Research Results in Pharmacology

Research Results in Pharmacology 7(4): 81–88
UDC 547.1: 615.2
DOI 10.3897/rrpharmacology.7.71455

Research Article

Impact of organotin compounds on the growth of epidermoid Lewis carcinoma

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Academic editor: Mikhail Korokin ♦ **Received** 12 July 2021 ♦ **Accepted** 25 September 2021 ♦ **Published** 20 December 2021

Citation: Dodokhova MA, Safronenko AV, Kotieva IM, Alkhuseyn-Kulyaginova MS, Shpakovsky DB, Milaeva ER (2021) Impact of organotin compounds on the growth of epidermoid Lewis carcinoma. Research Results in Pharmacology 7(4): 81–88. https://doi.org/10.3897/rrpharmacology.7.71455

Abstract

Introduction: Search for new compounds with a broad antitumor and antimetastatic potency due to multiple targeting remains important in medicinal chemistry, pharmacology and oncology. We report the efficacy of hybrid organotin agents bis-(3,5-di-*tert*-butyl-4-hydroxyphenylthiolate) dimethyltin (Me3) and (3,5-di-*tert*-butyl-4-hydroxyphenylthiolate) triphenyltin (Me5).

Materials and methods: The compounds were administered to mice bearing the spontaneously metastatic epidermoid Lewis lung carcinoma (LLC). The efficacy of the treatment was evaluated by mean life span, percentage of tumor growth inhibition, number of lung metastases, frequency of metastasis, tumor weight 21 days after tumor cell inoculation, and a degree of lung damage according to the method of D. Tarin and J.E. Price.

Results and discussion: For new organotin compounds containing an antioxidant protective fragment of 2,6-di-tert-butylphenol, moderate antitumor and pronounced antimetastatic effects were revealed in the Lewis model of epidermoid lung carcinoma; more active for Me5. Some features of the development of the process of metastasis were recorded with the introduction of various doses of hybrid organotin compounds.

Conclusion: Substances Me3 and Me5 possess specific activity on the model under investigation, which allows one to suggest these organotins as promising series of antitumor and antimetastatic agents with multiple targeting mode of action.

Keywords

organotin compounds, anticancer drugs, epidermoid Lewis lung carcinoma, antioxidants.

Introduction

The number of patients with verified diagnosis of cancer is permanently growing, at an annual rate of 1.5–2.5%. Official documents state that the share of patients with newly diagnosed disease at stages III–IV remains high (Kaprin et al. 2019, 2020). This cohort is traditionally treated with chemotherapy that frequently fails. This dictates the search for new drugs potent against primary as well as metastatic tumors. In particular, new drugs are aimed at tumor dissemination, a process that makes the disease fatal (Kholodenko et al. 2013). Organotin compounds are unique in this sense because they act on a variety of intracellular targets including DNA (Arshad et al. 2016). Furthermore,

organotin compounds are agonists of retinoid X receptors (RXR), thereby interefering with gene transcription (Nakanishi et al. 2008). Also, organotin agents can interact with biological membranes incluidng mitochondria (Davies et al. 1982). Finally, the pro-oxidant effect of organotin compounds results in apoptosis (Fickova et al. 2015).

Tin derivatives R_2SnX_2 that carry two organic moieties R are known to be anti-metabolic whereas tri-substituted derivatives R_3SnX transport the hydroxyde ion across the mitochondrial membrane. Imnportantly, R_3SnX with three Sn-C bonds are the most cytotoxic. Compoudnds with aryl groups are less potent than those with alkyl moieties. The X group in R_nSnX_{4-n} organotin compounds can influence the activity (Antonenko et al. 2018).

Testing of organotin compounds *in vivo* is frequently limited by indiscriminate toxicity, with kidneys, lever and brain as the most vulnerable organs due to their intensive metabolism The LD_{50} values after oral administration in Wistar rats normally do not exceed 150 mg/kg (Verginadis et al. 2010; Metsios et al. 2018). We therefore investigated the hybrid organotin compounds containing the bioactive tin fragment and an antioxidant protecting moiety.

The choice of 2,6-di-*tret*-butylphenol group is based on our previous studies that demonstrated a potent antioxidant property of this group as well as an antitumor efficacy of substituted phenol derivatives (Gaynutdinov et al. 2018; Menshchikova et al. 2018). 2,6-di-*tret*-butylphenols are biomimetics of natural antioxidants (α-tocopherol). These spatially limited phenols, being acceptors of free radicals, have been widely applied as inhibitors of free-radical processes.

Organotin compounds bis-(3,5-di-*tret*-butyl-4-hydroxyphenylthiolate) dimethyltin (**Me3**) and (3,5-di-*tert*-butyl-4-hydroxyphenylthiolate) triphenyltin (**Me5**) were selected on the basis of safety from the series of tin organic compounds with various structures of R. The OECD protocols (OECD, 2001; OECD, 2008) were used for the selection. **Me3** and **Me5** showed the best safety parameters, that is, the mean lethal dose after a single bolus oral administration in Wistar rats was > 2 g/kg and 950 mg/kg, respectively (Dodokhova et al. 2021). These parameters place **Me3** to class V, and **Me5** to class IV toxicity. Therefore, a high antitumor potential and structural characteristics of hybrid molecules make them promising antitumor and anti-metastatic drug candidates.

The aim of our study is to evaluate the antitumor and antimetastatic effect of the organotin compound bis-(3,5-di-tert-butyl-4-hydroxyphenylthiolate) dimethyltin (**Me3**) and (3,5-di-tert-butyl-4-hydroxyphenylthiolate) triphenyltin (**Me5**) in the Lewis epidermoid lung carcinoma (LLC) model.

Materials and methods

Compounds under study

The structures of bis-(3,5-di-*tret*-butyl-4-hydroxyphenylthiolate) dimethyltin (**Me3**) and (3,5-di-*tert*-butyl-4-hydroxyphenylthiolate) triphenyltin (**Me5**) are shown in Figure 1. Synthesis of **Me3** and **Me5** has been described earlier (Mukhatova et al. 2013; Shpakovsky et al. 2014).

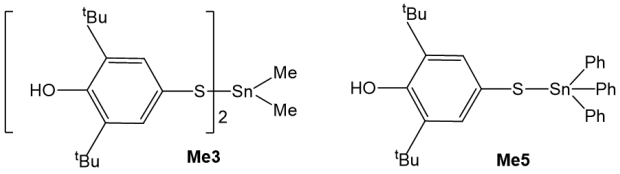


Figure 1. Structural formulas of **Me3** (bis-(3,5-di-*tret*-butyl-4-hydroxyphenylthiolate) dimethyltin) and **Me5** (3,5-di-*tert*-butyl-4-hydroxyphenylthiolate) triphenyltin). **Note:** tBu – *tret*-butyl, Me – methyl, Ph – phenyl.

Animals

Female C57Bl/6 mice (21–22 g, 8 weeks old) were obtained from Rappolovo Nursery (Leningrad Region, Russia). After a 14-day quarantine, the animals were examined, standardized and randomized for experimental cohorts. The animals with abnormalities were excluded from the experiments. The animals were kept in the facility at Rostov-on-Don Medical University according to The European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes. The study was approved by The Ethical Committee of Rostov-on-Don Medical University, minutes №.10/20, of May 28, 2020).

Experimental design

We used LLC (tumor strain collection of Blokhin Cancer Center, Moscow) for evaluation of antitumor potency of **Me3** and **Me5**. This tumor is characterized by a high frequency of metastasis; the macroscopic metastases are visible for a quantitative and qualitative analysis. LLC is useful for experimental therapy since its drug sensitivity profile is reminiscent of human solid tumors (Dyigay et al. 2010). Lungs are the primary sites of LLC metastasizing. The strain was obtained from the bank of tumor materials of N.N. Blokhin Scientific Research Institute for Experimental Diagnostics and Therapy of Tumors, Russian Cancer Research Center. The strain was routinely propagated in vivo by intrafemoral inoculation of 0.3 ml freshly dissected tumor in saline. Tumors after 3–4 passages were inoculated into the right axillary region (Ostrovskaya et al. 2018). Two days after the inoculations, the mice were injected with **Me3** or **Me5** i.p. daily for 5 consecutive days (Sofina et al. 1980). For both substances, the test was carried out according to the scheme used for the primary study of potential anticancer drugs in a wide range of doses. Single bolus doses varied from 30 mg/kg to 100 mg/kg, with the total doses reaching 150–500 mg/kg. The control cohort was injected with 1% aqueous gelatin solution (vehicle) in similar doses and modes. Each cohort consisted of 12 mice.

At the first stage of the experiment (screening), the lifetime of animals was recorded after injecting Me3 and Me5 in a wide range of doses. The animals were observed daily until their natural death. At the second stage of the study, 21 days after the inoculation of tumor material, the animals were euthanized on a guillotine. The postmortem examination was carried out according to the well-known method (Koptyaeva et al. 2018). On the 15th day after the end of the administration of the organotin compounds, the following parameters were determined: weight of the tumor, percentage of the tumor growth inhibition, the number of lung metastases per mouse, the frequency of tumor metastasis, the index of inhibition of metastasis, the degree of lung damage according to the method of D. Tarin and J.E. Price (Tarin and Price 1979; Habriev 2005). Table 1 presents the animal cohorts and treatment regimens for group 1–9 and group 1a–9a.

Table 1. Grouping and Treatment of LLC Transplant Bearing Mice

Treatment	Cohorts
Me3, 30 mg/kg* (150 mg/kg)**	1, 1a
Me3, 50 mg/kg (250 mg/kg)	2, 2a
Me3, 75 mg/kg (375 mg/kg)	3, 3a
Me3, 100 mg/kg (500 mg/kg)	4, 4a
Me5, 30 mg/kg (150 mg/kg)	5, 5a
Me5, 50 mg/kg (250 mg/kg)	6, 6a
Me5, 75 mg/kg (375 mg/kg)	7, 7a
Me5, 100 mg/kg (500 mg/kg)	8
Vehicle	9, 9a

Note: * – single dose; ** – total dose (single dose × 5 days); Me3 – bis-(3,5-di-tert-butyl-4-hydroxyphenylthiolate) dimethyltin; Me5 – (3,5-di-tert-butyl-4-hydroxyphenylthiolate) triphenyltin.

The group 8a was excluded due to general toxicity in group 8.

Formulas for assessment of therapeutic efficacy are the following:

$$\text{THIm},\% = \frac{(\text{Mc} \times \text{Me})}{\text{Mc}} \times 100\%$$

where Mc and Me are mean tumor masses in the control (vehicle) and experimental cohorts;

$$\text{FM},\% = \frac{q_{met}}{q_t} \times 100\%$$

where q_{met} is the number of mice with lung nodes, and q_t is the total number of animals in the group;

$$\text{MI},\% = \frac{(\text{FMc} \times \text{KMc}) - (\text{FMe} \times \text{KMe})}{(\text{FMc} \times \text{KMc})} \times 100\%$$

where FMc and FMe are frequencies of lung metastasis in control and experimental cohorts, respectively, KMc and KMe are mean numbers of lung nodes in the control and experimental groups, respectively.

Two series of experiments were conducted: firstly, we studied the life expectancy of animals (T, days) during treatment with **Me3** or **Me5,** using the doses indicated in Table 1. The mice were observed until death (cohorts 1–9). At this stage, the most appropriate doses were selected. At the second stage of the experiment, the animals were euthanized on the 21st day (cohorts 1a–9a); a pathoanatomic study was conducted in accordance with (Koptyaeva et al. 2018). After 15 days of treatment, tumor mass (M, g), TGI (%), average number of metastatic nodes in the lungs per animal (q), metastasis frequency (FM, %), metastasis inhibition index (MI, %) and a degree of lung damage were evaluated (Tarin and Price 1979; Khabriev 2005).

Tarin & Price criteria included the number and diameter of metastatic nodes: 0 – no nodes; 1 – (LCP-1) < 10 nodes, d > 1 mm; 2 (LCP-2) – 10–30 nodes, d > 1 mm; 3 (LCP-3) – > 0 nodes, no merge; 4 (HCP-4) – up to 100 nodes; 5 (HCP-5)>100 nodes and/or merged metastases.

Statistical analysis

Data are expressed as mean±standard error. The normality of data distribution was assessed by Anderson-Darling test, and Student's t-test was used for comparison of the experimental groups vs the control cohort. Differences > 95% were considered statistically significant.

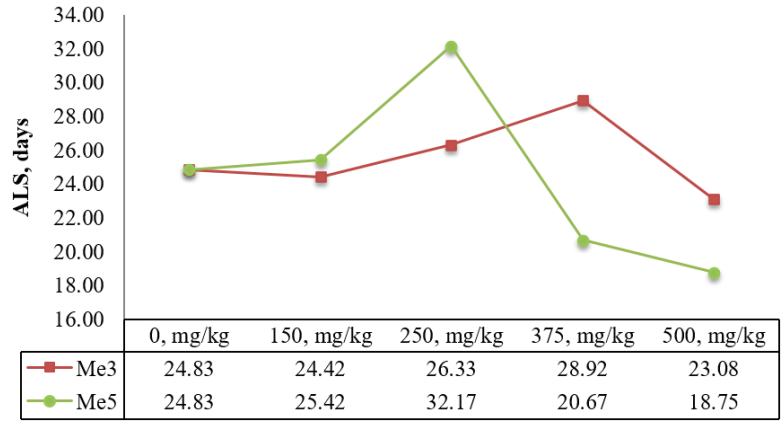
Results and discussion

First, we tested the life span of mice bearing LLC transplants. As shown in Figure 2, **Me3** and **Me5** (total dose of 150 mg/kg) caused no significant changes of this parameter. Dose escalation showed that the most efficient dose was 375 mg/kg for **Me3** and 250 mg/kg for **Me5**. At the latter dose, the biggest increase of life span was 29.5%. Further dose escalation caused an adverse effect: 16.75% and 24.9%, respectively, at 375 mg/kg of **Me5**. The earliest time of death was day 21 after tumor transplantation. This time point was used for euthanasia at the next step of experiments.

We next tested the effects of **Me3** and **Me5** on the primary and metastatic LLC foci (Figs 3, 4 and Tables 2, 3). Frequency of metastasis was 100%, that is, all tumor bearing animals had lung metastases. **Me3** (150 mg/kg) had no significant effect on the primary tumor sites and metastatic nodes; therefore we considered this dose inefficient. In contrast, **Me5** at the same dose decreased the number of metastatic nodes by 24.6% (stage II of metastatic lung injury according to Tarin & Price). Also, we observed a tendency to a shrinkage of the primary tumor.

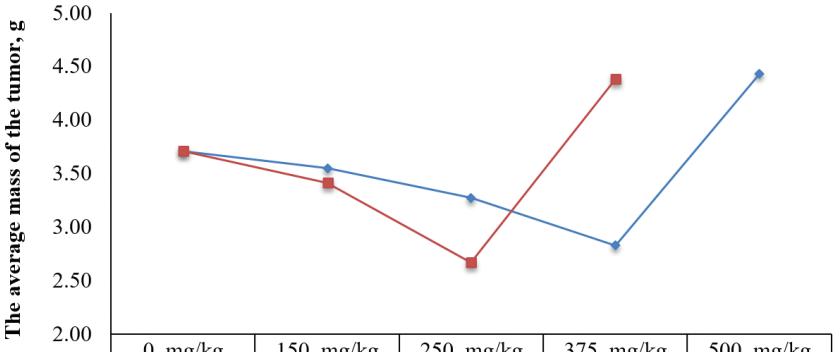
Me3 (group 2a) and **Me5** (6a) (single doses of 50 mg/kg) caused 11.9% and 28% TGI, respectively. FM decreased by 17% and 68%, respectively, accompanied by a sizeable decrease in the amount of lung nodes. For **Me5**, the total dose of 250 mg/kg was the most efficient. In group 3a, the antitumor efficacy was dosep-dependent, with maximum TGI 23.72% and FM 34.7%.

Gross anatomical examinations revealed no significant features.



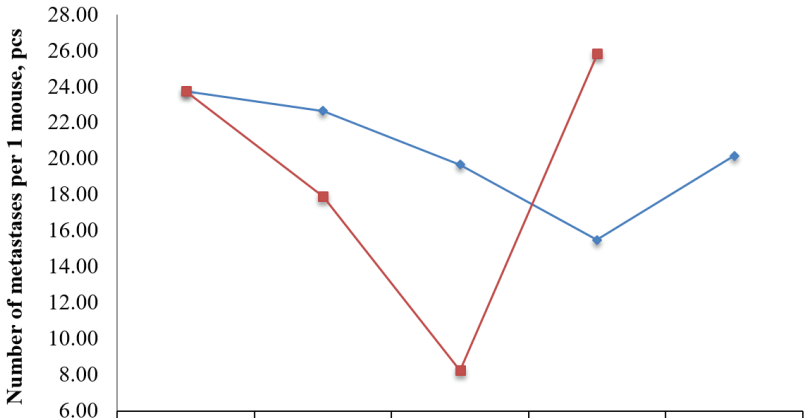
	0, mg/kg	150, mg/kg	250, mg/kg	375, mg/kg	500, mg/kg
Me3	24.83	24.42	26.33	28.92	23.08
Me5	24.83	25.42	32.17	20.67	18.75

Figure 2. Influence of Me3 and Me5 on the average life span of animals (mice – females of the C57Bl/6 line). **Note:** ALS – average life span of animals; Me3 – bis-(3,5-di-tert-butyl-4-hydroxyphenylthiolate) dimethyltin; Me5 – (3,5-di-tert-butyl-4-hydroxyphenylthiolate) triphenyltin.



	0, mg/kg	150, mg/kg	250, mg/kg	375, mg/kg	500, mg/kg
Me3	3.71	3.55	3.27	2.83	4.43
Me5	3.71	3.42	2.67	4.39	

Figure 3. Effects of **Me3** and **Me5** on the primary tumor weight. **Note:** Me3 – bis-(3,5-di-tert-butyl-4-hydroxyphenylthiolate) dimethyltin; Me5 – (3,5-di-tert-butyl-4-hydroxyphenylthiolate) triphenyltin.



	0, mg/kg	150, mg/kg	250, mg/kg	375, mg/kg	500, mg/kg
ME3	23.75	22.67	19.67	15.50	20.17
ME5	23.75	17.92	8.25	25.83	

Figure 4. Effects of **Me3** and **Me5** on the number of metastatic nodes. **Note:** Me3 – bis-(3,5-di-tert-butyl-4-hydroxyphenylthiolate) dimethyltin; Me5 – (3,5-di-tert-butyl-4-hydroxyphenylthiolate) triphenyltin.

With the introduction of **Me3** in a total dose of 500 mg/kg and **Me3** in a total dose of 375 mg/kg of the organotin compound, a pronounced toxic effect was observed, which was not accompanied, however, by the death of animals during the days of the treatment or immediately after its termination. The introduction of organotin compound in such high doses led to the activation of the tumor process at all stages of its development: early and more

Table 2. Efficacy of Antitumor and Anti-metastatic Treatment with Me3 and Me5 on Day 21 After LLC Transplantation

Parameters Cohorts	Tumor growth inhibition, %	Frequency of metastasis, %	Metastatic inhibition, %
1a (**Me3** 150 mg/kg)	4.3	100	4.5
2a (**Me3** 250 mg/kg)	11.86 $p \leq 0.05$	100	17
3a (**Me3** 375 mg/kg)	23.72 $p \leq 0.05$	100	34.7 $p \leq 0.05$
4a (**Me3** 500 mg/kg)	-19.4 $p \leq 0.05$	100	23.4 $p \leq 0.05$
5a (**Me5** 150 mg/kg)	8 $p \leq 0.05$	100	24.6 $p \leq 0.05$
6a (**Me5** 250 mg/kg)	28 $p \leq 0.05$	100	68 $p \leq 0.05$
7a (**Me5** 375 mg/kg)	-18.2 $p \leq 0.05$	100	-8.6 $p \leq 0.05$
9a (vehicle)	-	100	-

Note: Me3 – bis-(3,5-di-tert-butyl-4-hydroxyphenylthiolate) dimethyltin; Me5 – (3,5-di-tert-butyl-4-hydroxyphenylthiolate) triphenyltin.

Table 3. Efficacy of **Me3** and **Me5** on LLC Metastasis by Tarin&Price Criteria

Cohort	% lung metastasis				
	Low colonization			High colonization	
	1	2	3	4	5
1 (**Me3** 150 mg/kg)	0	100	0	0	0
2 (**Me3** 250 mg/kg)	0	100	0	0	0
3 (**Me3** 375 mg/kg)	0	100	0	0	0
4 (**Me3** 500 mg/kg)	0	100	0	0	0
5 (**Me5** 150 mg/kg)	0	100	0	0	0
6 (**Me5** 250 mg/kg)	58	42	0	0	0
7 (**Me5** 375 mg/kg)	0	100	0	0	0
8 (vehicle)	0	75	25	0	0

Note: LCP – low colonization potential; HCP – high colonization potential; Me3 – bis-(3,5-di-tert-butyl-4-hydroxyphenylthiolate) dimethyltin; Me5 – (3,5-di-tert-butyl-4-hydroxyphenylthiolate) triphenyltin.

pronounced metastasis, as well as dissemination to places atypical for Lewis epidermoid carcinoma and, as a consequence, early death of animals (a decrease in the average life expectancy below the control values). The peculiar course of malignant neoplasm was observed in the animals of Group 4a: despite the antimetastatic effect (23.4%), the growth of the primary focus was stimulated by 19.4%. In our opinion, it is with the size of the solid tumor that a significant decrease in the life span of animals in this group is associated. In Group 7a (**Me5**), when dissecting the animals, a more aggressive development (bifocal growth) of the tumor process was noted, with activation of the growth of a solid tumor and dissemination of tumor nodes into atypical zones: kidneys, uterus, pericardium, etc.

We used an established model of LLC transplants for evaluation of antitumor and anti-metastatic efficacies of dimethyl- and triphenyl derivatives of tin carrying the protective 2,6-di-*tret*-butylphenol fragment. Transplanted tumor of Lewis epidermoid carcinoma of mice is representative. It can spontaneously metastasize to the lungs with subcutaneous inoculation. Due to the high growth rate of the primary tumor, it can spread very quickly. To estimate the effects of dimethyl- and triphenyl derivatives of tin compounds containing a protective fragment of 2,6-di-tert-butylphenol on the multistep process of tumor progression, including metastasis, we used the parameters of life span.

The spread of malignant cells from primary tumors and their formation of new tumor colonies in distant tissues involve a multi-stage process known as the invasion-metastasis cascade (Markina et al. 2018). It is this process that determines a degree of tumor malignancy, life expectancy and the efficiency of treatment. It should be noted that we administered the tested the agents 48 h after tumor inoculation aiming to address the issue of prophylaxis of metastasis.

The molecular design of **Me3** and **Me5** presumes the introduction of 2,6-di-*tret*-butylphenol fragment, which makes the compounds safer and less cardiotoxic (Dodokhova et al. 2021) than similar compounds. Moreover, this modification made it possible to escalate the total tolerated dose up to 500 mg/kg. Therefore the resulting compounds combine the antitumor properties with the moiety for attenuation of general toxicity. Generally, the ratio of specific effect and general toxicity determines the possibility of using this substance as a drug.

For further development of a potential drug, it is necessary to characterize possible molecular targets and mechanisms of specific action, which have yet to be determined completely. For the biotransformation of **Me3** and **Me5** in the liver, hydrolysis with the formation of RSH (R = 3,5-di-tert-butyl-4-hydroxyphenyl) and $Me_2Sn(OH)_2$/ Ph_3SnOH, leading to the accumulation of a biocidal fragment containing Sn (IV) and a free antioxidant group.

Organotin compounds with different ligand groups showed a variety of activities *in vitro* and *in vivo* (Milaeva et al. 2021). Previously, we reported their significant prooxidant effects (Milaeva et al. 2006). The formation of reactive organic radicals R• can trigger chain reactions of substrate oxidation. Oxidative stress leads to the damage of membranes, including the mitochondrial ones, which is the cause of metabolic disorders. The level of free radical oxidation in organs and tissues can increase because of an increase of the active oxygen metabolites generation as well as an insufficient efficiency of antioxidant systems. The 2,6-di-*tret*-butylphenol fragment can regulate the balance between pro- and anti-oxidant systems in the cell. Such a dual structure of the hybrid organotin compounds molecule will allow us to apply the organotin compounds as anticancer drug candidates alone and in combinations with conventional chemotherapeutics.

The role of reactive oxygen species (ROS) in cancer biology is dubious. A moderate ROS increase can promote the tumor growth, whereas highly elevated ROS would overcome the antioxidant defense and lead to oxidative damage of lipids, proteins, and DNA. ROS levels correlate with tumor aggressiveness and negative prognosis (Milaeva et al. 2019). Such a multidirectional manner is associated with a plethora of factors, including the structure of antioxidant compounds, specific properties of metabolic products, origin of the tumor model and gender of tumor bearing animals (Mendelsohn et al. 2014; Martinovich et al. 2020).

A significant anti-metastatic effect, which is non-linearly dependent on the dose presumes the roles for the balance of oxidation/reduction, mitochondrial permeability and swelling (Le Gal et al. 2015; Durnova et al. 2019; Puzakov et al. 2019), and immune surveillance. Antioxidants based on spatially limited phenols stabilize the organs with a high metabolism, thereby attenuating the metastatic activity. Tumor progression leads to hypoxia and exhaustion of antioxidant resources of the cell. These factors play a role in the effects analyzed in the present study.

Conclusions

Bis-(3,5-di-tert-butyl-4-hydroxyphenylthio) dimethyltin (**Me3**) and (3,5-di-tert-butyl-4-hydroxyphenylthio) triphenyltin (**Me5**), administered intraperitoneally, reduce the metastatic process in the lungs on a mouse LLC tumor model. The efficacy of the compounds on the primary tumors was less pronounced. Mechanisms are complex and remain to be elucidated; they include direct cytocidal effect, as well as a disbalance between oxidation and reduction. Our results provide evidence in favor of antitumor drug candidates based on organotin compounds.

Funding

This study was funded by the Russian Foundation for Basic Research (Grant 20-03-00471) and Russian Science Foundation (Grant 19-13-00084).

Conflict of interests

Authors declare no conflict of interests.

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