity provides an opportunity to regulate the efficiency of enzymatic catalysis (both stimulation and inhibition are possible). Since AHBs are produced by microorganisms in the form of a mixture of homologues and isomers [14, 34, 36, 46], the described mechanism of the regulation of cell metabolic activities is important for the flexible physiological response of microorganisms to stress impacts.

The results obtained allow an assumption to be made that the structure of AHBs makes them able to change the solvate coatings of proteins and the properties of the water in them, thus influencing enzyme stability and activity; this does not contradict the earlier demonstrated ability of chemical chaperones (such as ectoine, betaine, and glycine, synthesized by bacteria) to modify the hydration of protein molecules [47, 48].

Taking into account the important role of nonenzymatic antioxidant defense of microorganisms from the ROS formed under stress impacts of different nature, we conducted experiments aimed at elucidating the molecular mechanisms of the antioxidant aspect of the protective effect of AHBs. The functioning of AHBs as ROS scavengers was studied under conditions of constant and pulsed radiolysis (γ irradiation) or photooxidation or chemical oxidation of AHB solutions [49]. By using HPLC and gas chromatography–mass spectrometry, we revealed conversions of native AHB molecules

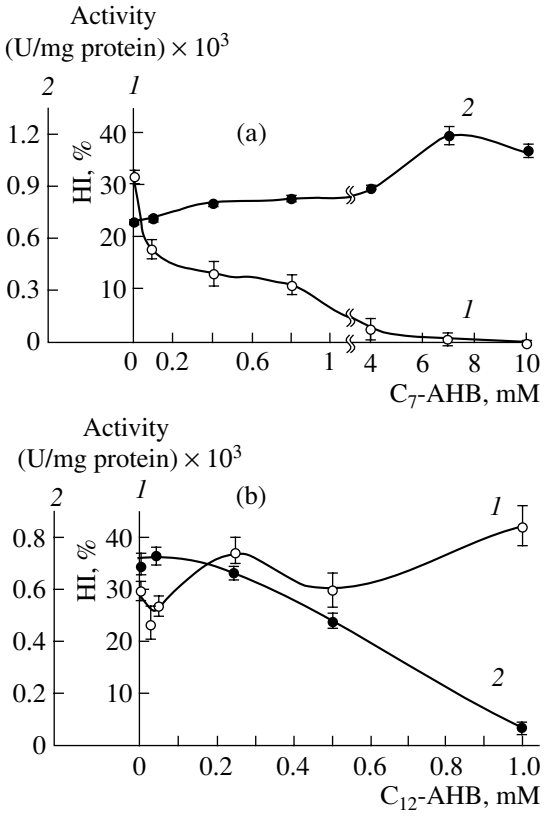

Fig. 8. Concentrational dependence of the effect of (a) C_7-AHB and (b) C_{12}-AHB on the (*1*) hydrophobicity index (HI) and (*2*) activity of trypsin. Preincubation time was 10 min for C_7-AHB and 60 min for C_{12}-AHB.

with the formation of "light" and "heavy" fractions, among which we discovered isomers of tri- and tetrahydroxyalkylbenzenes, corresponding quinones, and products of di- and trimeric condensation of oxidized and native AHB molecules.

Thus, the AHBs accumulating in microbial cells under conditions of oxidative stress function as ROS scavengers. It should be emphasized that, since the oxidation of AHBs is a multistage process, the oxidized AHB forms produced in the succession of redox reactions retain their functional activity as antioxidants and modifiers of the structure of cellular biopolymers [50].

The examples that we have considered allow a conclusion to be made that extracellular low-molecular-weight autoregulators performing adaptogenic functions play an important role in the development of the resistance of cells of proliferating microbial cultures to adverse environmental impacts. Under stresses, both those programmed to occur in the developmental cycle (new medium stress, starvation stress) and those nonprogrammed (temperature, pH, oxidative stresses, etc.), the extracellular adaptation factors control the reversible adhesion of cells in submerged cultures and the processes of cell resuscitation in the poststress period and are involved in the stabilization of cellular biopolymers (proteins and DNA) and subcellular structures

(membranes); the adaptogens of the phenolic type have one more function—they are efficient scavengers of ROS.

The protective effect of adaptogenic autoregulators is manifested in an increase in the resistance of microbial cells to stressors of different nature and in the retained proliferative capacity of the cells.

The fact that the adaptogenic autoregulators are not species-specific suggests their important role in the stabilization of the functioning of microbial communities.

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