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# EFFECTS OF CHEMICAL AND NATURAL COMPOUNDS ON THE BIOCHEMICAL ACTIVITY OF *STAPHYLOCOCCUS AUREUS*

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**Abstract**

Understanding the specific mechanisms of action of antimicrobial compounds is essential not only for evaluating their therapeutic potential but also for advancing a pharmaceutical product from concept to clinical application. In this study, three newly synthesized chemical compounds and two Spirulina extracts were evaluated for their effects on *Staphylococcus aureus* strains. Changes in key biochemical parameters were assessed, and all experimental results were analyzed using both descriptive and inferential statistical methods.

The results showed that Spirulina extracts exert no direct cytotoxic effects on *S. aureus*, as evidenced by stable levels of malondialdehyde and extracellular lactate dehydrogenase comparable to control values. In contrast, the chemical compounds, even at minimally inhibitory concentrations, induced pronounced toxic effects, including increased malondialdehyde levels, elevated extracellular lactate dehydrogenase activity, and suppression of primary antioxidant enzymes.

Notably, the combined application of chemical and Spirulina compounds enhanced these effects, despite the chemical compounds being used at 2–4 times lower concentrations than when applied individually. This observation indicates a synergistic interaction between the chemical and biological agents, highlighting their potential as effective antibacterial formulations with reduced cytotoxicity.

***Keywords:*** chemical compounds, Spirulina extracts, *Staphylococcus aureus*, biochemical parameters.

# EFECTELE COMPUȘILOR CHIMICI ȘI NATURALI ASUPRA ACTIVITĂȚII BIOCHIMICE A *STAPHYLOCOCCUS AUREUS*

**Rezumat**

Înțelegerea mecanismelor de acțiune ale compușilor antimicrobieni este esențială atât pentru evaluarea potențialului terapeutic, cât și pentru dezvoltarea unui produs farmaceutic, de la concept până la aplicarea clinică. În acest studiu au fost evaluați trei compuși chimici noi sintetizați și două extracte de Spirulina asupra tulpinilor de *Staphylococcus aureus*. Modificările parametrilor biochimici cheie au fost investigate, iar toate rezultatele experimentale au fost analizate prin metode statistice descriptive și inferențiale.

Rezultatele au arătat că extractele de Spirulina nu exercită efecte citotoxice directe asupra *S. aureus*, ceea ce se reflectă în menținerea nivelurilor de dialdehidă malonică și lactat dehidrogenază extracelulară comparabile cu valorile de control. În schimb, compușii chimici, chiar și la concentrații minim inhibitorii, au determinat efecte toxice semnificative, incluzând creșterea nivelului de dialdehidă malonică, creșterea activității lactat dehidrogenazei extracelulare și scăderea activității enzimelor antioxidante primare.

Aplicarea combinată a compușilor chimici cu extractele de Spirulina a amplificat aceste efecte, deși concentrația compușilor chimici a fost de 2–4 ori mai mică comparativ cu utilizarea individuală. Aceasta sugerează existența unui efect sinergic între agenții chimici și cei biologici, evidențiind potențialul lor ca formulări antibacteriene eficiente, cu citotoxicitate redusă.

***Cuvinte-cheie:*** compuși chimici, extracte de Spirulina, *Staphylococcus aureus*, parametri biochimici.

**Introduction**

The intensity of oxidative stress induced by various exogenous factors in living cells can be evaluated either through the direct measurement of reactive oxygen species and free radicals or indirectly, by assessing biomarkers that reflect the degradation of cellular components. From a methodological perspective, the use of biological markers is more practical, as these compounds are significantly more stable than reactive species. Moreover, they provide information not only about the current oxidative status but, more importantly, about cumulative and often irreversible cellular alterations [1,6].

Biomarkers derived from the oxidative degradation of major classes of biological macromolecules, namely nucleic acids, proteins, and lipids, are widely employed to assess cellular stress. Among these, 8-hydroxydeoxyguanosine is commonly used as an indicator of oxidative DNA damage, while protein oxidation can be evaluated by measuring carbonylated proteins and nitrated derivatives such as 3-nitrotyrosine. In addition, reactive oxygen species contribute to the formation of advanced glycation end products (AGEs) and advanced oxidation protein products (AOPP) [1-3].

However, the most reliable and extensively utilized indicators of oxidative stress are the end products of lipid peroxidation. This process generates a variety of secondary compounds, among which malondialdehyde (MDA) and 4-hydroxy-2-nonenal are predominant. MDA results from the breakdown of polyunsaturated fatty acids, including those derived from arachidonic acid metabolism during thromboxane $A_2$ synthesis. Its quantification is commonly based on its reaction with thiobarbituric acid under acidic conditions (pH 3.5), forming an MDA–TBA adduct that can be detected spectrophotometrically at 532 nm (thiobarbituric acid reactive substances assay). Measurement of intracellular MDA levels is widely applied for identifying stress conditions and evaluating the toxic effects of various compounds. Due to its broad applicability across different cell types, including prokaryotes, MDA is considered a universal biomarker and can also serve as an indicator in the assessment of pharmaceutical efficacy and safety [4, 12].

Another important indicator of cellular damage induced by xenobiotics is lactate dehydrogenase (LDH). This enzyme plays a central role in cellular metabolism by catalyzing the conversion of pyruvate to lactate while regenerating $NAD^+$, thereby sustaining glycolysis. Beyond its metabolic function, LDH contributes to microbial virulence and stress resistance by maintaining cellular redox balance. Reduced LDH activity has been associated with increased susceptibility of microorganisms to environmental stressors, including antimicrobial agents, as well as impaired capacity for host colonization. Under normal conditions, LDH activity is confined intracellularly; however, membrane damage or increased permeability caused by toxic agents leads to its release into the extracellular environment. Therefore, extracellular LDH activity is widely regarded as a sensitive marker of cell damage and cytotoxicity [7, 9].

Cellular defense against oxidative stress is mediated by antioxidant systems, in which enzymatic components play a pivotal role. Superoxide dismutase, catalase, and peroxidases constitute the primary antioxidant enzymes responsible for neutralizing reactive oxygen species and limiting oxidative damage. In pathogenic microorganisms, these enzymes may also be secreted into the extracellular environment, contributing to protection against host immune responses. This mechanism facilitates the neutralization of reactive species generated at the host-pathogen interface, thereby enhancing microbial survival and persistence [11].

**Materials and Methods**

*Chemical and natural compounds*

The study included newly synthesized chemical compounds, KSS ($C_{13}H_{16}Br_2CuN_4S$), TIS ($C_{14}H_{19}CuN_7O_4S$), and SVA ($C_{10}H_{14}CuN_4O_5S_2$), obtained in the Laboratory of Advanced Materials in Biopharmaceutics and Technics, Institute of Chemistry, Moldova State University.

High-purity reagents from Sigma-Aldrich, Acros Organics, and Alfa Aesar were used as synthesis precursors.

Biologically active compounds were represented by extracts and complexes (ES and MX) derived biotechnologically from the cyanobacterium Spirulina platensis CNMN CB-02, sourced from the National Collection of Non-pathogenic Microorganisms (Institute of Microbiology and Biotechnology).

The ES extract consists of an amino acid and oligopeptide complex (≤10 kDa), containing both non-essential (e.g., glycine, alanine, serine, cysteine) and essential amino acids (e.g., leucine, lysine, methionine), as well as functionalized macro- and microelements. For in vitro assays, ES was used as a 10 mg/mL solution in 50% ethanol.

The MX extract represents a myxoxanthophyll carotenoid pigment isolated from Spirulina biomass, with a concentration of 0.214 mg/mL in 80% aqueous ethanol.

*Bacterial strains*

The reference strain Staphylococcus aureus ATCC 25923, obtained from the American Type Culture Collection (ATCC), was used in this study. Prior to experimentation, the strain was pre-cultured in Tryptic Soy Broth.

Bacterial growth and maintenance were performed on Tryptic Soy Agar and Mannitol Salt Agar (bioMérieux, France), according to standard microbiological procedures.

Determination of biochemical parameters

Malondialdehyde (MDA) assay. Lipid peroxidation was assessed by measuring malondialdehyde (MDA), a key marker of oxidative stress, using the thiobarbituric acid (TBA) reaction. Briefly, 100 mg of bacterial biomass was homogenized in 1 mL of 20% trichloroacetic acid and centrifuged at 12,000 g for 5 min. An aliquot of 0.4 mL supernatant was mixed either with 0.4 mL of 20% trichloroacetic acid (control) or 0.4 mL of 0.5% TBA. Samples were incubated at 98°C for 30 min, cooled to room temperature, and absorbance was measured at 532 nm and 600 nm.

Lactate dehydrogenase (LDH) activity. LDH activity was determined in the culture supernatant by monitoring NADH oxidation. The reaction mixture contained 100 mM pyruvate and NADH in 500 mM potassium phosphate buffer (pH 7). After adding 100 µL of sample, absorbance was recorded at 340 nm for 5 min. Enzyme activity was expressed as U/L, where one unit corresponds to the oxidation of 1 µmol of NADH per minute.

Superoxide dismutase (SOD) activity. SOD activity was measured using a xanthine–xanthine oxidase system to generate superoxide radicals. These react with 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride (INT), forming a red formazan dye. SOD activity was evaluated based on the inhibition of formazan formation [8].

*Catalase (CAT) activity.* Catalase activity was assessed by quantifying residual hydrogen peroxide ($H_2O_2$) after enzymatic decomposition into water and oxygen. The reaction was stopped with sodium azide, and the remaining $H_2O_2$ was measured via a colorimetric reaction with 3,5-dichloro-2-hydroxybenzenesulfonic acid and 4-aminoantipyrine in the presence of peroxidase, forming a quinoneimine dye. Absorbance was measured at 520 nm, and activity was calculated using a calibration curve [8].

*Glutathione peroxidase (GPx) activity.* GPx activity was determined by monitoring the oxidation of reduced glutathione (GSH) by cumene hydroperoxide. In the presence of glutathione reductase and NADPH, oxidized glutathione (GSSG) is rapidly reduced back to GSH, accompanied by NADPH oxidation to $NADP^+$. The decrease in absorbance at 340 nm was recorded and is proportional to GPx activity [8].

*Statistical data analysis*

Experimental data were analyzed using descriptive statistics (mean ± standard deviation) and inferential statistics. Statistical significance was assessed using Student's t-test. All analyses were performed using Microsoft Excel.

**Results and discussion**

The level of toxicity of individual chemical and biological compounds and in combinations was assessed by the amount of malondialdehyde yde in the biomass of the studied microorganisms.

Natural compounds did not significantly affect malondialdehyde levels in *Staphylococcus aureus* strains, as the values obtained for myxoxanthophyll and Spirulina extract were comparable to the control (Figure 1).

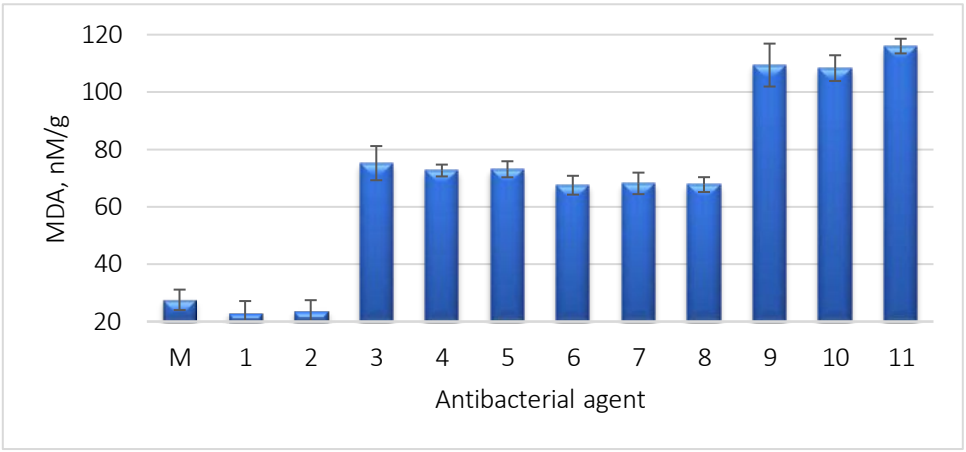



**Figure 1.** The influence of the tested compounds on the amount of malondialdehyde in the cell mass of *S. aureus*.

*M – control, 1 – myxoxanthophyll (MX), 2 – spirulina extract (ES), 3 – TIS; 4 – TIS+ES; 5 – TIS+MX; 6 – SVA; 7 – SVA+ES; 8 – SVA+MX; 9 – KSS; 10 – KSS+ES; 11 – KSS+MX*

In contrast, all tested chemical compounds induced a substantial increase in MDA content, indicating intensified lipid peroxidation. TIS and SVA, applied both individually and in combination with natural extracts, increased MDA levels by approximately 2.5–2.7 fold relative to the control. The most pronounced effect was observed for the KSS compound, which induced a 3.9–4.2 fold increase in MDA levels, regardless of the mode of application.

Overall, the elevated levels of lipid peroxidation suggest a high susceptibility of *S. aureus* to the tested chemical compounds.

The integrity and selective permeability of the bacterial cell membrane were evaluated by measuring lactate dehydrogenase activity in the extracellular medium. LDH is normally confined to the intracellular space and is released only upon cell lysis, whether due to physiological processes (e.g., programmed cell death) or exposure to toxic compounds.

In control cultures, LDH activity was 155 U/L. All tested chemical compounds induced an increase in extracellular LDH, indicating cellular stress, with KSS showing the most pronounced effect (figure 2).

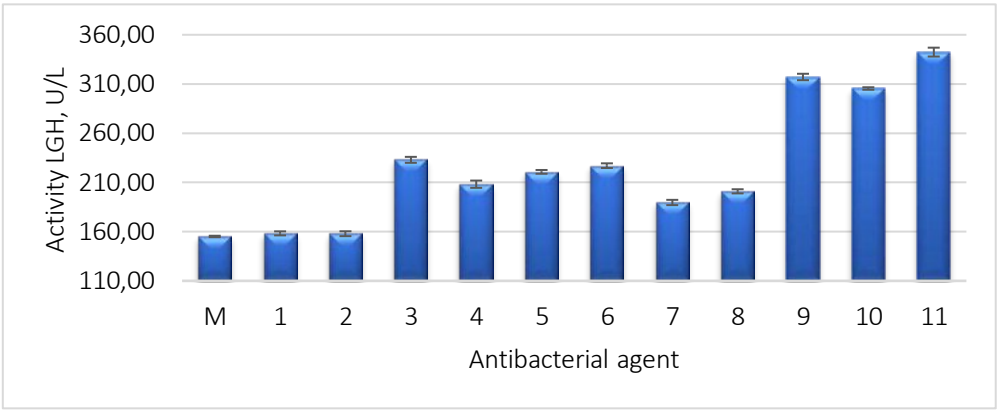



**Figure 2.** Influence of the tested compounds on the activity of lactate dehydrogenase released by *S. aureus*.

*M – control, 1 – myxoxanthophyll (MX), 2 – spirulina extract (ES), 3 – TIS; 4 – TIS+ES; 5 – TIS+MX; 6 – SVA; 7 – SVA+ES; 8 – SVA+MX; 9 – KSS; 10 – KSS+ES; 11 – KSS+MX*

Applied individually, KSS caused a twofold increase in LDH activity, which rose to 2.2-fold when combined with myxoxanthophyll, a statistically significant enhancement ($P = 0.0007$).

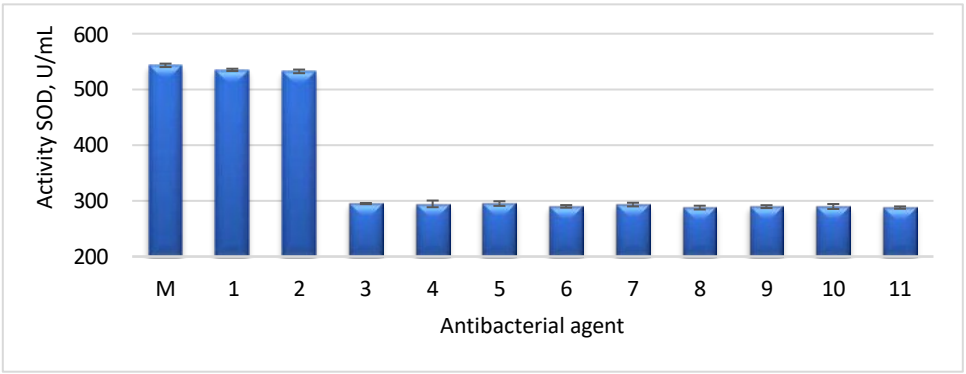
These results indicate that KSS exhibits the highest cytotoxicity among the tested compounds, as reflected by LDH release.

Under conditions of severe stress, the activity of antioxidant enzymes declines, which compromises the cell's ability to neutralize reactive oxygen species and other free radicals generated by exposure to toxic xenobiotics. Such a reduction in enzymatic activity diminishes the protective capacity of the cell, rendering it more susceptible to oxidative damage and associated disruptions of cellular functions.

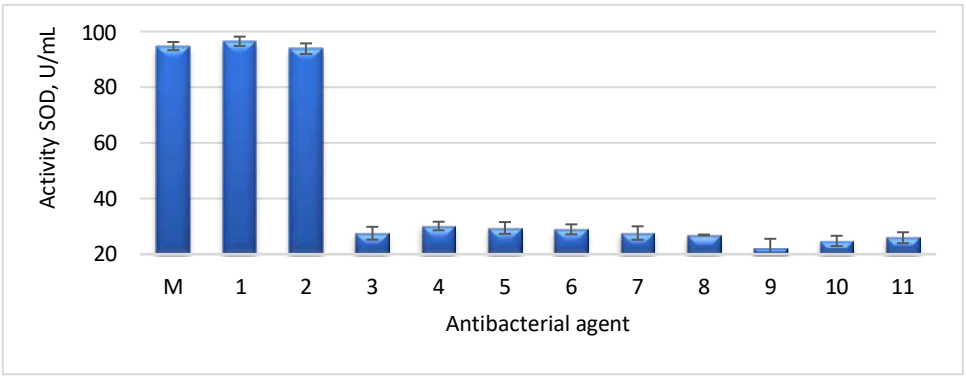
In the bacterial cultures studied, the primary line of antioxidant defense is provided by key enzymes that specifically target different reactive species. Superoxide dismutase catalyzes the dismutation of superoxide radicals into hydrogen peroxide, thereby preventing the accumulation of highly reactive superoxide anions. Hydrogen peroxide, in turn, is detoxified by catalase (CAT) and glutathione peroxidase (GPx), which convert it into water and molecular oxygen, limiting its potential to initiate lipid peroxidation and protein oxidation.

SOD activity was assessed both within the bacterial cells and in the culture medium, reflecting its role in intracellular defense as well as potential extracellular protective effects. In contrast, CAT and GPx activities were measured only in the cell mass, since their extracellular concentrations were below the detection threshold of the applied assays and considered physiologically insignificant. This observation highlights that, in these bacterial strains, the majority of hydrogen peroxide scavenging is confined to the intracellular environment, emphasizing the critical importance of these enzymes for maintaining redox homeostasis and cellular integrity under stress conditions.

Figure 3 shows the effect of antibacterial agents on SOD activity in *Staphylococcus aureus*. Natural compounds, myxoxanthophyll and ES Spirulina extract, did not produce significant changes, with intracellular and extracellular SOD activity remaining at control levels.




(a)




(b)

**Figure 3.** Influence of tested compounds on superoxide dismutase activity in (a) biomass and (b) culture liquid in *S. Aureus.*

*M – control, 1 – myxoxanthophyll (MX), 2 – spirulina extract (ES), 3 – TIS; 4 – TIS+ES; 5 – TIS+MX; 6 – SVA; 7 – SVA+ES; 8 – SVA+MX; 9 – KSS; 10 – KSS+ES; 11 – KSS+MX*

In contrast, all tested chemical compounds caused a pronounced reduction in SOD activity. Intracellular SOD activity decreased by 45–47% in all experimental variants, except those treated with individual natural compounds, while extracellular SOD activity was more strongly affected, decreasing by 69.8–77.9%. Among the chemical agents, KSS and SVA caused the most substantial reduction in intracellular SOD, whereas KSS exhibited the strongest effect on extracellular SOD. TIS also reduced extracellular SOD, but to a slightly lesser extent than KSS. The combination of chemical compounds with natural extracts did not produce significant differences compared to the individual chemical treatments, indicating that the presence of Spirulina derivatives does not mitigate the inhibitory effect on SOD.

The inactivation of SOD represents a critical stress for aerobic bacteria, as it impairs their ability to detoxify superoxide radicals produced during normal metabolism and in response to toxic agents. In pathogenic microorganisms, reduced extracellular SOD activity may lower their capacity to counteract reactive oxygen species released by host immune cells, effectively reducing pathogenicity. This mechanism suggests that the tested chemical compounds can impair bacterial antioxidant defenses and potentially enhance the efficacy of antimicrobial strategies, including against strains resistant to conventional antibiotics.

Hydrogen peroxide is a highly reactive molecule with pronounced cytotoxic effects, due to its relatively long lifetime compared to other free radicals. In living cells, its detoxification is mediated by several enzymes, with catalase and peroxidase serving as the primary defenses. Catalase activity in bacterial cultures exposed to the studied antibacterial agents is shown in Figure 4.

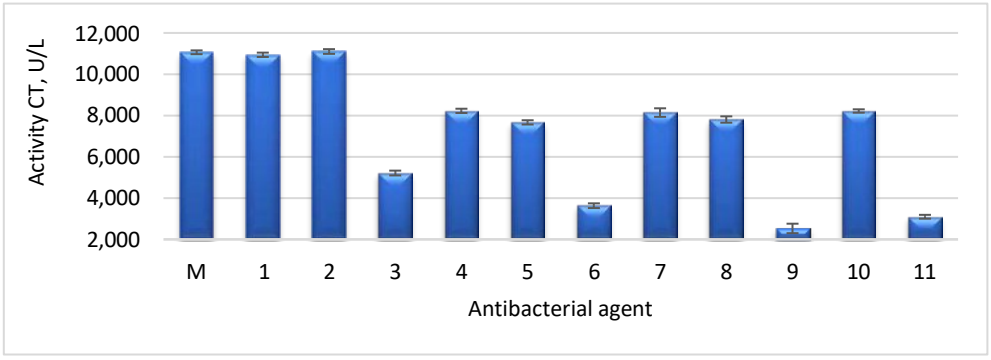



**Figure 4.** Influence of tested compounds on catalase activity in *S. aureus.*

*M – control, 1 – myxoxanthophyll (MX), 2 – spirulina extract (ES), 3 – TIS; 4 – TIS+ES; 5 – TIS+MX; 6 – SVA; 7 – SVA+ES; 8 – SVA+MX; 9 – KSS; 10 – KSS+ES; 11 – KSS+MX*

In *S. aureus*, the application of natural compounds, did not produce statistically significant changes in catalase activity compared to the control. In contrast, all tested chemical compounds caused a substantial decrease in CAT activity, reflecting oxidative stress, with partial mitigation observed when these compounds were combined with natural extracts.

The TIS compound reduced CAT activity by 52.9% when applied alone. In combination with ES extract, the reduction was limited to 25.6%, while with MX, the decrease was 30.7%. Similarly, the SVA compound applied individually decreased CAT activity by 67.2%, whereas its combination with ES reduced the effect to 26.4% and with MX to 30.0%.

The most pronounced inhibitory effect was observed with the KSS compound. Applied alone, KSS reduced CAT activity by 77.1%. When combined with ES extract, CAT activity was partially restored, showing a 25.7% decrease relative to control, whereas the KSS+MX combination still resulted in a 72.0% reduction, despite the lower concentration of the compound in this mixture.

Overall, these results indicate that the tested chemical compounds strongly impair catalase-mediated antioxidant defense in *S. aureus*, while natural Spirulina derivatives can partially protect enzymatic activity, with ES extract generally more effective than MX.

Another key enzyme responsible for the detoxification of hydrogen peroxide is glutathione peroxidase. The results of GPx activity in bacterial cultures exposed to the tested agents are presented in Figure 5.

In *S. aureus*, natural compounds (myxoxanthophyll and ES Spirulina extract) did not induce significant changes in GPx activity.

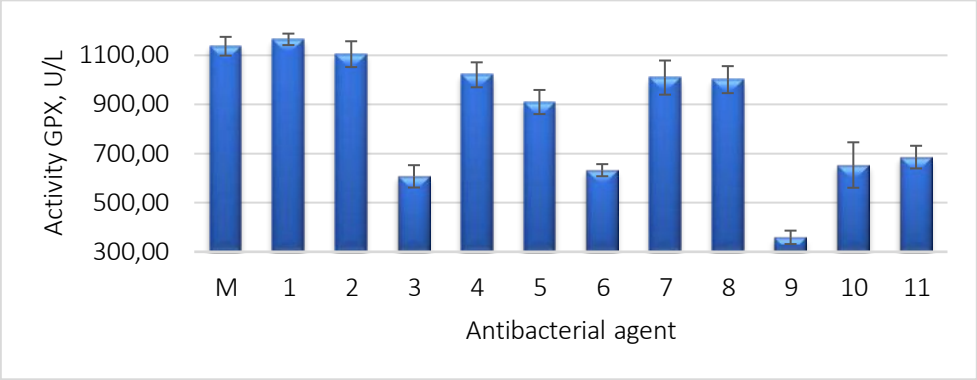



**Figure 5.** Influence of tested compounds on glutathione peroxidase activity in *S. aureus*

*M – control, 1 – myxoxanthophyll (MX), 2 – spirulina extract (ES), 3 – TIS; 4 – TIS+ES; 5 – TIS+MX; 6 – SVA; 7 – SVA+ES; 8 – SVA+MX; 9 – KSS; 10 – KSS+ES; 11 – KSS+MX*

All tested chemical compounds markedly reduced GPx activity when applied individually. The TIS compound caused a 46.6% decrease, while its combination with ES extract or MX resulted in smaller reductions of 10.2% and 20%, respectively. The SVA compound decreased GPx activity by 44.4% when applied alone, whereas combinations with ES or MX limited the reduction to 11.2% and 12.0%, respectively. KSS exhibited the most pronounced effect, reducing GPx activity by 68.4% when applied alone. In combination with ES extract or MX, the inhibition was still substantial but less severe, at 42.5% and 39.7%, respectively.

These results indicate that both individual chemical compounds and their combinations strongly impair the activity of GPx in *S. aureus*, paralleling the effects observed for catalase. The inhibition of these key antioxidant enzymes compromises the bacteria's ability to detoxify hydrogen peroxide, effectively blocking the first line of cellular antioxidant defense. When combined with previously observed decreases in superoxide dismutase activity, these effects render *S. aureus* cells highly vulnerable to oxidative stress, suggesting a potential mechanism through which these agents could enhance antibacterial efficacy.

The success of *Staphylococcus aureus* in establishing infections is closely linked to its ability to withstand oxidative stress generated by the host immune system. Macrophages and other immune cells produce superoxide radicals through NADH-oxidase activity, which are subsequently converted to hydrogen peroxide via superoxide dismutase (SOD). Hydrogen peroxide is highly reactive, particularly with Fe(II)-containing proteins, leading to irreversible oxidative modifications such as carbonylation and protein aggregation. Certain amino acids, including cysteine, methionine, and tryptophan, are especially susceptible to oxidation, resulting in both reversible (sulfenic acid formation and thiolation) and irreversible (sulfinic and sulfonic acids) modifications. These post-translational changes can trigger bacterial stress responses, including activation of specific signal transduction pathways that help maintain cell survival under oxidative pressure [9].

In *S. aureus*, exposure to metal ions, such as silver (I), or natural compounds like glabridin, induces oxidative stress by increasing the intracellular levels of reactive oxygen species (ROS), including hydrogen peroxide and nitric oxide radicals. This ROS accumulation can damage key macromolecules, including DNA, lipids, and proteins, highlighting the vulnerability of pathogenic bacteria to oxidative stress [10].

Bacterial survival under oxidative conditions relies heavily on antioxidant enzymes, including SOD, catalase (CAT), and glutathione peroxidase (GPx). These enzymes neutralize

superoxide radicals and hydrogen peroxide, preventing cellular damage. In *S. aureus*, exposure to bactericidal antibiotics such as vancomycin or ciprofloxacin has been associated with increased hydroxyl radical formation, reduced catalase expression (katA), and decreased CAT activity. Such changes underscore the role of antioxidant defenses in mediating bacterial tolerance to both endogenous and exogenous ROS [5, 11-13].

Overall, antibacterial agents induce a state of oxidative stress in *S. aureus*, characterized by ROS accumulation, decreased total antioxidant capacity, and inhibition of key protective enzymes. Monitoring these responses in bacterial biomass provides valuable insight into the mechanism of action of tested compounds and their potential therapeutic efficacy. The observed sensitivity of *S. aureus* to oxidative imbalance emphasizes the importance of targeting antioxidant defenses in the development of new antimicrobial strategies.

**Conclusions**

1. ES Spirulina extract and myxoxanthophyll exhibit no direct cytotoxicity toward *Staphylococcus aureus*, as evidenced by stable levels of malondialdehyde and lactate dehydrogenase comparable to control values. Similarly, these natural compounds do not impair the activity of primary antioxidant enzymes, indicating the preservation of cellular redox homeostasis.

2. Chemical compounds TIS, SVA, and KSS, even at minimally inhibitory concentrations, exert pronounced toxic effects on S. aureus. These effects include elevated malondialdehyde levels, reflecting lipid peroxidation, increased extracellular lactate dehydrogenase activity, indicating membrane damage, and suppression of primary antioxidant enzymes, demonstrating disruption of intracellular redox balance.

3. Combinations of chemical compounds with ES Spirulina extract or myxoxanthophyll effectively modulate these toxic effects, even at 2–4 times lower concentrations than those applied individually. This highlights their potential as efficient antibacterial formulations with reduced cytotoxicity.

4. Synergistic interactions between the chemical compounds (TIS, SVA, KSS) and natural extracts (ES, MX) appear to enhance antimicrobial activity through mechanisms not fully elucidated in this study, offering promising prospects for the development of antibacterial agents with low toxicity and reduced potential for resistance development.

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