Digest Journal of Nanomaterials and Biostructures Vol. 16, No. 2, April - June 2021, p. 585 - 592

Inhibition potency of disulphides and trisulphides on various tumor cell lines growth

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Tumor is one of the leading diseases of today. Chemotherapy and radiation therapy healing chances are limited, so some alternative methods are resorted to. Many papers indicated that garlic and organosulphur compounds diallyldisulphide (DADS) and diallyltrisulphide, which are main components of garlic decrease the cancer risk and inhibit the cell proliferation. In this paper inhibition potency of disulphides (DADS and its synthetic analogues) and trisulphides with different alkyl and phenyl substituents on growth of various tumor (Non-Small cell Lung Cancer, Colon cancer, CNS Cancer, Melanoma, Ovarian Cancer, Renal Cancer, Prostate Cancer, Breast Cancer, Leukemia) cell lines was investigated. Concentration of each compound (DADS, diethyl disulphide, dipropyl disulphide, diphenyl disulphide, tetraethylthiuram disulphide (TETUDS), dimetil trisulphide, dipropyl trisulphide and metilpropyl trisulphide (MPTS) was 10 μmol/L. It was found that DADS has an inhibitory effect on the growth of several cancer cell lines, but synthetic analogues TETUDS and MPTS exhibit stronger effect on certain cells lines. MPTS inhibits the growth of even 12 cell lines for more than 10%, especially leukemia cell line SR and NCI-H522 cell line of Non-Small cell Lung Cancer (reduction of growth for 24% and 47%, resp.). Trisulphide analogues exhibit little higher inhibitory effects in comparison to disulphide ones.

(Received January 21, 2021; Accepted May 4, 2021)

Keywords: Garlic, Diallyl disulphide and its synthetic analogues, Trisulphides, Tumor cell lines inhibition

1. Introduction

Tumors represent mass of altered cells which uncontrollably proliferation account for the 12% of the global death rate and in the West they are the second greatest cause of death. Cancer is a major public health problem in every region of the world. Chemotherapy and radiation therapy healing chances are either limited or not good enough [1–4].

Garlic is one of the oldest medicinal herbs. Alternative medicine today recommends garlic for the treatment of stomach, pharyngeal, esophageal, laryngeal, breast, colon, pancreatic, lung, ovarian and prostate cancer[5–10]. Epidemiological researches have supported a positive association between dietary intake of *Allium* vegetables and lower cancer risk[11].

Meta-analysis given by Levi et al.[12] suggested a potentially broader favorable effect of garlic on digestive tract carcinogenesis. Intake of raw and/or cooked garlic decreased the risk of colorectal cancer.

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Biological activity of the garlic has mostly been associated with the thiosulfinate allicin. To now days, most of the chemical and biochemical aspects of allicin formation (from γ-glutamyl-S-alk(en)yl-l-cysteine) and transformation processes are well established [13]. A great number of studies conducted so far have shown that certain organosulphur compounds can inhibit the proliferation, that is, induced apoptosis [14,15]. It was shown that diallylsulphide (DAS), diallyldisulphide (DADS) and diallyltrisulphide (DATS), which are major components of garlic, induce apoptotic effect [16]. The mentioned compounds attracted the attention of scientists because of their ability to induce apoptosis *in vitro*[17] and to inhibit tumor growth *in vivo*[18,19]. Recent studies have also demonstrated anticancer effects of DATS against breast cancer [20–22]. In addition, it was postulated that the number of sulfur atoms in compounds accounts for the significance of their biological activity [23,24].

Therefore, in the present work we investigated the influence of disulphides (DADS and its synthetic analogues) and trisulphideson growth inhibition potency of various tumor (Non-Small cell Lung Cancer, Colon cancer, CNS Cancer, Melanoma, Ovarian Cancer, Renal Cancer, Prostate Cancer, Breast Cancer, Leukemia) cell lines. In order to test the effect of different alkyl and phenyl substituents presence in the molecules of organosulphur compound son their activity, diethyl disulphide (DEDS), dipropyl disulphide (PDS), diphenyldisulphide (DPDS), tetraethylthiuramdisulphide (TETUDS), dimetiltrisulphide (DMTS), dipropyltrisulphide (DPTS)and metilpropyltrisulphide (MPTS) were selected.

2. Experimental

All reagents (purchased from Sigma-Aldrich Chemical, St. Louis, Missouri) were of high commercial grade.

Analysis of the effects of all already mentioned substances on different tumors cells growth were done by standard procedure of Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, Maryland, United States [25,26]. Concentration of each compounds solution was 10 μmol/L.

Different cell lines of tumors were used: Leukemia (cell line CCRF-CEM, HL-60(TB), K-562, MOT-4, RPMI-8226, SR), Non-Small cell Lung cancer (cell line A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, NCI-H460, NCI-H522), Colon cancer (cell line COLO 205, HCC-2998, HCT-15, HT29, KM12), CNS Cancer (SF-268, SF-295, SF-539, SNB-19, SNB-75, U251), Melanoma (LOX IMVI, MALME-3M, M14, MDA-MB-435, SK-MEL-2, SK-MEL-28, SK-MEL-5, UACC-257, UACC-62), Ovarian Cancer (IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, NCI/ADR-RES, SK-OV-3), Renal Cancer (786-0, A498, ACHN, CAKI-1,RXF-393, SN12C, TK-10, UO-31, PC-3), Prostate Cancer (PC-3, DU-145), Breast Cancer (MCF7, MDA-MB-231/ATCC, HS 578T, BT-549, T-47D, MDA-MB-468).

3. Results

Results obtained for the inhibition of growth of different tumor cells lines by disulphides and trisulphides are presented in Table 1. As it mentioned above concentration of each organosulphur compound was the same (10 μmol/L).DADS, one of the major components of garlic inhibits the growth of several tumor cell lines. The highest effect (about 15%) it exerts on breast cancer cell line MCF7. Synthetic analogues of DADS (DEDS, PDS and DPDS) exhibit similar effects on cell lines growth of the most tested tumors (Table 1). But, in comparison to DADS, some of renal cancer cell lines are more sensitive to analogues DEDS and PDS. DPDS, analogue with two phenyl groups demonstrates stronger effect on almost all leukemia cell line comparing to DADS (Figure 1). It inhibits the growth of CCRF-CEM and MOLT-4 cell lines for 27 and 21% resp. The most effective disulphide is TETUDS, which inhibits the growth of three Leukemia cell lines and three cell lines of Non-Small cell Lung Cancer. The strongest inhibitory effect it exerts on melanoma cell line UACC-257 (reduction of growth for 30%).

Table 1. The effect of organosulphur compounds on different tumors cells lines growth

Panel/Cell Line		Growth Percent							
		DADS	DEDS	PDS	DPDS	TETUDS	MPTS	DPTS	DMTS
Leukemia	CCRF-CEM	104.40	119.2	103.94	72.35	102.37	96.12	81.19	110.11
	HL-60(TB)	101.31	104.51	101.50	89.04	73.67	92.53	/	99.76
	K-562	95.03	93.15	97.53	/	80.48	84.82	101.14	98.96
	MOLT-4	103.07	122.13	98.58	79.36	93.16	104.13	108.34	120.82
	RPMI-8226	109.10	111.63	109.53	96.40	109.75	115.91	103.06	112.29
	SR	97.45	115.49	96.26	97.25	89.01	63.86	95.00	116.65
Non-Small Cell Lung Cancer	A549/ATCC	99.54	101.66	96.19	90.00	85.49	81.46	94.56	98.64
	EKVX	87.76	108.83	93.28	104.76	112.54	102.92	95.62	100.22
	HOP-62	92.28	106.03	98.83	96.81	88.71	82.37	96.83	93.50
	HOP-92	113.27	110.09	124.18	100.10	109.76	105.59	92.24	109.20
	NCI-H226	111.78	102.82	116.49	98.12	104.45	112.16	97.92	106.25
	NCI-H23	100.60	93.09	91.11	103.39	111.17	107.62	101.03	102.49
	NCI-H322M	96.91	101.25	101.17	103.98	101.81	108.38	96.35	81.28
	NCI-H460	114.62	109.05	107.53	105.70	111.05	92.08	107.48	108.26
	NCI-H522	96.96	95.02	96.51	91.68	88.77	53.50	88.65	95.54
Colon Cancer	COLO 205	113.41	108.2	105.85	111.09	105.95	82.00	108.62	111.74
	HCC-2998	103.24	98.46	88.98	107.76	102.28	109.87	106.62	99.61
	HCT-116	94.57	94.51	93.90	92.38	93.84	94.53	89.63	91.69
	HCT-15	91.36	100.64	100.45	109.66	109.34	98.08	97.62	106.17
	HT29	101.43	99.07	101.95	98.38	94.45	88.95	96.42	104.02
	KM12	98.93	96.50	107.33	101.51	97.51	93.02	105.18	99.07
	SW-620	103.83	107.66	107.40	102.20	109.08	101.20	100.80	107.59
CNS Cancer	SF-268	102.55	103.16	104.60	101.55	95.71	98.12	100.32	100.77
	SF-295	92.90	100.51	93.98	104.34	103.41	98.33	97.79	105.75
	SF-539	99.32	104.69	102.4	105.41	92.75	101.74	95.65	103.32
	SNB-19	108.69	108.73	106.99	100.14	97.03	100.35	96.68	103.57
	SNB-75	90.41	93.86	100.91	89.60	93.19	92.99	93.82	82.78
	U251	103.77	102.55	101.27	102.99	100.27	89.42	98.74	101.36
Melanoma	LOX IMVI	90.83	98.21	91.43	102.58	98.36	107.05	98.06	96.68
	MALME-3M	101.59	98.72	107.87	102.57	112.99	102.58	104.76	96.60
	M14	91.50	106.77	95.56	102.49	92.41	88.39	95.92	111.02
	MDA-MB-435	106.41	105.18	106.39	107.48	106.26	102.65	97.54	100.05
	SK-MEL-2	96.65	100.69	99.95	113.87	/	/	105.05	102.48
	SK-MEL-28	103.50	111.37	104.21	109.79	105.95	106.29	100.71	103.29
	SK-MEL-5	104.45	106.38	102.52	100.94	110.02	80.71	97.75	104.33
	UACC-257	103.60	106.53	96.91	90.94	69.54	85.26	85.77	106.84
	UACC-62	104.59	92.10	100.88	93.59	104.56	95.44	100.51	92.27
Ovarian Cancer	IGROV1	96.13	109.48	107.85	97.49	112.97	97.56	101.14	98.70
	OVCAR-3	107.05	101.36	106.39	108.04	108.09	106.73	104.25	97.50
	OVCAR-4	97.22	105.79	107.32	108.81	94.57	94.65	98.98	94.25

	OVCAR-5	101.27	110.56	101.29	106.67	100.42	95.30	97.68	103.36
	OVCAR-8	108.80	105.07	104.43	97.69	89.42	101.64	99.31	96.19
	NCI/ADR-RES	100.22	93.03	99.45	109.27	105.79	110.96	104.33	96.94
	SK-OV-3	95.65	98.69	89.47	105.99	101.90	97.47	101.32	96.57
Renal Cancer	786-0	91.63	97.56	88.36	102.65	91.73	96.04	96.13	100.30
	A498	99.56	83.27	88.99	95.20	111.38	101.57	92.97	104.22
	ACHN	100.86	98.91	100.13	104.43	101.46	103.78	100.80	99.35
	CAKI-1	93.93	95.31	92.01	89.34	87.50	95.75	97.30	86.08
	RXF-393	107.51	117.54	117.77	109.59	130.86	125.84	114.89	102.87
	SN12C	103.89	94.48	103.23	98.21	105.79	100.92	99.95	97.75
	TK-10	88.65	105.13	85.97	103.64	96.91	98.35	97.31	105.87
	UO-31	93.51	89.23	96.24	90.20	90.67	89.37	85.87	84.04
Prostate Cancer	PC-3	103.06	107.50	101.28	83.49	108.39	100.56	92.99	100.21
	DU-145	112.36	110.01	111.14	109.28	109.01	110.43	102.08	111.20
Breast Cancer	MCF7	84.76	92.18	84.32	95.51	95.87	87.21	89.56	100.03
	MDA-MB-231/ATCC	115.75	107.22	104.89	103.50	102.24	108.79	99.51	98.86
	HS 578T	105.06	102.51	101.06	100.42	/	/	94.71	105.05
	BT-549	102.85	101.37	98.72	100.26	90.25	94.10	101.56	98.51
	T-47D	93.02	87.41	92.86	105.03	87.34	73.83	90.46	83.94
	MDA-MB-468	98.54	117.77	111.62	98.80	111.41	113.89	86.78	119.42

*/ - indicates that effect was not tested. DADS - diallyl disulphide; DEDS - diethyl disulphide; PDS - dipropyl disulphide; DPDS - diphenyl disulphide; TETUDS - tetraethylthiuram disulphide; DMTS - dimetil trisulphide; DPTS - dipropyl trisulphide; MPTS - metilpropyl trisulphide

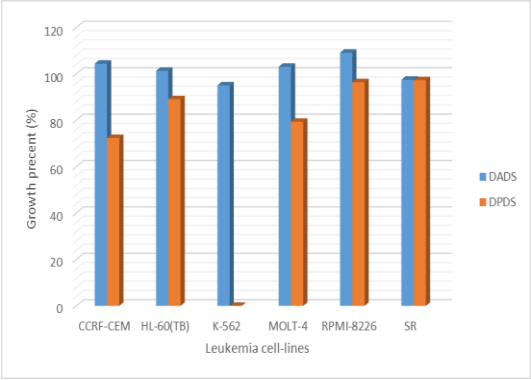

Fig. 1.Comparison of the effects of DADS and DPDS on leukemia cell lines growth. Concentration of both substances was 10 µmol/L. The effect of DPDS on K-562 growth is not tested.

Trisulphide analogues exhibit little higher inhibitory effects in comparison to disulphide, especiallyon NCI-H522 of Non-Small cell Lung Cancer (Table 1) and on breast cancer T-47Dcell line(Figure 2). Trisulphide with methyl and propyl group (MPTS) is the most effective sulphur compound, inhibiting growth of even 12 cell lines for more than 10%. Especially sensitive to its action are leukemia cell line SR(reduction of growth to 63.86%)and NCI-H522cell line of Non-Small cell Lung Cancer(reduction to 53.50%).MPTS also reduced growth of breast cancer cell lines MCF7 for 13% and T47D for 26% (Figure 3).

All investigated organosulphur compounds exert the same effect on colon cancer line HCT-116, decreasing its growth.

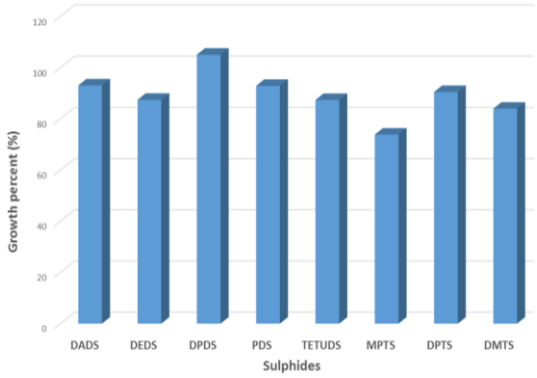

Fig. 2.Comparison of the effects of disulphidesand trisulphides on the growth of T-47Dbreast cancer cell line. Concentration of all substances was 10 µmol/L.

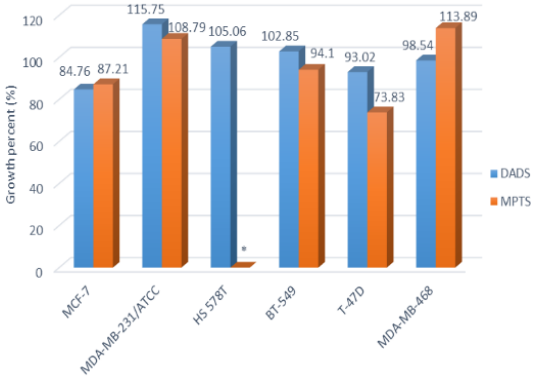

Fig. 3. Effects of DADS and MPTS(concentration of 10 µmol/L) on the growth of breast cancer cell lines.

4. Discussion

Projected incidence of 22.2 million of cancer cases by 2030[27] and the failure of many methods for cancer treatment, motivates scientists towards new strategic methods and new therapies [28–30]. Studies conducted so far were shown that garlic compounds have curative effect on certain types of cancer [7,8]. As one of the main components of garlic, DADS was extracted through the degradation of S-allycyteinesulphoxide *via* the application of the allinase enzyme [31]. Many evidences indicate that DADS could have broad-spectrum anti-tumor effects, but has no toxic effects in healthy cells.

The mechanisms of its action include: the activation of metabolizing enzymes that detoxify carcinogens; suppression of the formation of DNA adducts; antioxidant effects; regulation of cell-cycle arrest; induction of apoptosis and differentiation; histone modification; and inhibition of angiogenesis and invasion[18,32,33]. Disulphides are generally identified as a prototype for development of novel cancer preventive agents that target redox-regulatory Cys switches in PKC isozymes (PKC delta and PK Cepsilon)[34]. Our results (Table1) indicates that DADS in concentration of 10 µmol/L weakly inhibits the growth of several tumor cell lines, with the highest effect (about 15%) on breast cancer cell line MCF7. Xiao-yong et al. [35] suggested that DADS inhibits cell proliferation, but also induces apoptosis of MCF-7 line. The best inhibitory effect they reached with significantly higher concentration of DADS (400 µmol/L) in comparison to the concentration that was used in this investigation.

Disulphides analogues of DADS, with two ethyl and two propyl groups exhibit similar effects on tumor cells growth. Presence of bulkier substituents, two phenyl groups in DPDS increases disulphide inhibition potency on leukemia CCRF-CEM and MOLT-4 cell lines growth.

Disulphide TETUDS (trade name of antabuse or disulfiram) is used as a medication for the treatment of alcohol, cocaine, or co-occurring alcohol + cocaine dependence. This drug has been shown to inhibit different thiol-containing enzymes, inhibit proteolytic processing of the caspase-3 proenzyme (enzyme involved in apoptosis [36], and cause an irreversible mitochondrial injury as a result of induction of the mitochondrial permeability transition [37]. Two diethylthiocarbamoyl groups in TETUDS molecule make it as the most effective disulphide. TETUDS exerts the strongest inhibitory effect on melanoma cell line UACC-257, with reduction of growth for 30%. On the other hand, TETUDS does not affect the PC-3 and DU-145 prostate cancer cell lines growth. It is in accordance with the findings of Ketola et al.[38], that disulfiram alone does not block prostate cancer growth *in vivo* nor induce apoptosis *in vitro*. They proposed combinatorial approaches to inhibit prostate cancer cell growth. As sunitinib alone has also been reported to lack efficacy in prostate cancer clinical trials, its combination with disulfiram was identified as one of the potent synergistic approaches.

Diallyl trisulphide (DATS) was noted as cytotoxic to cell lines for human cancers of the bladder, bone, breast, lungs and stomach, in each case with strong evidence of apoptosis[10,22]. Much of the research into the DATS mechanisms of action refers to regulate several cancer-related pathways including cell cycle arrest, apoptosis, chemical detoxification, invasion, migration, and angiogenesis[39].We investigated the activity of DATS analogues with different aliphatic side chains (DMTS, DPTS and MPTS), i.e. differentlipophilicity. In spite of the fact that lipophilicity of DPTS is almost two times higher than DMTS[40]there was no significant difference in their activity on cancer cell growth. But, trisulphide with methyl and propyl group (MPTS) is the most effective sulphur compound; especially against leukemia cell line SR and NCI-H522cell line of Non-Small cell Lung Cancer. Later is in accordance with the results obtained when anti-tumor properties of trisulphide DATS on lung cancer *in vitro* and *in vivo* was investigated [41]. Significantly decreased cell viability and induction of apoptosis were observed in human lung carcinoma cell line (NCI-H460) treated with DATS. Injection of DATS to Balb/c mice significantly inhibited the growth of human NCI-H460 cell tumor xenograft.

If disulphides and trisulphide action is comparing, a little higher inhibitory effects of trisulphides is noticeable, especially in the case of NCI-H522 of Non-Small cell Lung Cancer and breast cancer T-47D cell line growth (Figure 2).

Breast cancer represents a top leading cause of death related to the cancer in women worldwide[42]. It was estimated that one in eight women (about 12 %) will developbreast cancer in their life time[43]. Therefore, identification of new nontoxic agents that can delay breast cancer progressions is very important. Our data showed that two of six breast cancer cell lines (MCF7 and T47D) explore sensitivity on almost all selected disulphides and trisulphides. DADS and PDS inhibited the MCF7 growth for 15%. MPTS reduced growth of MCF7 for 13% and T47D for 26% (Figure 3). Malki et al. showed that 100 μM DATS treatmentsuppressed viability of MCF-7 human breast cancer cells by inducing apoptosisvia activation of p53[22].

It is interested that prostate and ovarian cancer cell lines are almost insensitive on all tested disulphides and trisulphide. Even in prostate cancer induction of growth is detected (Table 1).

5. Conclusions

Based on the depicted results we found that DADS, main component of garlic has an inhibitory effect on the growth of several cancer cell lines, but synthetic analogues TETUDS and MPTS exhibit stronger effect on certain cells lines. MPTS inhibits the growth of even 12 cell lines for more than 10%. Trisulphide analogues exhibit higher inhibitory effects in comparison to disulphide ones.

Funding

This work was supported by the Ministry of Education and Science of the Republic of Serbia (Contract numbers: 451-03-68/2020-14/200168 and 451-03-68/2020-14/200026) and Department of Chemistry, University of Houston, 112 Fleming Building, Houston TX 77204-5003, USA.

Acknowledgments

Authors gratefully acknowledge Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, Maryland, United States, who did the testing.

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