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The Effect of Decoglitz on Rat Tumors and Nucleic Acid Synthesis

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Abstract **The aim** of this study was to investigate the antitumor activity of a new colchicine derivative Decoglitz in rats with Walker 256 carcinosarcoma and ovarian tumor strains in comparison with the effect of decocin, 5-fluorouracil, taxol, etoposide, oral xylode, as well as to identify the effect of the new substance on nucleic acid synthesis. **Background.** The pronounced general toxic effect of a large number of cytostatic drugs used, rapidly developing resistance, and the lack of sensitivity of a number of tumors to existing drugs necessitate the creation of new anticancer drugs with a complex of new properties. **Material and methods.** The study was conducted on 61 mongrel rats with transplanted Walker carcinosarcoma tumors and ovarian tumor, which were administered intraperitoneally on the 4th-5th day after tumor transplantation once a day for 10 days, in addition, Decoglitz was administered orally. The results were evaluated according to standard criteria: tumor growth inhibition (TGI), body weight, and spleen weight of animals. Differences were considered significant at $p<0.05$. **Results.** The antitumor activity of the drug Decoglitz on the Walker 256 carcinosarcoma tumor strain was 96/97% with a remission rate of 40% when administered intraperitoneally, and 98/97% with a regression rate of 60% when administered orally. Its effect was higher than the comparison drugs: decocin by 23-28%, taxol by 7-11%, 5-fluorouracil by 15-18%, and etoposide by 7-9%. In ovarian tumor, the effect of Decoglitz upon intraperitoneal administration reached 89/76% with a regression rate of 40%, while upon oral administration, it reached 96/86% with a regression rate of 60%. **Conclusion.** The study of the new drug Decoglitz on two rat tumors with intraperitoneal and oral administration revealed its higher activity compared to the original Decocin, taxol, 5-fluorouracil and etoposide with fewer side effects.

Keywords Antitumor activity, Walker 256 carcinosarcoma, Ovarian tumor, Decoglitz, Decocin, 5-fluorouracil, Taxol, Etoposide

1. Introduction

In recent years, computational screening, docking studies, and cheminformatics have become indispensable in predicting anticancer activity and pharmacokinetics. These approaches provide an important platform for the rational design of new colchicine-derived complexes such as Decoglitz [1-2].

Moreover, several antiviral molecules with antitumor activity, including cordycepin and riboprine, have been shown to suppress nucleic acid synthesis and promote apoptosis in cancer cells, reinforcing the translational relevance of dual-acting compounds [3-4].

Another important class of agents includes antioxidant and anti-inflammatory molecules, such as gallates and teriflunomide, which exert both tumor-inhibitory and immunomodulating effects, thus expanding the rationale for combination therapies [5-6].

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Alongside synthetic derivatives, natural cytotoxic compounds such as gingerol, bromelain, and plant polyphenols have attracted increasing attention for their ability to modulate tumor cell proliferation and improve the therapeutic window of cytotoxic drugs [7-8].

Recent advances in colchicine derivatives have highlighted their potential as effective anticancer agents. Colchicine-based molecules and their oxadiazole and isoquinoline modifications demonstrated significant cytotoxicity and apoptosis induction in multiple tumor models [9-10].

The pronounced general toxic effect of a large number of cytostatic drugs used, rapidly developing resistance, and the lack of sensitivity of a number of tumors to existing drugs necessitate the creation of new anticancer drugs with a complex of new properties.

Medicines based on licorice root have been used for several millennia. The main active ingredient in licorice root is the triterpenoid glycyrrhizic acid (GA) also known as glycyrrhizin. GA as a solubilizer of many water-insoluble organic substances is used in the creation of low-dose, low-toxicity drugs [11]. For example, gossypol and its derivatives, hydrocortisone, prednisolone, kratil, nystatin,

and other drugs that are practically insoluble in water, when combined with monoammonium salt of glycyrrhizic acid (MASGA), become soluble in water [12-13]. All these positive properties of GA and its derivatives are associated with its ability to form supramolecular complexes, which have very low critical micelle concentration values in aqueous solutions. All researchers note the very low toxicity of drugs containing GA, MASGA and their derivatives created on their basis. Besides the above properties, GA and its derivatives have a strong anti-inflammatory, analgesic, anti-edema, hypotensive, and virus-neutralizing effect, improve tissue regeneration in the early stages of viral diseases and in ulcerative forms. However, GA has not been widely used in combination with anti-tumor drugs.

We have previously developed new promising substances based on tropolone alkaloids, which have been shown to have both a decrease in toxicity compared to the original alkaloids and an increase in activity from 20 to 40%, and in particular, Decocin (a derivative of the alkaloid colchicine) with an activity higher than 80% on Sarcoma S 180, cervical cancer-5 and ACATOL, which allowed us to propose this drug for clinical trials [14]. The clinical data obtained on the antitumor drug decocin indicate high sensitivity of skin cancer to 3-4% decocin ointment, which proved to be efficient in combination with radiation therapy [15-16].

Since some derivatives are insoluble in water, which complicates both their parenteral administration and bioavailability, a method of molecular encapsulation of these substances with GA and MASGA, which have efficient solubilizing properties, was used. A number of new water-soluble supramolecular complexes were obtained, one of which was an active complex of the drug Decocin and GA, differing in its physical and chemical parameters from the original Decocin, as well as a marked reduction in toxicity, called Decoglitz. A number of studies have investigated the antitumor activity of Decoglitz, as a rule, upon intraperitoneal administration. Our task was to determine the effect of the drug upon oral administration. In addition, it was necessary to determine the activity of the new drug in comparison with known cytostatics in order to decide on the feasibility of introducing it into practice, which is usually done not due to the lack of antitumor activity, but because the drugs have no advantages over existing ones.

The aim of this study was to investigate the antitumor activity of a new colchicine derivative Decoglitz in rats with Walker 256 carcinosarcoma and ovarian tumor strains in comparison with the effect of decocin, 5-fluorouracil, taxol, etoposide, oral xylode, as well as to identify the effect of the new substance on nucleic acid synthesis.

2. Material and Methods

The object of the study was the drug Decoglitz, as well as the drug Decocin, from which Decoglitz was obtained. Both drugs were synthesized from colchicine in the laboratory for the development of anticancer drugs at the Republican Specialized Scientific and Practical Medical Center for Oncology and Radiology. The study used 61 mongrel rats from the vivarium of the Sanitary and Epidemiological Service of the Ministry of Health of the Republic of Uzbekistan, weighing 90-140 g. The animals were kept in groups of 5-6 individuals under natural lighting conditions with free access to water and food. In the experiment with the Walker 256 carcinosarcoma strain (n=35), there were 7 experimental groups (n=5), in the ovarian tumor strain (n=26) there were experimental groups (n=6) and control groups (n=8) with saline administration. Rats were administered Decoglitz at a dose of 20 mg/kg (intraperitoneally) and 20 mg/kg (per os), and decocin at a dose of 15 mg/kg. The following drugs were used: taxol (Intaxel, Dabur Pharma LTD, India) at a dose of 6 mg/kg, etoposide (Etoposide phosphate, Bristol-Myers Squibb) at a dose of 8 mg/kg and 5-fluorouracil (manufacturer Getwell Pharmacutikals, India) at a dose of 10 mg/kg. All comparison drugs were administered intraperitoneally once daily for 10 days.

Tumor strains were obtained from the tumor bank of the Institute of Oncology of Kazakhstan and passaged on donor rats, according to the strain protocol.

Tumor transplantation was performed according to generally accepted methods: tumors were inoculated subcutaneously with a suspension of tumor cells at 30-60 mg in 0.3-0.5 ml of nutrient medium per rat [17]. Treatment of animals began 4-5 days after tumor implantation. The drugs were administered to all groups 10 times once a day. All experimental groups received 0.3 ml of the drug per 100 g of rat weight. The animals were slaughtered on the 19^{th}-21^{st} day after tumor implantation. The animals were euthanized using humane methods for laboratory animals. The body weight of the animals was determined before and at the end of the experiment.

During the experiment, tumor growth dynamics were studied by measuring tumor volumes through the skin of animals in the treated and control groups of rats (in three projections) at the beginning of the trial, every five days after the start of treatment and before the slaughter. At the end of the experiment, the efficiency was determined in the euthanized rats by the volume (V) of the extracted tumor tissue, as well as by the tumor mass in the compared groups. Tumor growth inhibition was calculated using the formulas [17]. The tolerability of treatment was evaluated based on rats' mortality, and the spleen weight of euthanized rats was determined to indirectly assess possible hematotoxicity. Statistical analysis was performed using Statistica software, version 6.0. The level of statistical significance was taken as $p < 0.05$.

3. Results

The study of the antitumor activity of the drugs on the Walker 256 carcinosarcoma strain began 5 days after tumor transplantation; all drugs were administered once a day for 10 days. The slaughter was carried out on day 22, with a 20% mortality rate only in the group treated with etoposide.

In group 2, Decoglitz showed high antitumor activity in 96/96% of cases after intraperitoneal administration, with 40% of tumors regressing. The drug caused an increase in body weight (by 4%) and a significant increase in the spleen (by 60%).

In group 3, the antitumor effect of Decocin was less pronounced (70/73%); the drug caused a slight decrease in body weight (by 6%) and spleen weight (by 20%).

In group 4, Decoglitz showed high antitumor activity in 98/97% of cases when administered orally, with 60% of tumors regressing; at the same time, the drug caused an increase in body weight (by 3.7%) and a significant increase in the spleen (by 60%).

In group 5, the antitumor effect of the comparison drug taxol was high—87/89%, with 20% of tumors regressing. The drug caused a slight decrease in body weight (by 5.1%) and a more significant decrease in spleen weight (by 20%).

In group 6, the comparison drug 5-fluorouracil at a dose of 10 mg/kg showed high antitumor activity in 80/82% of cases. The drug caused a slight decrease in body weight (by 6%) and a more significant decrease in spleen weight (by 40%).

In group 7, the antitumor effect of the comparison drug etoposide was high—89/89%; the drug caused the following side effects: death of 20% of animals, some decrease in body weight (by 7.1%), and no decrease in spleen weight compared to the control group (Tab. 1).

Thus, the new drug Decoglitz demonstrated the highest activity, both in comparison with decocin, from which it was obtained, and with known cytostatics. Moreover, its effect was higher than the comparison drugs: decocin by 23-28%, taxol by 7-11%, 5-fluorouracil by 15-18%, and etoposide by 7-9%. The absence of such side effects as decreased body weight and spleen was noted. It should be noted that Decoglitz was studied at a dose that was significantly lower than that of Decocin in relation to LD_{50}. That is, for GA and MASGA derivatives, it was observed that their activity manifested itself at doses 2-4 times lower than the maximum tolerated dose [18].

The study of the antitumor activity of the drugs on the Ovarian Tumor strain began 4 days after tumor transplantation, the drugs were administered 10 times. There were no deaths of animals during the experiment. Slaughter was carried out on the 19th day.

Table 1. Antitumor activity of drugs in rats with Walker 256 carcinosarcoma

Groups of animals, drug, doses (mg/kg), way of adminis-tration	Number of animals gr/death	Animal weight (g)		Tumor volume (cm^3)			Weight of tumor (g)	Spleen weight (mg)	% of inhibition	
		before experiment	after experiment	5	10	22			By volume and weight	% of regression
1. control	5/0	171±15	166±12	0.3±0.1	2.1±0.44	4.6±0.49	4.4±0.52	0.5±0.024		
2. Decoglitz (20) intraperitoneal	5/0	105±4.5	109±5.5	0.3±0.1	0.3±0.1	0.2±0.07*	0.2±0.09*	0.8±0.08	96/96	40%
3. Decocin (15) intraperitoneal	5/0	132±17	124±12.4	0.3±0.07	0.5±0.14	1.4±0.31*	1.2±0.29*	0.4±0.03	70/73	
4. Decoglitz (20) per orally	5/0	190±4.5	197±4.4	0.3±0.1	0.2±0.1	0.09±0.008	0.14±0.1	0.8±0.06	98/97	60%
5. Taxol (4) intraperitoneal	5/0	125±17	121±17	0.4±0.1	0.7±0.1	0.6±0.15*	0.5±0.16	0.4±0.04	87/89	20%
6. Fluorouracil (10) intraperitoneal	5/0	112±4.5	104±4.1	0.2±0.02	1.2±0.2	0.9±0.1*	0.8±0.2*	0.3±0.03	80/82	
7. Etoposide (8) intraperitoneal	5/1	97±1.3	92±1.3	0.4±0.08	0.8±0.07	0.5 ±0.1*	0.5 ±0.17	0.5±0.07	89/89	

Note: n=5 * the differences are statistically significant in comparison with the control at P< 0.05

Table 2. Antitumor activity of Decoglitz compared to Decocin in rats with ovarian tumors

Groups of animals, drug, doses (mg/kg)	Animal weight (g)		Tumor volume (cm3)		Weight of tumor (g)	Spleen weight (mg)	% of inhibition		
	before experiment	after experiment	Day 8	Day 19			By volume and weight		% of regression
1. Control	160±11	162±10,2	1,7+0,5	2,8+0,5	2,5+0,6	0,9+0,07			
2 Decocin (15) intraperitoneal	97±1,3	118±0,02	0,2±0,02	1,3±0,1*	1,4 ±0,4*	0,8± 0,1	54	44	
3. Decoglitz (20) intraperitoneal	119±4,6	135±7,0	0,7±0,1	0,3± 0,02*	0,6±0,1*	0,8±0,07	89	76	40
4. Decoglitz (40) per orally	110±3,2	139±5,7	0,6±0,1	0,1±0,01*	0,1±0,03*	0,8±0,1	96	86	60

Note: in treatment groups n=6, in control groups n=8; * differences are statistically significant in comparison with control group at P< 0.05

In group 2, the drug Decocin was active by 54/44%, while the drug caused a slight decrease in spleen weight (by 11%) and an increase in body weight by 21%.

In group 3, the antitumor effect of Decoglitz at a dose of 20 mg/kg administered intraperitoneally was lower (89/76%) than that observed in Walker 256 carcinosarcoma, but it caused tumor regression in 40% of animals. There was a slight decrease in the spleen (by 11%), and body weight was 13% higher than the initial value.

In group 4, the antitumor effect of Decoglitz at a dose of 40 mg/kg when administered orally was higher—96/86%—while causing tumor regression in 60% of animals. The side effects of the drug were only a slight decrease in the spleen (by 11%); body weight was 26% higher than the initial value (Table 2).

It should be noted that Decoglitz was studied at a dose that was significantly lower in relation to the LD_{50} (1/32) than that of Decocin (1/17). Moreover, it showed similarly high activity at the same oral dose (20 mg/kg), although this dose was 1/250 of its oral LD_{50}, which is very unusual for antitumor agents. Previously, it was observed [18] that the activity of tropolone alkaloid derivatives with GA and MASGA when administered intraperitoneally was manifested at doses 2-4 times lower than the maximum tolerated dose; however, the oral administration of this drug is being studied for the first time.

The high antitumor activity of the drug Decoglitz, as well as its further study as a cytostatic, suggests studying such aspects of its mechanism of action as the alkylating effect on the synthesis of DNA and RNA and on internucleosomal degradation and fragmentation of DNA, which was carried out in vitro on tumor cells Sarcoma 180.

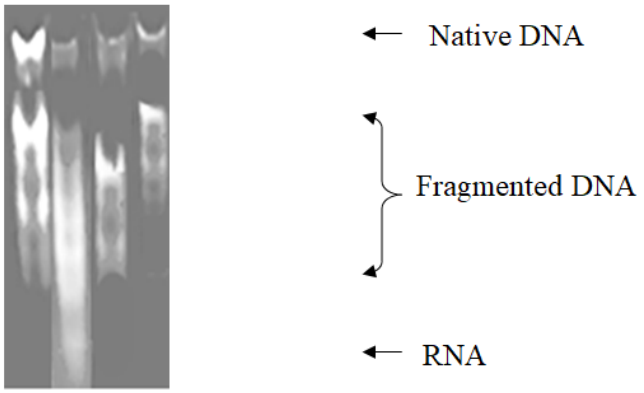

Figure 1. Effect of antitumor drugs on internucleosomal degradation of DNA in sarcoma 180 cells in vitro. Tracks: a). Etoposide, b). Decoglitz, c). K-18, d). GC. Electrophoresis was performed in 1.5% agarose, TAE buffer, 2 hours, 60V

The first experiment investigated the effect of Decoglitz and Decocin (K-18) drugs, as well as GA, compared to etoposide on DNA and RNA synthesis, and internucleosomal DNA degradation with exposure to tumor cell culture (Fig.1. b). Fig. 1 shows the results of intact exposure (in vitro) of the studied preparations for 2 hours on the synthesis of DNA, RNA and internucleosomal degradation of DNA in sarcoma cells 180.

The electropherogram shows that with 2 hours of incubation of the studied antitumor drugs in comparison with the control standard etoposide (a known inhibitor of DNA synthesis), all drugs contribute to the disruption of the integrity (nativity) of DNA, with a difference in the effect of each drug on the qualitative and quantitative assessment of cellular DNA. Regarding the effect on RNA synthesis in the presence of these drugs, there was also a difference in both the qualitative and quantitative evaluation of cellular RNA. The most striking results in this experiment were observed in relation to internucleosomal DNA degradation - one of the criteria for assessing cell apoptosis.

DNA/RNA synthesis was inhibited under the influence of K-18 (Decocin) and Decoglitz by 62/70% and 70/85%, respectively; Etoposide suppressed synthesis by 60/45% and GA - by 35/15%.

It was found that under the influence of Decoglitz, DNA was fragmented by 85% within 2 hours, and K-18 contributed to DNA fragmentation by 77%. Etoposide contributed to DNA fragmentation within 75% and GA - within 25%.

The investigated anticancer drugs Decocin, Decoglitz, and Etoposide were also cultured on sarcoma 180 cells for 4 hours. The results of the drugs effect on DNA synthesis, RNA synthesis and internucleosomal DNA degradation are presented in Fig. 2.

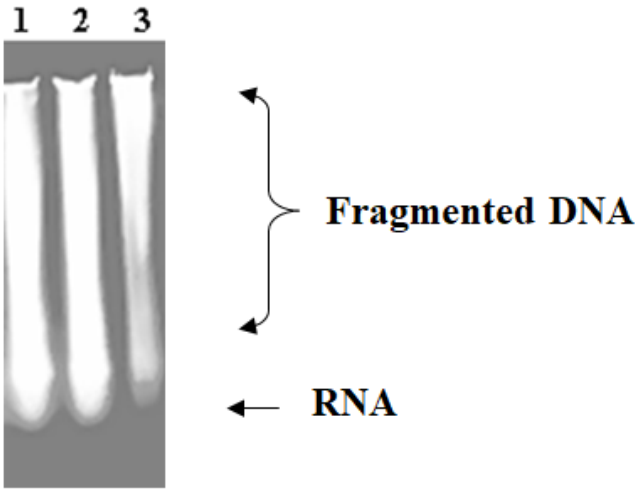

Figure 2. Effect of antitumor drugs on DNA, RNA synthesis and internucleosomal degradation of DNA in sarcoma 180 cells in vitro. Tracks: a) K-18; b) Decoglitz; c) control Etoposide. Electrophoresis was performed in 1.5% agarose, TAE buffer, 4 hours, 60 V

The synthesis of DNA was inhibited by 95% within 4 hours under the impact of three anti-tumor drugs. RNA synthesis was less inhibited due to the following factors: under the impact of etoposide RNA synthesis was inhibited by 55.0%, under the impact of K-18 and Decoglitz – by 75.0%. Regarding inter-nucleosomal DNA degradation, it has been shown that Decocin (K-18) and Decoglitz promote DNA fragmentation by 100.0% and Etoposide - by 90.0%.

4. Discussion

Limitations of this study include the lack of advanced in silico docking and pharmacokinetics modeling, as well as the absence of combination trials with natural cytotoxics and antiviral agents. Future work will integrate computational screening and combination therapy evaluation to maximize translational value. Computational approaches confirm that colchicine analogues, when complexed with solubilizing agents such as GA, display favorable ADMET parameters and target engagement scores, supporting our findings of strong in vivo activity with reduced toxicity [19]. The antiviral-tumor axis is particularly relevant. Compounds such as cordycepin and riboprine, originally developed for viral infections, exhibit significant DNA/RNA synthesis inhibition in tumor models, similar to the nucleic acid suppression observed for Decoglitz [20]. Natural compounds including polyphenols, bromelain, and gingerol are reported to act synergistically with classical cytostatics, providing a safer toxicity profile and expanding potential combination regimens [21].

The superior antitumor activity of Decoglitz observed in our experiments can be contextualized with recent findings on colchicine derivatives. Studies have demonstrated that such modifications enhance DNA intercalation and microtubule destabilization, resulting in increased apoptosis [22].

Table 3 presents the results of 3 antitumor drugs and GA effect on DNA, RNA synthesis and internucleosomal DNA degradation on sarcoma 180 cells with exposure to these drugs for 2 and 4 hours.

As it is known, internucleosomal degradation and fragmentation of DNA up to 80%, and at 4 hours' incubation - up to the observed 100% degradation of nucleosomes and fragmentation of DNA in the form of a ladder, is a sign of further apoptosis [9-10]. It means that the studied antitumor drugs Decoglitz and Decocin during 2 hours and 4 hours incubation promote the activation of apoptosis processes in sarcoma cells 180 in vitro. It should be noted that GA itself does not have cytotoxic activity and was used due to its solubilizing properties, but the question of whether GA has the ability to suppress nucleic acid synthesis was raised out of interest in GA itself. According to the data obtained, GA suppresses nucleic acid synthesis to a small extent (by 25/15%). The effect of Decoglitz is even more surprising, as it has more pronounced alkylating properties than Decocin and GA, with a sharp decrease in toxicity compared to Decocin (K-18).

Thus, the GA/K-18 complex, named Decoglitz, inhibits DNA/RNA synthesis more significantly (by 70/85%) and significantly affects internucleosomal DNA degradation (by 85%) than K-18 (Decocin) and GA, from which it was derived.

5. Conclusions

Studies of the new drug Decoglitz in animals with Walker 256 carcinosarcoma revealed significantly higher activity with 60% of tumors regressing, which was 23-28% higher than the original Decocin, Taxol – by 7-11%, 5-fluorouracil – by 15-18%, and Etoposide – by 7-9%. There were no side effects such as reduction in body weight and size of the spleen.

Decoglitz also had a high effect on ovarian tumors when administered intraperitoneally, which was 30-40% higher than the effect of Decocin, in addition, 40% of tumors regressed.

However, the drug showed even higher activity when administered orally, with 60% of tumors regressing. This effect is confirmed by the more intense impact of on nucleic acid synthesis, which was 8-15% higher than that of Decocin, 10-40% higher than that of Etoposide, taken as a control, and 37-55% higher than that of GA. Evidently, the high ability of the new drug Decoglitz to suppress nucleic acid synthesis and carry out internucleosomal degradation and fragmentation of tumor DNA explains its antitumor efficiency which is greater than that of Decocin (K-18) in experiments on tumors.

Thus, the established fact of the formation of stable GA complexes with the antitumor drug Decocin allows GA and its salts to be considered as promising molecular containers in pharmaceutical substance delivery systems and for the creation of new drugs based on them.

Table 3. Effect of antitumor drugs on DNA/RNA synthesis and internucleosomal degradation of sarcoma 180, *in vitro*

Antitumor drugs	Cultivation for 2 hours			Cultivation for 4 hours		
	Internucleosomal DNA degradation, %	Inhibition of synthesis		Internucleosomal DNA degradation %	Inhibition of synthesis	
		DNA, %	RNA, %		DNA, %	RNA, %
Decocin (K-18)	77.0	62.0	70.0	100.0	95.0	75.0
Decoglitz	85.0	70.0	85.0	100.0	95.0	75.0
GA	25.0	25.0	15.0	-	-	-
Etoposide	75.0	60.0	45.0	90.0	95.0	55.0

Conflict of Interests' Statement

The authors declare no conflict of interest.

The article is published for the first time and is part of a scientific work.

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