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COMPARATIVE STUDY OF THE GENOTOXICITY OF 9-AMINOACRIDINE AND 8-METHOXYPSORALEN USING A BACTERIAL BIOSENSOR

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SUMMARY

A comparative study based on the genotoxicity of 9-aminoacridine (9-AA) and 8-methoxypsoralen (8-MOP) transpired using a lux biosensor *E. coli* MG1655 (pColD-lux), having a recombinant plasmid with a lux operon under a gene promoter colD. The colD (cda) gene is part of the *E. coli* SOS regulon that also ensures DNA repair and cell resistance to DNA damage. The Gen colD (cda) includes SOS-regulon *E. coli*. The lux operon performs a reporter function characterizing the SOS response to DNA damage. The considered genotoxicity of 9-AA and activated UVA (λ = 365 nm) 8-MOP came from manipulating the luminescence intensity of the biosensor. The 8-MOP induction in bacteria of the SOS response depended on concentrations of UVA and 8-MOP. With higher doses of UVA, a 25-fold decrease emerged in the survival of bacterial cells (from $2x10^8$ to $8x10^6$ KOE), while an increase in the intensity of the SOS response by 675 times for 10^6 cells was evident in viable cells. The DNA-damaging and lethal effect of 8-MOP in bacteria relied on the concentrations of UVA and 8-MOP.

Keywords: 9-aminoacridine, 8-methoxypsoralen, lux-biosensor, *E. coli,* gene promoter ColD, SOS response, UV irradiation, monoadducts, diadducts

Key findings: A comparative study of the genotoxicity of 9-aminoacridine (9-AA) and UVA-activated 8-methoxypsoralen (8-MOP) using a lux biosensor in *E. coli* MG1655 (pColD-lux) showed a considerable enhancement in the SOS response. Exposure to the highest concentrations of UVA and 8-MOP resulted in a 25-fold decrease in bacterial survival and a 675-fold increase in SOS response intensity in viable cells, with DNA damaging based on their concentrations.

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INTRODUCTION

Environmental pollution has become a global problem, and the impact of genotoxic substances rises as one of the challenging issues. Genotoxicology is a branch of science comprising the study of interactions of DNA-damaging agents with the cells' genetic material. Genotoxic substances include carcinogens and mutagens, which also affect the structural integrity of DNA and the accuracy of its biological expression. The consequences of exposure to genotoxic agents on the biota are an additional concern, as these agents can also cause harmful variations at the cell and organism levels (Shugart and Theodorakis, 1994). Various chemicals, especially medicines, pesticides, food additives, and beauty products, are common treatments. Therefore, the assessment of chemicals through genotoxic tests is earnestly crucial. A genetic toxicology study comprises the negative effects of chemicals and physical agents on natural heredity processes. Several protocols can be helpful to measure the genetic toxicity of the different compounds, such as assays like comet, Ames test, micronucleus, chromosomal aberration, bacterial reverse mutation test, and chromatid exchange (Abilev and Glazer, 2013).

Genotoxicity is an important matter requiring valuation along with the safety assessment processes. Several modern in vitro and in vivo assays offer tools to investigate the agents and identify those risks. Genetic toxicological tests have become a regulatory requirement for all new chemicals and other materials in developed countries due to their carcinogenicity and hereditary effects (Turkez *et al*., 2017). Genotoxic mutagens cause the mutation by damaging the DNA and chromosomal material. Genotoxins may include both chemicals and radiation. Mutations exist in different forms, which can involve the repetition, insertion, and deletion in the genetic material. These mutations can later cause varied problems, including different diseases and even cancer. Confusing genotoxicity often occurs with mutagenicity. All mutagens are genotoxic, while all the genotoxic substances are not mutagenic agents (Verheyen *et al*., 2017).

Genetic material damage results from the interaction of genotoxic substances with DNA molecules and sequences. These genotoxic substances interact at a specific location of the DNA structure, causing damage, rupture, synthesis, destruction, improper segregation, and mutation. For instance, in its high oxidation state, intermediate metal chromium interacts with DNA; hence, DNA damage leads to carcinogenesis (Phillips and Arlt, 2009). Carcinogens are the substances that can cause cancer. For example, it can be chemicals, medical and environmental radiation, some viruses, lifestyle factors, and even some medications. Various biological tests enable scientists to study the environmental genotoxicants. For the detection of environmental mutagens, the *Salmonella*/Microsome Ames test is the most common, being also recommended by the OECD for assessing the mutagenic activity of chemical compounds (Ames *et al*., 1973).

The lux biosensors based on luminescent microorganisms are the easiest method to use in genotoxicological studies. The said test relied on a bacterial cell containing a hybrid plasmid carrying two main elements: a regulatory region (promoter and operator) that selectively reacts to the agent being studied, and reporter genes encoding proteins that form luminous luciferin-luciferase complexes. Lux biosensors are characteristic of the highest sensitivity and specificity, determined by the interaction of receptor protein and the tested chemical (Vollmer and Van-Dyk, 2004; Deryabin, 2009; Kotova *et al*., 2009). By studying the activity of 47 substances on three biosensors *E. coli* MG1655: pColD-lux, pSoxS-lux, and pKatG-lux, 16 substances induced an SOS response, indicating their ability to damage the DNA, and six substances induced oxidative stress. In comparison with the Ames test, the results on the mutagenic activity of these chemical compounds showed complete analogy for 42 substances (Igonina *et al*., 2016). The substances on the pColD-lux sensor coincided with the large number of substances in the SOS Chromotest (Quillardet and Hofnung, 1993).

The pSoxS-lux and pKatG-lux biosensors aided in studying the effect of 29 substances, including known antioxidants and anti-radiation agents, on the paraquat and peroxide-induced oxidative stress in *E. coli* bacterial cells, respectively (Abilev *et al*., 2019). Antioxidant activity was evident in 79% of substances on the pKatG-lux biosensor and 76% of substances on the pSoxS-lux biosensor. The studied anti-radiation agents showed varied degrees of pro- and antioxidant activity. In cell-free culture supernatants of lactobacilli strains isolated from the human microbiota, the antioxidant activity manifested in more than 60% of the studied strains (Marsova *et al.*, 2018).

Biosensors based on the *E. coli* MG1655 strain were helpful for studying genotoxicity as individual chemicals (Igonina *et al*., 2016; Ordzhonikidze *et al*., 2021; Sviridova *et al*., 2021) and genotoxic environmental factors (Lovinskaya *et al*., 2019, 2021). In studying the genotoxicity of 8-methoxypsoralen (8-MOP) and 9-aminoacridine (9-AA) using the *E. coli* MG1655 (pColD-lux) biosensor, it luminesces when DNA synthesis incurred damages by the agent with SOS response. The choice of these compounds was because both compounds were able to intercalate into DNA. The 8-MOP's insertion between DNA strands occurred, while the 9-AA insertion was between adjacent double-stranded DNA.

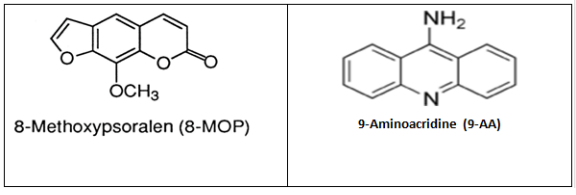
The Xanthotoxin 8-MOP belongs to the class of furocoumarins, which are photosensitizing agents of plant origin and mostly used in photochemotherapy of psoriasis and vitiligo called PUVA therapy (Lerner *et al*., 1953; Canton, 2002). With this therapy, the patients receive oral prescriptions of 8-MOP, then the affected areas of the skin undergo irradiation with ultraviolet A (UV-A), with a wavelength of 320–400 nm. With photoactivation, the 8-MOP causes damage to DNA and eventually leads to numerous morphological and biochemical variations in the cells, culminating in apoptosis (Averbeck, 1989). The 8-MOP mechanism of action depends on its ability to intercalate into DNA and form adducts with DNA pyrimidine bases upon UV-A irradiation.

The 9-Aminoacridine is a fluorescent dye used clinically as a topical antiseptic. The 9-AA also served as a mutagen in experimental work, causing frameshift-type mutation in bacteria (Ames *et al*., 1973; Mortelmans and Zeiger, 2000; Verheyen *et al*., 2017). Several derivatives of 9-AA are a group of heterocyclic compounds, with antitumor, antiviral, and antibacterial effects (Conrad and Topal, 1986; Zavil`gel`skij, 2013). The presented research aimed to study the genotoxicity of 9-AA and 8-MOP using the *E. coli* MG1655 (pColD-lux) biosensor.

MATERIALS AND METHODS

E. coli strains

The *E. coli* MG1655 (pColD-lux) lux biosensor used carried a recombinant plasmid with the luxCDABE operon of the soil photobacterium Photorhabdus luminescens, managed by the promoter of the inducible colD gene (cda). The luxCDABE operon is responsible for the functioning of luciferases and provides bioluminescence, and its intensity denotes the expression levels of the colD gene being a part of the *E. coli* SOS regulon. *E. coli* strain MG1655 (pColD-lux), provided by G.B. Zavilgelsky and A.V. Manukhov (Gos-NIIgenetika, Moscow), had the strain genotype and recombinant plasmid constructs, as follows (Kotova *et al*., 2009).



8-Methoxypsoralen (8-MOP) | 9-Aminoacridine (9-AA)

Growth and cultivation conditions

Bacteria grown on nutrient agar comprised the Luria-Bertani broth (LB) at 37 °C until noticeable colonies appeared. The use of individual colonies then served to cultivate overnight cultures, adding ampicillin to nutrient media at a concentration of 100 μg/mL.

Chemical substances

In the given experiments, the use of 9-aminoacridine (9-AA) and 8-methoxypsoralen (8-MOP) with analytical purity came from Sigma-Aldrich, USA. A pure 8-MOP diluted in 70% alcohol obtained a 1% solution. Then, diluting a 1% solution in water reached the desired concentration to get the dose-dependent effect.

Procedure and SOS response measurement

The preparation of an overnight culture comprised a small amount of culture taken from the shoals (2 µg/ml) sustained dilution in 5 ml LB and left to grow overnight at 37 °C. The 2 ml of an overnight culture and 20 µg/ml of ampicillin, diluted in 20 ml of fresh LB, proceeded to grow for two hours at 37 °C with aeration to a culture density of 3.0. Then, placing the samples of 180 µl containing cell suspension in special plates had 20 µl of the 8-MOP solution with various concentrations added to it. Tablets with 8-MOP, irradiated for three minutes to activate the substance, used an ultraviolet lamp (UV-A with a wavelength of 365 nm). The UV-A light dose measurement employed a TKA-PKM-12 UV radiometer. A culture without the addition of 8-MOP served as the control, using an additional plate with the required concentrations of 8-MOP but without irradiation. Then, placing the tablets in a thermostat for 90 min, continued at a temperature of 37 °C. At the end of incubation, luminescence measurement on a LuxMate instrument ensued, with the data being recorded as relatively light unit (RLU).

Bacteria survival test

Determining the viability of biosensor bacteria included the number of colony-forming units (CFU), cultures in the wells of the tablet after measuring the luminescence serially diluted from 10-2 to 10-6. A test tube with 10 ml of saline received 100 µl of the contents of the well. Later, the contents of the tube incurred mixing, with 100 µl taken from this tube and placed in the next tube. Then, 100 µl taken from different dilutions proceeded pouring onto a Petri dish with frozen nutrient agar. For uniformity of the layer over the agar surface, the solution's trituration used a spatula. The sequence of the actions for each variant of the experiment (8-MOP concentration or UV radiation dose) was in triplicate. Then, leaving the cups overnight continued at 37 °C. The next day, counting the individual colonies proceeded manually.

Statistical analysis

The data compilation and analysis utilized the Microsoft Excel, StatPlus, and WINPIPI. In all cases, the plots showed the means and errors of the m
eans.

RESULTS

9-aminoacridine (9-AA) effect on the luminescence of biosensor *E. coli* 1655 (pColD-lux)

The 9-AA molecule appeared capable of inserting among the adjacent DNA bases and caused a frameshift, which leads to the mutation during subsequent DNA replication. Therefore, 9-AA was effective as a positive control in the Ames test on *S. typhimurium* strains TA 1537 and TA 97 by studying the mutagenic activity of the chemical compounds (Ames *et al*., 1973; Mortelmans and Zeiger, 2000).

In the relevant investigations, the ability of 9-AA to induce DNA damage in *E. coli* cells reached probing if it can cause an SOS response, which works as an indicator of the activation of the DNA repair system. The results of testing 9-AA on the *E. coli* MG1655 (pColD-lux) biosensor in a wide range of concentrations (0.0001 to 0.25 mol/l) are available in Figures 1 and 2. The 9-AA proved to be a weak DNA-damaging agent, with a significant excess of luminescence in relation to spontaneous, as also observed at the 9-AA concentration (0.01 mol/l) and higher. However, at the same time, it did not exceed a twofold level (Figure 2).

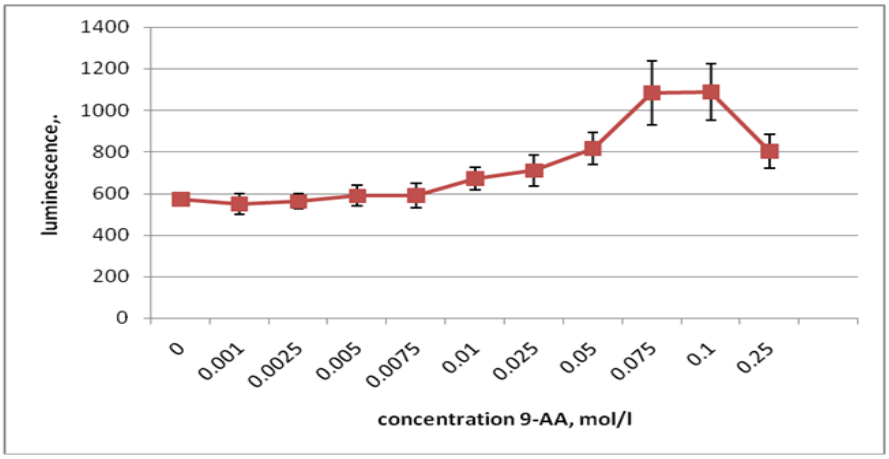


Figure 1. Dependence of the luminescence of the biosensor *E. coli* (pColD-lux) on the concentrations of 9-AA.

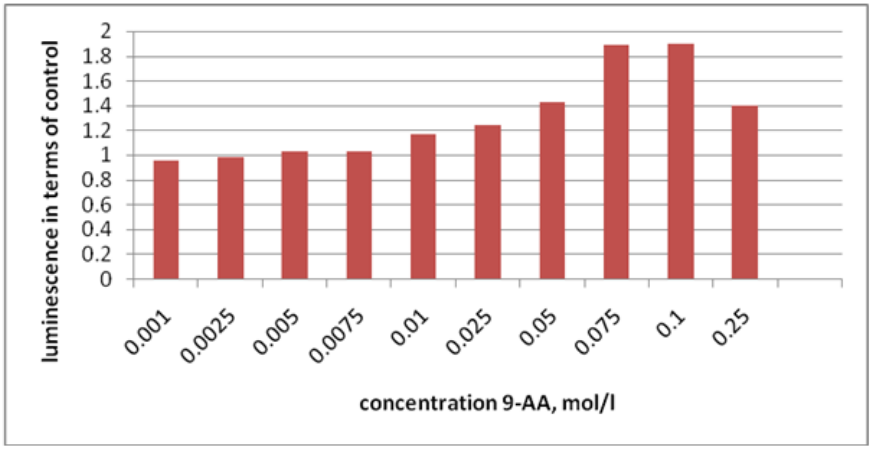


Figure 2. Luminescence intensity ratio of *E. coli* biosensor (pColD-lux) in variants with 9-AA to the luminescence intensity in the control.

8-Methoxypsoralen effect on biosensor Luminescence *E. coli* MG1655 (pColD-lux)

Irradiation of the *E. coli* MG1655 (pColD-lux) biosensor with UV-A (365 nm) for 1 to 5 min did not lead to considerable variations in the spontaneous luminescence level. By irradiating the UV-A biosensor under the same regimes in the presence of 8-MOP concentration (9.2 × 10-4 mol/l), a sharp increase occurred in the luminescence intensity. However, when the biosensor gained irradiation for 1 min in the presence of 8-MOP, the luminescence intensity was 47351 arb. units, which was 78 times higher than the spontaneous luminescence level of the biosensor in the control variant (602 arb. units). These results indicated that activating 8-MOP results from UV-A, forms adducts with DNA, and blocks its further replication. In response to blockage of DNA synthesis in bacterial cells, it induced the SOS-repair system, which gained further fixing by increased biosensor luminescence intensity. With longer exposure to UV-A, the luminescence intensity of the biosensor decreased based on the duration of exposure. With an increased duration of irradiation (more than 3 min), the luminescence intensity

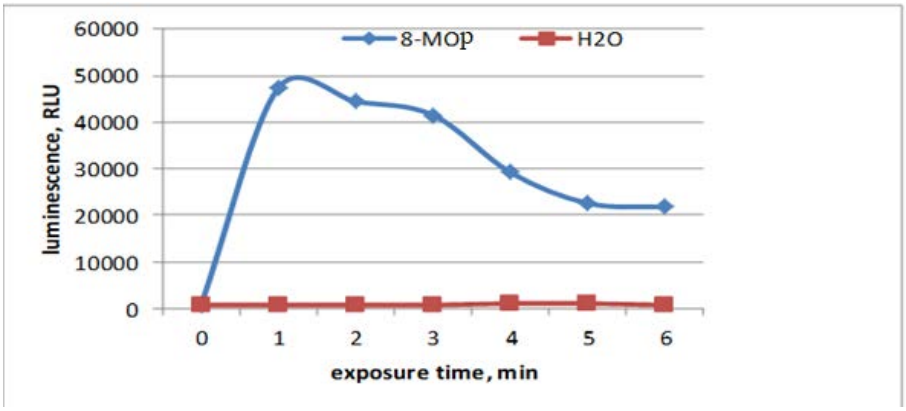


Figure 3. Dependence of the luminescence intensity of the biosensor *E. coli* MG1655 (pColD-lux) on the duration of UV-A irradiation without 8-MOP (1), with 8-MOP (2) at the concentration of 9.2x10-4 mol/l and without it.

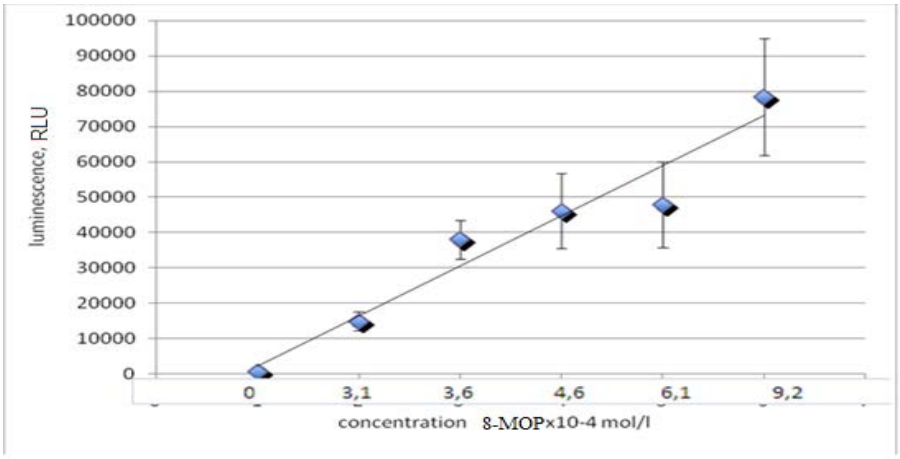


Figure 4. Dependence of the luminescence intensity of *E. coli* MG1655 (pColD-Lux) on the concentration of 8-MOP after 3 min of UV-A irradiation.

decreases, and the toxic effects of the combination of 8-MOP + UV-A on bacteria were prominent (Figure 3).

The dependence of the luminescence intensity of the biosensor *E. coli* MG1655 (pColD-lux) on the 8-MOP concentrations at the fixed irradiation duration (3min), corresponded to a UV-A (2.16 J/m^2) (Figure 4). However, in this case, almost linear dependence of the luminescence intensity was evident with 8-MOP concentrations. This implies that with an increased 8-MOP concentration and a low dose of UV-A irradiation, the SOS response of the biosensor increased. In comparison of the luminescence plots versus UV-A dose at the fixed 8-MOP concentration (9.2 × 10), the toxic effect of the combination of UV-A + 8-MOP was notable, while in the second case, a linear dependence of the increase in luminescence intensity emerged with 8-MOP concentration.

Table 1. Luminescence intensity of the *E. coli* MG1655 (pColD-lux) biosensor upon activation of 8-MOP by UV irradiation for 1 to 5 min.

UV-irradiation (min)	Luminescence (200 µl, RLU)	Number of CFU (200 µl)	Luminescence at 10^6 (RLU/CFU)
0	680 ± 75	2×10^8	3.4
1	38540 ± 2660	2×10^8	192.7
2	36170 ± 1970	2×10^8	180.8
3	34625 ± 2355	5×10^7	692.7
4	24820 ± 1730	2×10^7	1241.0
5	18365 ± 1551	8×10^6	2295.6

Further exploring this phenomenon investigated the toxic effects of UV-A-activated 8-MOP on bacteria. The 96-well plates were samples for the experiment, with each variant comprising eight repetitions. After irradiation of bacteria with various doses of 8-MOP and incubation at 37 °C for 90 min, the intensity of biosensor luminescence in each well of the plate helped determine gene expression. Based on the variants of the experiment, the combining of suspensions of bacteria in the wells underwent diluting serially to consider the weighted average number of colony-forming units (CFU). In doing this practice, sowing 100 µl of suspension from various dilutions continued on Petri dishes with nutrient agar.

The results revealed the number of CFUs presented in terms of 200 µl corresponds to the volume of the luminescent culture in the well of the (Table 1). Thus, the decrease in survival begins at 3 min of irradiation, which corresponds to the UV (2.16 J/m^2). At 5 min irradiation (2.7 J/m^2), the survival decreases from 2 × 108 (control without irradiation) to 8 × 106 CFU, which corresponds to a 25-fold decrease in survival. The recalculation of the biosensor luminescence indices in conventional units per 10^6 CFU showed the luminescence intensity increased from 3.4 conventional units in the control variant without irradiation to 2295.6 with 5-minute irradiation. In the latter case, the luminescence intensity rises by 675.2 times in relation to the indicator in the control.

DISCUSSION

Comparing the results obtained with the ability of 9-AA and 8-MOP to induce an SOS response in the *E. coli* biosensor (pColD-Lux), these revealed the DNA intercalation plays a decisive role in their activity. The planar structure of a 9-AA molecule allows it to integrate between the adjacent bases of double-stranded DNA and move them apart by one nucleotide. In turn, it causes the insertion or loss of one nucleotide (frameshift mutation) in the daughter strands as a result of DNA replication (Conrad and Topal, 1986). Such intercalation does not block DNA synthesis and, accordingly, does not lead to the induction of SOS repair. However, it can only happen at the highest concentrations of 9-AA. The weak SOS response of the biosensor at a 9-AA concentration of more than 0.01 mol/l was noteworthy (Figures 1 and 2). In this case, the biosensor luminescence induced by 9-AA did not exceed a twofold level over the spontaneous luminescence background.

The mode of intercalation with 8-MOP into DNA differed from that of 9-AA. First, the structure of the 8-MOP molecule allows it to be freely located inside the double-stranded DNA helix, which does not interfere with the latter's replication. However, with UV-A action, the 8-MOP binds to one of the DNA strands or to both opposite strands, leading to the formation of a monoadduct or a diadduct. A diadduct is an interstrand cross-link capable of blocking DNA replication.

In Escherichia coli bacteria, the SOS response was a coordinated induction of about 40 genes in response to DNA damage and stopping its replication by various chemical and physical agents, such as UV radiation, hydrogen peroxide, mitomycin, and bleomycin. The SOS system response sought to enhance the ability of cells to repair and replicate the DNA, increase the cells' resistance to DNA damage, and eventually reduce the intensity of mutagenesis. The products of the *lex*A and *rec*A genes, as well as, the presence of single-strand breaks in DNA (ssDNA), play a remarkable role in the induction of the SOS response. The lexA gene encodes the LexA protein, which is a repressor of the SOS regulon genes (Baharoglu and Mazel, 2014).

In *E. coli* cells, the molecular mechanisms of SOS response induction have reached evaluation and summary (Zavil`gel`skij, 2013). The expression of the SOS regulon genes occurs alternately. First, the genes for nucleotide excision repair were expressed, then the expression of the *rec*A and *rec*N genes begins, and the products appeared resulting in their recombination. If DNA damage still persists after the induction of the first SOS genes, the expression of the *umu*D and *umu*C genes encoding DNA polymerase V (mutasome) and the genes encoding colicins, the induction of which leads to the cell lysis. According to estimates, this occurs approximately 40 min after the induction of the first SOS genes. Thus, the *E. coli* MG1655 (pColD–lux) biosensor used in the present studies carries the promoter of the terminal SOS regulon gene, which was activated with the DNA damage. These include bulky adducts, thymine dimers, and interstrand crosslinks that block the DNA replication.

The design of lux biosensors primarily aimed to study the ability of a tested agent to damage the DNA, as promoters of such inducible genes of the SOS system using *recA, dinI,* and *colD (cda)* as a sensor. The study used the *E. coli* MG1655 (pColD-lux) biosensor carrying a plasmid, with the *pColD* promoter transcriptionally fused with the *lux*CDABE operon. The biosensor, as characterized by a low level of spontaneous luminescence and the highest amplitude of the response, had a high level of response exceeding the spontaneous level during induction (Norman *et al*., 2005; Kotova *et al*., 2009; Igonina *et al*., 2016).

The results revealed the induction of the SOS response by 8-MOP was dose-dependent with the UV-A (365 nm). However, the 8-MOP and UV-A separately did not show such ability. With the fixed concentration of 8-MOP, the induction of the SOS response depended upon the UV dose. With the highest doses of UV-A, a decline occurred in the survival of bacterial cells from 2 x 10^8 to 8 x 10^6 CFU in 200 µl, accompanied by an increased level of induction of the SOS response by 675 times for 10^6 CFU. This indicates that with the higher doses of UV-A, some cells die, while the remaining cells appeared viable, with the highest expression of the DNA repair genes. These events may be due to the specific binding of UV-A-activated 8-MOP to DNA bases. At low doses of UV irradiation, 8-MOP forms a monoadduct, which binds to one A or T base, and with the higher doses of irradiation, two pyrimidine bases located on opposite strands of DNA form a diadduct (Tessman *et al*., 1985; Bankmanna and Brendel, 1989).

The resulting interstrand crosslinks lead to the blockage of DNA synthesis, caused by the formation of single-strand breaks, and accordingly, activation of the SOS regulon in *E. coli* cells. The monoadducts removal can take place from the DNA by an excision repair system, and the diadducts were most often lethal. Determining the ratio based on the number of diadducts and monoadducts induced by 8-MOP in DNA packaged in the head of bacteriophage λ and in DNA of plasmid pBR322 under UVA irradiation (λ ≥ 320 nm) showed that repairing 8-MOP diadducts (crosslinks) came from the bacterial SOS system with a probability of S = 0.28–0.29. Meanwhile, reconstructing 8-MOP monoadducts also resulted from the bacterial SOS system with a probability of Sm = 0.41 only with the MucA'2B enzyme's participation, with its genes located in the pKM10 conjugative plasmid (Kotova *et*

al., 2021). The toxic effect of diadducts correlated with the inhibition of DNA replication and with the inhibition of transcription by blocking the progress of RNA polymerase at the DNA cross-linked sites.

CONCLUSIONS

The comparative study of the genotoxicity of 9-AA and 8-MOP using the *E. coli* MG1655 (pColD-lux) biosensor showed their activity depends on the mode of their intercalation in DNA. The 9-AA proved to be a weaker inducer of the SOS response, detected only at its highest concentration. In the case of 8-MOP, the induction of SOS response in bacteria relies on the dose of UV irradiation and 8-MOP concentration. With the highest doses of UV-A, some bacteria died due to 8-MOP-induced interstrand crosslinks. However, in this case, the intense luminescence of the biosensor was notable in viable cells, indicating the maximum level of the SOS response.

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