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# NEW PERSPECTIVES FOR PREVENTION AND TREATMENT OF SULFUR MUSTARD INTOXICATION

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**ABSTRACT**
Chemical weapons are weapons of mass destruction. They have caused numerous deaths during wars and terrorist acts. Among them there is no other military toxic substance, like sulfur mustard, which not only causes directly but also inflicts severe long-term health harm to those exposed. At present there is not a universally approved treatment of sulfur mustard intoxication.
The purpose of this publication is to briefly explore the intoxication mechanisms of sulfur mustard and to propose a new medicament for prevention and therapy.

**Key words:** chemical weapon, EPR, Vitasil

## INTRODUCTION

In a historical retrospect, it can be concluded that there has been no other chemical weapon, that has caused so much and so long-lasting health harm to a great number of people, like sulfur mustard. Only for the period 12.07.1917-11.11.1918, during the First World War 400,000 people were harmed. The number of soldiers who suffered exposure to sulfur mustard in the British Army alone was 125,000 (1). From then on that chemical substance has been used in a series of military conflicts. Italy used a vast quantity of sulfur mustard in its war against Ethiopia, during which almost all military attacks of the Italian army were supported by aviation and artillery chemical assaults. During the period December 1935 to April 1936 the loss of human life in the Ethiopian army was enormous and one-third of the casualties were caused by chemical weapons (2). There were many casualties among civil citizens as well. The use of sulfur mustard in Ethiopia revealed an interesting fact: the substance turned out to be substantially more toxic to Negroid people, compares to Caucasians. Later that fact was once again observed in cases of sulfur mustard intoxication among soldier in (3). During the period 1980-1988, in the war between Iran and Iraq, enormous quantity of sulfur mustard was used, as the number of intoxicated Iranians alone exceeded 100,000 (4). Many of them still continue to experience sulfur mustard-related health problems. On 16 March 1988 Iraqi military bombers bombarded the Kurdish town of Halabadja with sulfur mustard-charged bombs, which caused the death of about 7,000 people and more than 20,000 people suffered injuries and different levels of intoxication (5).

## EXPOSITION

Sulfur mustard is considered to be one of the major substances used in chemical weapons because synthesizing it is a matter of a simple and cheap chemical process, which makes it easily attainable not only for military purposes but for terrorist acts as well. Gas masks do not provide sufficient protection against sulfur mustard because of its good absorption capacity through the skin. It acts as an alkylating agent, which has a destructive effect on nuclein acids and proteins, destroys cellular

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homeostasis and eventually causes cellular death. Sulfur mustard quickly reacts with the ophthalmic, respiratory and dermal tissues as well as with the bone marrow and the cells of the gastro-intestinal tract mucosa, which causes many harmful long-term effects on human health (6). Even though some antidote substances against systematic sulfur mustard intoxication of test animals are available, none of them has yet been approved to be used on humans (7).

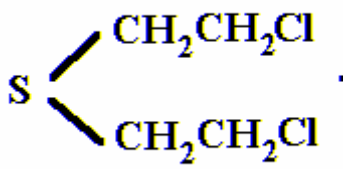


**Fig. 1** Sulfur mustard structural formula. UPAC name - dichlorinediethylsulphide

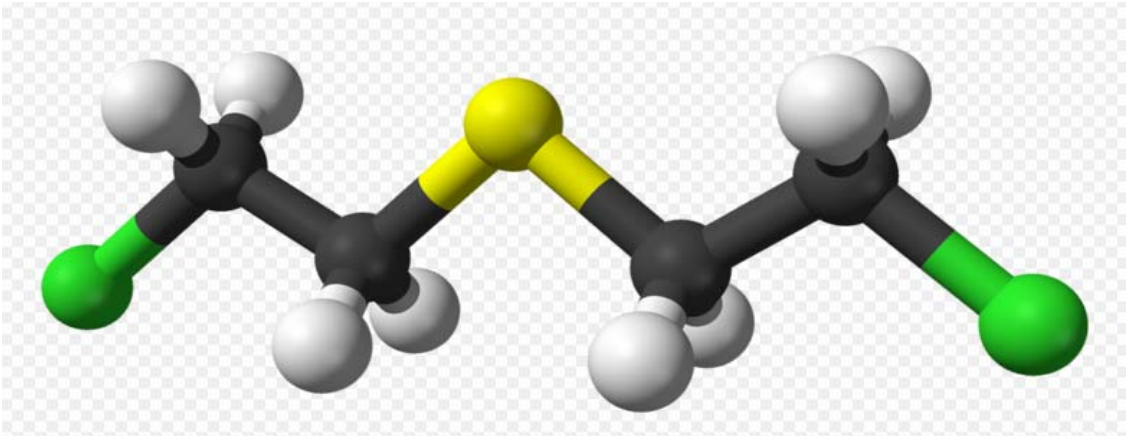

**Fig. 2** Stoichiometric structure of sulfur mustard

Exposure to sulfur mustard corresponds well with the biochemical knowledge we have about intoxication processes and free radicals formation. In addition, sulfur mustard solutions contain spontaneously formed cyclic ions, which produce carbon containing radicals and can be reduced enzymicly by forming active metabolites (8). Sulfur mustard has been proved to interact with glutathione (9). Radical in vitro formation by using a metabolic system and electronic paramagnetic resonance (EPR) has been proved (8).The results maintain the hypothesis of free carbon radicals. The free radicals model explains the similarity between the origin of the injuries caused by exposure to sulfur mustard and those caused by exposure to heat, ultraviolet and nuclear radiation.

Lung complications are observed in more than half of the number of patients who suffered exposure to sulfur mustard. Many investigations have focused on clinical complications but the pathogenesis of the injuries has often been ignored. Apart from that the mechanisms of inflicting lung damage, caused by exposure to sulfur mustard have not been fully explained yet. The correlation between superoxidedismutase (SOD) and catalytic (cat) activity and the lung function in patients exposed to sulfur mustard has been investigated. Comparative cross investigation has been carried out. Two hundred and fifty people who have survived sulfur mustard intoxication were compared with a control group of people, who were not exposed to sulfur mustard. With regard to the results received, it can sensibly be hypothesized that a restored balance between oxidant and anti-oxidant agents can be viewed as a therapeutically beneficial strategy, which diminishes lung damage caused by sulfur mustard intoxication (10). The effect of N-

acetylcystein (NAC) administration has been investigated for a period of four months (daily doses of 1200 mg), in patients with bronchiolitis obliterans caused by sulfur mustard intoxication. That medication has a positive effect in treating lung diseases caused by sulfur mustard intoxication (11). Similar experiments, regarding sulfur mustard intoxication treatment with 1,800 mg daily intake of NAC, for a period of 2 and 4 months have been carried out. Spirometric data was taken at the beginning of the experiments, two and four months after the administration of 1,800 mg of NAC per day or placebo, distributed in three equal doses. Dispnoea, coughing and phlegm secretion improved after administering N-acetylcystein for four months, compared to the results of the control group. After the period of four months spirometric data was found to have improved substantially, compared to the group of people, who took placebo (12). Ebselen has been proved to have diminishing effect on sulfur mustard toxicity, as in vitro tests of its properties on dermal cells of cell line A-431 have shown (13). Butilhydroxianisol is a type of phenol group anti-oxidant. That chemical compound is effective in treating mechlorineetamin intoxication (a type of chemical weapon substance, which causes rash, and is similar to sulfur mustard in its mechanism of interaction) but is ineffective, with respect to sulfur mustard intoxication (13).

Based on all this data, it can be suggested that a powerful free radicals combining agent can be used for treating sulfur mustard intoxication.

In the Chemistry and Biochemistry Department of the Medical Faculty of Trakia University, Stara Zagora, Bulgaria, we developed the patent medicine called *Vitasil.* Quantum-chemical tests of Silibin (a compound element of *Vitasil*) were carried out (14, 15). The medicine underwent the necessary clinical tests and was approved for public use by the responsible authorities. The premise for the development of *Vitasil* was the structural analogy between the chroman ring of vitamin E and the flavonoid silibin on the one hand and the different positions and mechanisms of free radical compounding activity of the three elements included in the medicine on the other, as well as some clinical tests. This is what determines *Vitasi*l's advantage over pure Silibin.

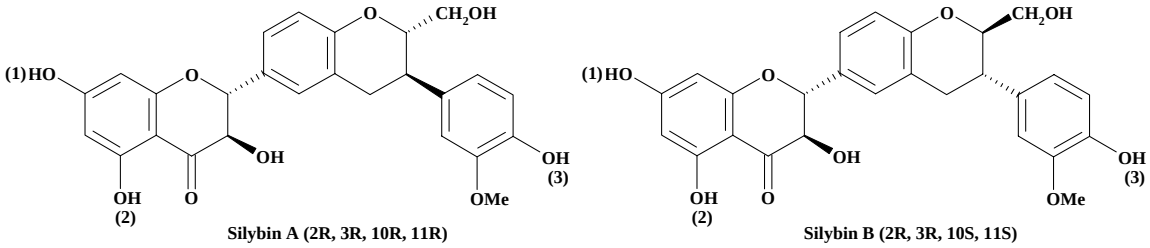


**Fig. 3** Silibin A and Silibin B structural formulas

## CONCLUSION

With respect to the present importance of the problem, the mechanism of toxic impact of sulfur mustard and the counteractive properties of *Vitasil* we assume that it can be applied as a useful medicine in the prevention and treatment of sulfur mustard intoxication cases, as well as in cases of intoxication with similar chemical substances, presently used in chemical weapons, such as nitrogen mustard, luizit, etc.

## REFERENCE

1. Salovsky P. *Chemical, nuclear and biological terrorism. Medical aspects.* Sofia, 2006 г.
2. Dikov Al., Dimitrov G., Stanev T. *Chemical weapons*, issued by the Bulgarian Ministry of Defence Publishing House, 1986
3. Smith SL. Mustard gas and American race-based human experimentation in World War II. *J Law Med Ethics.* 2008 Fall;36(3):517-21

4. Shohrati M., Peyman M., Peyman A., Davoudi M., Ghanei M. Cutaneous and ocular late complications of sulfur mustard in Iranian veterans. *Cutan Ocul Toxicol.* 2007;26(2):73-81
5. Dworkin J., Prescott M., Jamal R., Hardawan SA., Abdullah A., Galea S. The long-term psychosocial impact of a surprise chemical weapons attack on civilians in Halabja, Iraqi Kurdistan. *J Nerv Ment Dis.* 2008 Oct;196(10):772-5.
6. Balali-Mood M., Hefazi M. The pharmacology, toxicology, and medical treatment of sulfur mustard poisoning. *Fundam Clin Pharmacol.* 2005 Jun;19(3):297-315
7. Kulkarni AS., Vijayaraghavan R., Anshoo G., Satish HT., Pathak U., Raza SK., Pant SC., Malhotra RC., Prakash AO. Evaluation of analogues of DRDE-07 as prophylactic agents against the lethality and toxicity of sulfur mustard administered through percutaneous route. *J Appl Toxicol*. 2006 Mar-Apr;26(2):115-25
8. Brimfield AA., Mancebo AM., Mason RP., Jiang JJ., Siraki AG., Novak MJ. Free radical production from the interaction of 2-chloroethyl vesicants (mustard gas) with pyridine nucleotide-driven flavoprotein electron transport systems. *Toxicol Appl Pharmacol.* 2009 Jan 1;234(1):128-34. Epub 2008 Oct 15
9. Gross C.L. Nealley EW, Nipwoda MT., Smith WJ. Pretreatment of human epidermal keratinocytes with D,L-sulforaphane protects against sulfur mustard cytotoxicity. *Cutan Ocul Toxicol.* 2006;25(3):155-63
10. Hayakawa K. Decomposition and treatment of environmental pollutants. *Yakugaku Zasshi*. 2009 Jan;129(1):35-43. Japanese
11. Ghanei M., Shohrati M., Jafari M., Ghaderi S., Alaeddini F., Aslani J. N-acetylcysteine improves the clinical conditions of mustard gas-exposed patients with normal pulmonary function test. *Basic Clin Pharmacol Toxicol.* 2008 Nov;103(5):428-32. Epub 2008 Sep 17
12. Shohrati M., Aslani J., Eshraghi M., Alaedini F., Ghanei M. Therapeutics effect of N-acetyl cysteine on mustard gas exposed patients: evaluating clinical aspect in patients with impaired pulmonary function test. *Respir Med*. 2008 Mar;102(3):443-8. Epub 2007 Nov 26.
13. Pino M.A., Billack B. Reduction of vesicant toxicity by butylated hydroxyanisole in A-431 skin cells. *Cutan Ocul Toxicol*. 2008;27(3):161-72.
14. Ivanov V., Atanasov V., Raikova El.., Raikov Z. Quantum-chemical investigations of silibin. *Trakia Journal of Sciences*. Volume 6, Number 2, suppl. 1, 2008, 37-39
15. Velkov Zh.., Tadjer Al.. Quantum-Chemical Approach to Silybin A and Silybin B Antioxidant Activity Investigation. Annual of Konstantin Preslavsky University, Shumen, Faculty of Natural Sciences, 2007, vol. XVIII B2, 178-187