



Genotoxic and genoprotective effects of 1,4-dihydropyridine derivatives: a brief review

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This review summarises current knowledge about the genotoxic and genoprotective effects of 1,4-dihydropyridines (DHP) with the main focus on the water-soluble 1,4-DHPs. Most of these water-soluble compounds manifest very low calcium channel blocking activity, which is considered “unusual” for 1,4-DHPs. Glutapyrone, diludine, and AV-153 decrease spontaneous mutagenesis and frequency of mutations induced by chemical mutagens. AV-153, glutapyrone, and carbatones protect DNA against the damage produced by hydrogen peroxide, radiation, and peroxyxynitrite. The ability of these molecules to bind to the DNA may not be the only mechanism of DNA protection, as other mechanisms such as radical scavenging or binding to other genotoxic compounds may take place and enhance DNA repair. These uncertainties and reports of high 1,4-DHP concentrations damaging the DNA call for further *in vitro* and *in vivo* preclinical research, pharmacokinetic in particular, as it can help pinpoint the exact mechanism(s) of the genotoxic and/or genoprotective action of 1,4-DHPs.

KEY WORDS: 1,4-DHP; AV-153; diludine; DNA binding; carbatones; glutapyrone

Synthetic derivatives of 1,4-dihydropyridine (1,4-DHPs, Figure 1) produce various important biochemical and pharmacological effects (1), which are mainly owed to the blocking of calcium channels with subsequent modulation of different intracellular pathways. However, not all 1,4-DHPs are calcium antagonists, and some of their effects are owed to alternative mechanisms such as direct scavenging of free radicals (2), protection against mutagens, and activation of DNA repair (3). Some of these 1,4-DHPs have genoprotective properties (3–5) and others are genotoxic (6). The aim of this brief review is to summarise literature data on the genoprotective and genotoxic activities of these 1,4-DHPs. We relied on our own studies and those indexed in the PubMed database.

ANTI- OR PRO-OXIDANT PROPERTIES OF 1,4-DHPs

Many 1,4-DHPs have a significant ability to donate hydrogen and electrons and participate in redox reactions. Like ascorbic acid and tocopherols, they have been reported dual anti- and pro-oxidant effects, depending on their structure and reaction conditions (7).

1,4-DHP derivatives can scavenge nitric oxide (8), alkyl, alkyl peroxy radicals, and the 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) radical cation (2, 9, 10). In our earlier

research (11–13) our group tested 1,4-DHPs for peroxyxynitrite- and hydroxy radical-scavenging potential, which singled out cerebrotorone, etafitorone, fenofitorone, and some 2,6-dimethyl-3,5-diethoxycarbonyl-4-(Na carboxylate)-1,4-dihydropyridine (AV-153) salts as efficient peroxyxynitrite scavengers, whereas hydroxy radical scavenging turned out to be modest (Table 1). Considering that many of these compounds manifest DNA-protective effects in living cells (see below), it is reasonable to assume that these effects are not owed to peroxyxynitrite and hydroxy radical scavenging or that these interactions play a minor role. On the other hand, AV-153-Na, AV-154-Na, and carbatone have a rather high scavenging capacity for oxygen radicals. In the human osteosarcoma cell line (HOS), AV-153-Na and carbatone lowered free radical production caused by hydrogen peroxide if pre-incubated with the HOS cells but were not effective if administered to those already treated with H₂O₂ (14). Pre-treatment with AV-153-Na, AV-154-Na, and carbatone showed a concentration-dependent, bell-shaped curve of protective effects, that is, they generally improved as the applied concentrations reached the middle range of 250 to 500 µmol/L, after which ROS levels increased (14). Milkovic et al. (14) also reported an interesting finding that 1,4-DHPs increased glutathione levels, which was an indirect antioxidative effect.

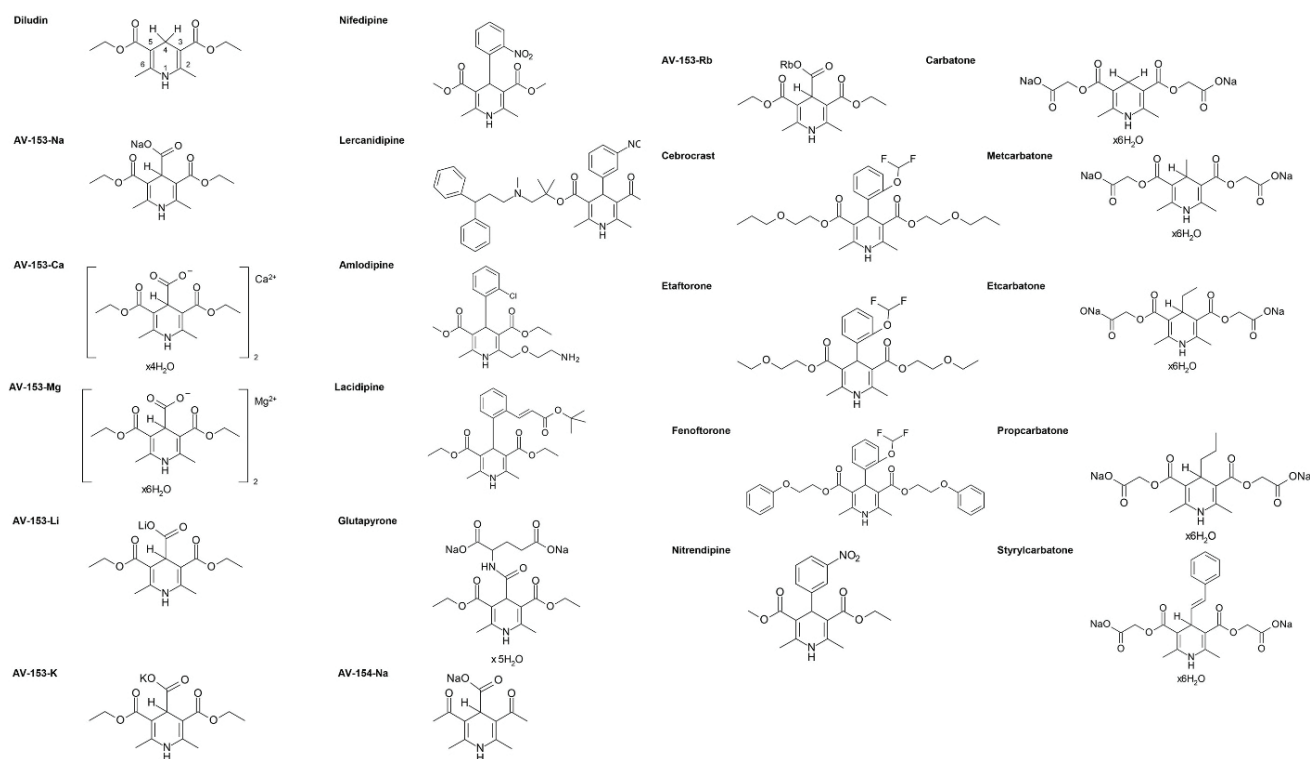


Figure 1 Chemical structure of 1,4-DHP derivatives included in this review

In vitro molecular interactions and DNA binding

Testing for 1,4-DHP effects in simple systems such as plasmid can reveal some interesting properties of 1,4-DHPs. Plasmid relaxation, which is indicative of DNA strand breaks, has been reported with some novel 1,4-DHP derivatives containing halogen atoms and/or nitro groups. Moreover, these compounds competed with restrictases for their binding sites (6). One of our earlier studies (13) singled out nitrendipine and AV-153-Ca and AV-153-Mg as the best DNA protectors, followed by etcabarbonate and styrylcarbatone (Figure 2, previously unpublished). The effect was not concentration-dependent. In another study (15), we showed that etafatorone, fenofatorone, and cerebrocrast protected plasmid DNA against peroxynitrite-induced damage. At that point, it was believed that cerebrocrast, a lipid-soluble 1,4-DHP derivative with promising antidiabetic and neuroprotective activities but very weak Ca-channel blocking, and its analogue etafatorone act mainly on mitochondria (16–18), but both compounds turned out to be DNA binders (15).

The ability of 1,4-DHPs to bind to the DNA was first reported as early as in 1975 (19), suggesting an intercalative mode of DNA binding on the example of diludine and its analogues, but this research was discontinued. Diludine and its methylated analogue were shown to increase the melting temperature of DNA by 2.9 and 1.4 °C, respectively. One of our studies (20) called the attention to the DNA-binding capacity of antimutagenic AV-153-Na, as the docking experiment predicted its insertion in the DNA molecule at

the place of a single-strand break, and the prediction was proven experimentally, as AV-153-Na forced ethidium bromide out of the DNA complex and showed higher affinity to damaged DNA than the intact molecule. Another, more recent study (12) has shown that DNA-binding capacity and DNA protection depend on metal ions forming salts with the AV-153 residue. In it, the fluorescence assay showed that the binding affinity dropped with each metal in the following order: Mg>Na>Ca>Li>Rb>K. Later use of spectroscopic and electrochemical methods has suggested intercalation as the main mode of action, although other types of interaction are also possible (21).

Another group of water-soluble 1,4-DHPs, i.e. carbatonides, disodium-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(carboxyloxyacetate) derivatives, including carbatone, metcarbatone, etcabarbonate, and styrylcarbatone have also been reported to interact with DNA but to have a lower affinity for DNA than AV-153 salts. Among them, styrylcarbatone had the highest affinity and suggested a different binding mechanism (13). This and our another study (22) also suggest that the DNA-binding affinity of water-soluble monocyclic 1,4-dihydropyridine derivatives with a carboxylate group in position 4 depends on substituents in positions 3 and 5.

We also demonstrated that 1,4-DHP derivatives, more specifically AV-153 salts, can bind to the G-quadruplexes (G4), with Na and K salts effectively binding to the human telomere repeat

Table 1 Comparison of some properties of studied 1,4-DHP derivatives (11, 12, 15, 20, 25)

1,4-DHP derivative	DNA binding constant (UV/VIS spectroscopy) (M^{-1})	Stern-Volmer binding constant (EtBr extrusion) (M^{-1})	DNA binding constant (spectrofluorimetry) (M^{-1})	Effect on hydroxyl radical production (EPR; %)	Peroxynitrite decomposition time compared to control	Decrease in DNA damage in HeLa cells by peroxynitrite after pre-incubation with 10 nmol/L of a 1,4-DHP (%)
AV-153-Na	7.21328x10 ⁴	9.4x10 ⁴	4.40x10 ⁵	96.8	0.75	50
AV-153-Ca		1.7x10 ⁵	4.04x10 ⁵		3.44	57
AV-153-Mg		2.3x10 ⁵	5.43x10 ⁵		7.52	NS
AV-153-Li		9.9x10 ⁴	3.32x10 ⁵		3.48	NS
AV-153-K		8.7x10 ⁴	2.70x10 ⁵		3.13	19
AV-153-Rb		8.9x10 ⁴	3.07x10 ⁵		3.00	14
AV-154-Na	No binding			98.7	0.29	NS
Carbatone	1.09x10 ²			100	N/A	
Metcarbatone	0.82x10 ²		3.8x10 ²	31.4		
Etcabatone	0.54x10 ²		9.5x10 ²	98.3		
Propcarbatone	1.11x10 ²			86.4		
Styrylcarbatone	1.9x10 ³	?	1.4x10 ⁴	106		
Glutapyrone	No binding					27
Cerebrocrast			2.2x10 ³		8.61	29
Etaftorone					2.25	27*
Fenoftorone					2.28	

* at the concentration of 1 nmol/L. NA – not assayed; NS – not significant

(18). Other authors confirmed G-quadruplex binding with a series of other novel 1,4-DHP derivatives (23).

Another recent study (24) has shown that widely used 1,4-DHPs with Ca blocker activity such as nifedipine, lercanidipine, and amlodipine can bind to the minor groove of the DNA, yet their binding affinity is low.

Modification of gene and protein expression

One of our earlier studies (16) has shown that pre-incubation with AV-153-Na (50 nmol/L) protects the DNA of HeLa cells against damage produced by peroxynitrite (200 μ mol/L), as AV-153-Na penetrates the cell nucleus and up-regulates DNA excision repair enzymes. We then tested different salts of AV-153 for protective DNA effects to learn that they were modified by the metal ions (12). AV-153-Na and AV-153-Ca effectively reduced DNA damage, AV-153-K and AV-153-Rb were less effective, whereas AV-153-Li did not protect the DNA, and AV-153-Mg even increased the damage. The AV-153 Na salt decreased DNA damage in HeLa cells through the over-expression of the pro-apoptotic protein DUX4 (Figure 3, previously unpublished). In human B-lymphocytes AV-153 Na, K, Ca, and Mg salts reduced DNA damage produced by oxidative stress caused by incorporation of the HIV-derived Tat protein (12). In another study (25), we have also found that glutapyrone protects HeLa cells against peroxynitrite, but to a lower extent than AV-153-Na.

Lipid-soluble cerebrocrast and etaftorone also seem to alleviate peroxynitrite-induced DNA damage (15). Cerebrocrast (50–500 nmol/L) is effective when administered before or together with peroxynitrite, but etaftorone is effective only when given at the same time.

1,4-DHPs AS DNA REPAIR ENHANCERS

Cell studies

In a study using single-cell gel electrophoresis (the comet assay) (4), AV-153-Na was reported to reduce the number of spontaneous DNA strand breaks in HL-60 human blood lymphocytes and Raji cells. It also reduced DNA damage produced by exposure to 2 Gy of gamma-radiation, 100 μ mol/L ethylmethane sulphonate (EMS), or 100 μ mol/L hydrogen peroxide by up to 87 % at AV-153-Na concentrations between 1 and 10 nmol/L. A later study (3) showed that AV-153-Na stimulated the synthesis of poly(ADP-ribose) in hydrogen peroxide-treated cells and that the short-term increase in the polymer's synthesis correlated with the higher rate and efficiency of DNA repair (3). In another study (5), AV-153-Na also reduced the number of micronucleated and apoptotic cells in a culture of human lymphocytes exposed to 2 Gy gamma radiation. The authors suggested that this effect was owed to its similar structure with the

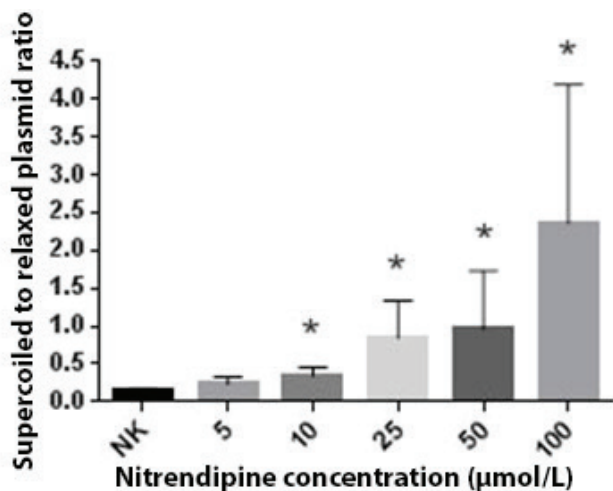


Figure 2 Protective effects of nitrendipine against pTZ57R DNA plasmid damage caused by Fenton reaction products. The pTZ57R DNA plasmid (1.4 µg) was incubated for 30 min with 0.003 % H₂O₂ in 0.01 mmol/L FeSO₄ with no or 5, 10, 25, 50 or 100 µmol/L nitrendipine. And electrophoresed following the standard procedure. NK – negative control

nicotinic acid and its involvement in NAD⁺ recovery and poly(ADP-ribosylation) (5). In a culture of Chinese hamster ovary cells (CHO-K1) treatment with AV-153-Na before exposure to X-rays did not affect the formation or repair of single-strand DNA breaks, but – judging by the FPG-modified comet assay – did prevent the formation of 8-oxoguanine (26).

Animal studies

When orally administered to laboratory rats (0.05 or 0.5 mg/kg) for three days, metcarbatone, etcarbatone, and styrylacarbatone caused damage to the DNA in nucleated blood cells. However, in animals with diabetes mellitus, metcarbatone and styrylacarbatone lowered DNA damage, whereas etcarbatone increased it (13). In our most recent (still unpublished) studies, oral AV-153-Na and glutapyrone also increased DNA damage in blood cells of control rats, but AV-153-Na did not significantly change the expression of the histone γ-H2AX in rat myocardium and mitigated the frequency of double-strand breaks. In another study using an experimental model of myocardial infarction (27), lacidipine decreased the level of 8-oxoguanine and therefore the DNA damage caused by oxidative stress.

Several studies using a rat streptozotocin-induced diabetes model looked into how 1,4-DHPs modify the expression of several genes and proteins involved in radical production and DNA repair (12, 15, 28). In most cases 1,4-DHPs increased the gene expression, which implies some level of influence on pathways regulating gene transcription. Other studies with diabetes mellitus have reported down-regulation of NO production and/or inducible NO synthase (iNOS) by carbatonides, etafterone, fenofafterone, cerebrocrast (13) and AV-153 (29), which looks promising.

Antimutagenic and anticlastogenic action

The first findings about the effects of 1,4-DHP derivatives on spontaneous mutations were reported for *Drosophila melanogaster* in 1980 by Goncharova et al. (29). The larvae fed with diludine and AV-153 had a decrease in both point mutations and chromosome aberrations. The authors concluded that these mononuclear 1,4-DHPs were more efficient antimutagens than trinuclear compounds and that their antimutagenic efficiency was related to the presence of a carboxylate group in position 4.

Studies that followed reported AV-153-Na to reduce the frequency of genetic damage (point mutations and chromosome breakage) induced by EMS in *Drosophila melanogaster* larvae and imagoes more efficiently than standard radioprotectors cysteine and cysteamine (30). Similar protective effect against EMS-induced mutations was reported for glutapyrone in the spermatozoa of *Drosophila* pre-treated at the larval stage (31). Both compounds also showed an anticlastogenic effect in mice (32), whereas glutapyrone was also reported for an antineoplastic effect in rats exposed to continual gamma irradiation (33).

Back to *Drosophila*, lipid-soluble 1,4-DHPs cerebrocrast and diethone (diludine) also showed antimutagenic and anticlastogenic effects (34). More recently, diludine was shown to favour gamete storage in fish (35).

CONCLUSIONS

Considering the puzzling ability of 1,4-DHP derivatives to bind to the DNA, it would be important to establish the mechanisms by which they protect or damage the genome. Of course, this consideration should include their antioxidative potential, even though not all 1,4-DHPs seem to scavenge peroxynitrite or hydroxyl radicals. What we have learned so far is that some potent DNA binders, such as AV-153-Na and AV-153-Ca, produce stronger DNA-protective effects than the weak ones, such as AV-153-K and AV-153-Rb, yet some strong binders, such as AV-153-Mg and AV-153-Li, do not protect the DNA. Furthermore, glutapyrone, which is a weak binder, produces effects comparable to those of some strong DNA binders. All this suggests that DNA binding may not be the only mechanism of DNA protection, but may include radical scavenging or chemical binding of other genotoxic compounds. We also cannot exclude the possibility that some weak binders metabolise in the organism into strong binders. For example, glutapyrone easily metabolises to AV-153. Furthermore, even though DNA binding mobilise DNA repair enzymes, high concentrations of potent binders such as AV-153Na, Mg, or Li salts can damage the DNA.

All these considerations call for further testing of novel as well as clinically approved 1,4-DHPs for their DNA-binding, genoprotective or genotoxic potential, including their metabolites. We hope that future preclinical research (*in vitro* and *in vivo*) and

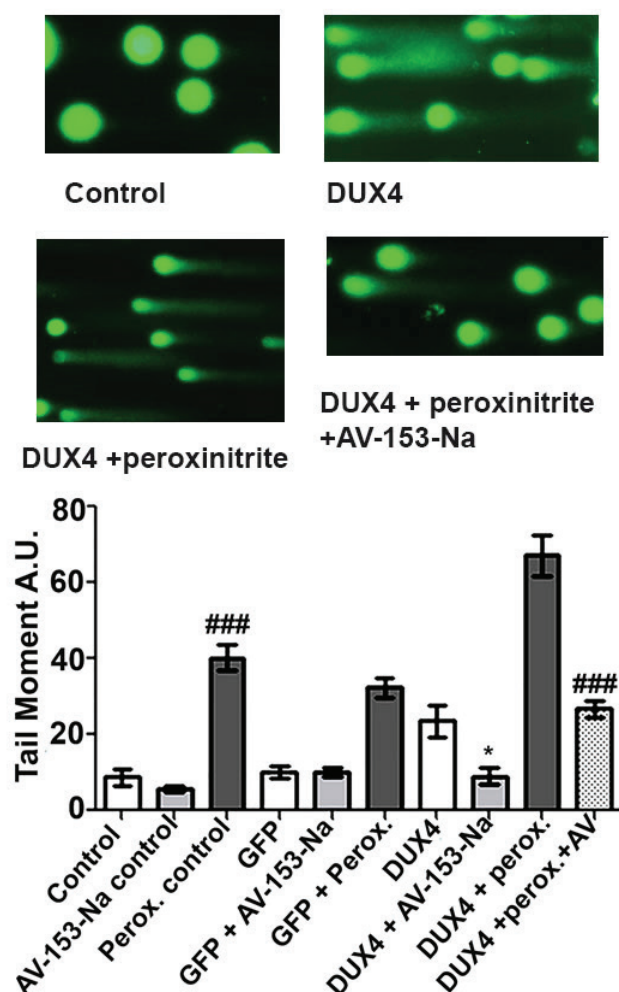


Figure 3 Protective effects of AV-153-Na (50 nmol/L) against DNA oxidative damage caused by the DUX4 protein in the HeLa cell line. * $p < 0.05$ vs DUX4. ### $p < 0.001$ vs DUX4 + peroxynitrite. A.U. – arbitrary units; GFP – transfection control

pharmacokinetic studies in particular, will be able to pinpoint the exact mechanism(s) of their genotoxic and/or genoprotective action.

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REFERENCES

- Mishra AP, Bajpai A, Rai AK. 1,4-Dihydropyridine: A dependable heterocyclic ring with the promising and the most anticipable

- therapeutic effects. *Mini Rev Med Chem* 2019;19:1219–54. doi: 10.2174/1389557519666190425184749
- Núñez-Vergara LJ, Salazar R, Camargo C, Carbajo J, Conde B, Navarrete-Encina PA, Squella JA. Oxidation of 4-hydroxyphenyl 1,4-dihydropyridines in dimethylsulfoxide and its reactivity towards alkylperoxyl radicals in aqueous medium. *Bioorg Med Chem* 2007;15:4318–26. doi: 10.1016/j.bmc.2007.03.042
- Ryabokon NI, Goncharova RI, Duburs G, Hancock R, Rzeszowska-Wolny J. Changes in poly(ADP-ribose) level modulate the kinetics of DNA strand break rejoining. *Mutat Res* 2008;637:173–81. doi: 10.1016/j.mrfmmm.2007.08.005
- Ryabokon NI, Goncharova RI, Duburs G, Rzeszowska-Wolny J. A 1,4-dihydropyridine derivative reduces DNA damage and stimulates DNA repair in human cells *in vitro*. *Mutat Res* 2005;587:52–8. doi: 10.1016/j.mrgentox.2005.07.009
- Ryabokon NI, Nikitchenko NV, Dalivelya OV, Goncharova RI, Duburs G, Konopacka M, Rzeszowska-Wolny J. Modulation of cellular defense processes in human lymphocytes *in vitro* by a 1,4-dihydropyridine derivative. *Mutat Res* 2009;679:33–8. doi: 10.1016/j.mrgentox.2009.07.010
- Pal S, Singh V, Das P, Choudhury LH. PEG-mediated one-pot multicomponent reactions for the efficient synthesis of functionalized dihydropyridines and their functional group dependent DNA cleavage activity. *Bioorg Chem* 2013;48:8–15. doi: 10.1016/j.bioorg.2013.03.003
- Velena A, Zarkovic N, Troselj KG, Bisenieks E, Krauze A, Poikans J, Duburs G. 1,4-dihydropyridine derivatives: dihydronicotinamide analogues-model compounds targeting oxidative stress. *Oxid Med Cell Longev* 2016;2016:1892412. doi: 10.1155/2016/1892412
- López-Alarcón C, Speisky H, Squella JA, Olea-Azar C, Camargo C, Núñez-Vergara LJ. Reactivity of 1,4-dihydropyridines toward SIN-1-derived peroxynitrite. *Pharm Res* 2004;21:1750–7. doi: 10.1023/B:PHAM.0000045224.97323.8b
- López-Alarcón C, Navarrete P, Camargo C, Squella JA, Núñez-Vergara LJ. Reactivity of 1,4-dihydropyridines toward alkyl, alkylperoxyl radicals, and ABTS radical cation. *Chem Res Toxicol* 2003;16:208–15. doi: 10.1021/tx025579o
- Valenzuela V, Santander P, Camargo C, Squella JA, López-Alarcón C, Núñez-Vergara LJ. 1,4-dihydropyridines: reactivity of nitrosoaryl and nitroaryl derivatives with alkylperoxyl radicals and ABTS radical cation. *Free Radic Res* 2004;38:715–27. doi: 10.1080/10715760410001711486
- Leonova E, Rostoka E, Baumanė L, Borisovs V, Smelovs E, Bisenieks I, Brūvere I, Bisenieks E, Duburs G, Sjakste N. DNA-binding studies of a series of novel water-soluble derivatives of 1,4-dihydropyridine. *Biopolym Cell* 2018;34:129–42. doi: 10.7124/bc.000977
- Leonova E, Ošiņa K, Duburs G, Bisenieks E, Germini D, Vassetzky Y, Sjakste N. Metal ions modify DNA-protecting and mutagen-scavenging capacities of the AV-153 1,4-dihydropyridine. *Mutat Res Genet Toxicol Environ Mutagen* 2019;845:403077. doi: 10.1016/j.mrgentox.2019.06.007
- Ošiņa K, Leonova E, Isajevs S, Baumanė L, Rostoka E, Sjakste T, Bisenieks E, Duburs G, Vigante B, Sjakste N. Modifications of expression of genes and proteins involved in DNA repair and nitric oxide metabolism by carbatonides [disodium-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(carboxyloxyacetate) derivatives] in intact and diabetic rats. *Arh Hig Rada Toksikol* 2017;68:212–27. doi: 10.1515/aht-2017-68-2945
- Milkovic L, Vukovic T, Zarkovic N, Tatzber F, Bisenieks E, Kalme Z, Bruvere I, Ogle Z, Poikans J, Velena A, Duburs G. Antioxidative

- 1,4-dihydropyridine derivatives modulate oxidative stress and growth of human osteoblast-like cells *in vitro*. *Antioxidants* (Basel) 2018;7(9):123. doi: 10.3390/antiox7090123
15. Leonova E, Sokolovska J, Boucher JL, Isajevs S, Rostoka E, Bauman L, Sjakste T, Sjakste N. New 1,4-dihydropyridines down-regulate nitric oxide in animals with streptozotocin-induced diabetes mellitus and protect DNA against peroxynitrite action. *Basic Clin Pharmacol Toxicol* 2016;119:19–31. doi: 10.1111/bcpt.12542
16. Leonova E, Rostoka E, Sauvaigo S, Bauman L, Selga T, Sjakste N. Study of interaction of antimutagenic 1,4-dihydropyridine AV-153-Na with DNA-damaging molecules and its impact on DNA repair activity. *PeerJ* 2018;6:e4609. doi: 10.7717/peerj.4609
17. Briede J, Stivrina M, Vigante B, Stoldere D, Duburs G. Acute effect of antidiabetic 1,4-dihydropyridine compound cerebocrast on cardiac function and glucose metabolism in the isolated, perfused normal rat heart. *Cell Biochem Funct* 2008;26:238–45. doi: 10.1002/cbf.1442
18. Pupure J, Isajevs S, Gordjushina V, Taivans I, Rumaks J, Svirskis S, Kratovska A, Dzirkale Z, Pilipenko J, Duburs G, Klusa V. Distinct influence of atypical 1,4-dihydropyridine compounds in azidothymidine-induced neuro- and cardiotoxicity in mice *ex vivo*. *Basic Clin Pharmacol Toxicol* 2008;103:401–6. doi: 10.1111/j.1742-7843.2008.00221.x
19. Grīnberga S. 1,4-Dihidropiridīnu rindas antioksidantu iedarbība uz bioloģiskām membrānām un biopolimēriem [Effects of antioxidants from the 1,4-dihydropyridine row on biological membranes and biopolymers, in Latvian]. [graduation thesis]. Riga: Faculty of Chemistry, State University of Latvia; 1975.
20. Buraka E, Chen CY, Gavare M, Grube M, Makarenkova G, Nikolajeva V, Bisenieks I, Brūvere I, Bisenieks E, Duburs G, Sjakste N. DNA-binding studies of AV-153, an antimutagenic and DNA repair-stimulating derivative of 1,4-dihydropyridine. *Chem Biol Interact* 2014;220:200–7. doi: 10.1016/j.cbi.2014.06.027
21. Leonova E, Shvirksts K, Borisovs V, Smelovs E, Sokolovska J, Bisenieks E, Duburs G, Grube M, Sjakste N. Spectroscopic and electrochemical study of interactions between DNA and different salts of 1,4-dihydropyridine AV-153. *PeerJ* 2020;8:e10061. doi: 10.7717/peerj.10061
22. Fernandes MAS, Santos MS, Vicente JAF, Moreno AJM, Velen A, Duburs G, Oliveira CR. Effects of 1,4-dihydropyridine derivatives (cerebocrast, gammapyrone, glutapyrone, and diethone) on mitochondrial bioenergetics and oxidative stress: a comparative study. *Mitochondrion* 2003;3:47–59. doi: 10.1016/S1567-7249(03)00060-6
23. Aghaei R, Mazloum-Ardakani M, Abdollahi-Alibeik M, Moshtaghion SM, Rezaei-poor-Anari A, Haghighijoo Z, Zamani L. A new electrochemical biosensor based on telomeric G-quadruplex DNA: In silico and experimental study of dihydropyridine derivatives potential effect on telomerase inhibition. *J Electroanal Chem* 2017;796:24–32. doi: 10.1016/j.jelechem.2017.04.055
24. Shahzad S, Dogan-Topal B, Karadurmus L, Caglayan MG, Tok TT, Uslu B, Shah A, Ozkan SA. Electrochemical, spectroscopic and molecular docking studies on the interaction of calcium channel blockers with dsDNA. *Bioelectrochemistry* 2019;127:12–20. doi: 10.1016/j.bioelechem.2018.12.007
25. Leonova E, Dislere K, Rostoka E, Bauman L, Bisenieks E, Duburs G, Sjakste N. Study of impact of a 1,4-DHP derivative glutapyrone on DNA using *in vitro* tests. *Proc Latvian Acad Sci* 2023;77(1):49–52.
26. Wojewódzka M, Grądzka I, Buraczewska I, Brzóška K, Sochanowicz B, Goncharova R, Kuzhir T, Szumiel I. Dihydropyridines decrease X-ray-induced DNA base damage in mammalian cells. *Mutat Res* 2009;671:45–51. doi: 10.1016/j.mrfmmm.2009.08.015
27. Keles MS, Bayir Y, Suleyman H, Halici Z. Investigation of effects of Lacidipine, Ramipril and Valsartan on DNA damage and oxidative stress occurred in acute and chronic periods following isoproterenol-induced myocardial infarct in rats. *Mol Cell Biochem* 2009;328:109–17. doi: 10.1007/s11010-009-0080-y
28. Ošiņa K, Rostoka E, Isajevs S, Sokolovska J, Sjakste T, Sjakste N. Effects of an antimutagenic 1,4-dihydropyridine AV-153 on expression of nitric oxide synthases and DNA repair-related enzymes and genes in kidneys of rats with a streptozotocin model of diabetes mellitus. *Basic Clin Pharmacol Toxicol* 2016;119:458–63. doi: 10.1111/bcpt.12617
29. Goncharova RI, Kuzhir TD, Dubur GYa, Uldrikis YaR. Comparative study of the antimutagenic actions of the compounds of dihydropyridine series in connection to their antioxidant activity. *Doklady Akad Nauk SSSR* 1980;255:1483–6.
30. Goncharova RI, Kuzhir TD. A comparative study of the antimutagenic effects of antioxidants on chemical mutagenesis in *Drosophila melanogaster*. *Mutat Res* 1989;214:257–65. doi: 10.1016/0027-5107(89)90170-X
31. Kuzhir TD, Dalivelia OV, Savina NV. [Modification of the repair processes in chemical mutagenesis in *Drosophila melanogaster*, in Russian]. *Genetika* 1999;35:919–24. PMID: 10519070
32. Goncharova R, Zabrejko S, Dalivelya O, Kuzhir T. Anticlastogenicity of two derivatives of 1,4-dihydroisonicotinic acid in mouse micronucleus test. *Mutat Res* 2001;496:129–35. doi: 10.1016/S1383-5718(01)00223-6
33. Vartanian LP, Ivanov EV, Vershinina SF, Markochev AB, Bisenieks EA, Gornaeva GF, Pustovalov IuI, Ponomareva TV. [Antineoplastic effect of glutapyrone in continual gamma-irradiation of rats, in Russian]. *Radiats Biol Radioecol* 2004;44:198–201. PMID: 15174381
34. Savina NV, Nikitchenko NV, Dalivelya OV, Bisenieks E, Duburs G, Goncharova RI. Дилудин и цереброкраст как биопротекторы в модельных тест-системах *in vivo* [Diludine and cerebocrast as bioprotectors in the model test systems *in vivo*, in Russian]. *Ekol Genet* 2009;7:30–43. doi: 10.17816/ecogen7330-43
35. Arslan M, Gulen S, Tacer-Tanas S, Yanik T, Gurdal A, Kocaman M, Atasever A, Slukvin A, Goncharova R. Long-term dietary diludine (diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) intake and gamete storage affect α -tocopherol status and reproductive performance in female rainbow trout, *Oncorhynchus mykiss*. *Aquaculture* 2021;533:736172. doi: 10.1016/j.aquaculture.2020.736172

Kratki pregled genotoksičnoga i genoprotektivnoga djelovanja derivata 1,4-dihidropiridina

Ovaj pregledni rad donosi sažetak onoga što smo dosad naučili o genotoksičnom i genoprotektivnom djelovanju 1,4-dihidropiridina (DHP), s posebnom pažnjom na 1,4-DHP-ove topljive u vodi. Većina tih u vodi topljivih spojeva slabo aktivira blokiranje kalcijevih kanala, što se smatra “neuobičajenim” za 1,4-DHP-ove. Glutapiron, diludin i AV-153 ublažavaju spontanu mutagenezu i učestalost mutacija prouzročene kemijskim mutagenima. AV-153, glutapiron i karbatoni štite DNA od oštećenja prouzročenih vodikovim peroksidom, zračenjem i peroksinitritom. Sposobnost tih molekula da se vežu za DNA vjerojatno nije jedini mehanizam njegove zaštite, budući da su mogući i drugi mehanizmi, poput uklanjanja radikala ili vezanja za druge genotoksične spojeve koji pospješuju popravak DNA. Zbog tih nepoznanica i izvještaja da visoke koncentracije 1,4-DHP-ova oštećuju DNA, potrebno je napraviti daljnja neklinička istraživanja *in vitro* i *in vivo*, napose ona farmakokinetička, budući da mogu pomoći razaznati točne mehanizme genotoksičnoga i/ili genoprotektivnoga djelovanja derivata 1,4-dihidropiridina.

KLJUČNE RIJEČI: 1,4-DHP; AV-153; diludin; glutapiron; karbatoni; vezanje za DNA