A review on symptoms, treatments protocols, and proteomic profile in sulfur mustard-exposed victims

By: Panahi, Y (Panahi, Yunes)[1] ; Abdolghaffari, AH (Abdolghaffari, Amir H.)[2,3] ; Sahebkar, A (Sahebkar, Amirhossein)[4]

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Author Information

Reprint Address: Abdolghaffari, AH (reprint author)

ACECR, Inst Med Plants, Med Plants Res Ctr, Karaj, Iran.

Reprint Address: Sahebkar, A (reprint author)

Mashhad Univ Med Sci, Dept Med Biotechnol, Sch Med, POB 91779-48564, Mashhad, Iran.

Addresses:

[1] Baqiyatallah Univ Med Sci, Chem Injuries Res Ctr, Tehran, Iran

[2] ACECR, Inst Med Plants, Med Plants Res Ctr, Karaj, Iran

[3] USERN, GPIG, Tehran, Iran

[4] Mashhad Univ Med Sci, Biotechnol Res Ctr, Mashhad, Iran

E-mail Addresses: amirhosein172@hotmail.com; sahebkara@mums.ac.ir

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Prospects

A review on symptoms, treatments protocols and proteomic profile in sulfur mustard-exposed victims†

Amir Hossein Abdolghaffari,[1] Yunes Panahi,[1*] Amirhossein Sahebkar[2*]

[1]Chemical Injuries Research Centre, Baqiyatallah University of Medical Sciences, Tehran; Iran

[2]Biotechnology Research Centre, Baqiyatallah University of Medical Sciences, Tehran; Iran

***Corresponding Authors:**

Yunes Panahi, PhD, Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran, Tel/Fax: +982188211524; E-mail: yunespanahi@yahoo.com

Amirhossein Sahebkar, PharmD, PhD, Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, P.O. Box: 91779-48564, Iran. Tel: 985118002288; Fax: 985118002287; E-mail: sahebkara@mums.ac.ir; amir_saheb2000@yahoo.com

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Abstract

Sulfur mustard (SM) as an alkylating and vesicating agent was used for 100 years as a chemical weapon. SM as bi-functional mustard can attacks and alkylates lots of biomolecules. Different cellular mechanism and molecular pathways are responsible for damages to body tissues. Such as DNA damages, oxidative stress, Apoptosis and inflammation. Sulfur mustard penetrated body organs and induces long term eye, skin, lung, gastrointestinal, urogenital damages and can cause carcinogenic and mutagenic consequences. Currently there is no definitive treatment protocol for SM exposed patients. The goal of treatment is relieving the symptoms with fast healing rate and retrieval of damaged tissues to normal function and appearance in short period of time. Evaluation of proteomics profile in SM-exposed victims has been performed in animal model and human patients. These studies revealed that different protein were involved in the patients with SM damages to skin and lungs.Apolipoprotein A1, type I cytokeratins K14, K16 and K17, S100 calcium-binding protein A8, α1 haptoglobin isoforms, Amyloid A1, albumin, haptoglobin, and keratin isoforms, immunoglobulin kappa chain are defined expressed proteins in the damaged tissues. This article is protected by copyright. All rights reserved

Keywords: Sulfur mustard, Proteomics, Treatment, Lung, Eye, Skin

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Introduction

Sulfur mustard (SM) as an alkylating and vesicating agent was used for 100 years as a chemical weapon [Ghabili et al., 2011].SM in pure form is viscous colorless fluid. It is fat soluble so absorbed by skin. Vapor of SM accumulate near the ground and can remain in the underground for many years depending on the climatic conditions [Ashmore and Nathanail, 2008; Ghabili et al., 2011]. SM as a bi-functional mustard can attacks and alkylates lots of biomolecules [Reid and Walker, 1969].

The lethal dose of SM after cutaneous or respiratory exposure is 64mg/kgand1500 mg/min/m^{3}respectively [Marshall, 1987].SM is prohibited by the Chemical Weapons Convention (CWC) and Organization forthe Prohibition of Chemical Weapons (OPCW), but it was used by Iraq in Iraq-Iran war and caused to acute and long term damages to Iranian veterans [Balali-Mood and Hefazi, 2006b; Kehe and Szinicz, 2005].

SM enters the body through eye, skin, respiratory tracts and sometimes gastrointestinal tract [Kehe et al., 2009c] and can cause acute and delayed effects on different body organs. Different cellular mechanism and molecular pathways are responsible for damages to body tissues such as DNA damages, oxidative stress, apoptosis and inflammation [Ghabili et al., 2011].

General treatments in SM-exposed victims are removal of SM from the contaminated body area e.g. washing out the eyes and skin, triage and medical treatment such as the use of antidote, general treatments and particular organ cares [Balali-Mood and Hefazi, 2005]. Identification of novel biomarkers and potential therapeutic targets would help better management of SM-related complications. Proteomics is an efficient systems biology tool to elucidate alterations in proteins following different pathologies. Hence, identification of proteomic changes would be useful to

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explore biomarkers of SM injuries that might potentially serve as treatment targets. The aim of this study is to review acute and delayed clinical signs, routine treatment protocols, molecular mechanism and proteomic profile alterations in the exposed patients to SM.

Methods

Published and accepted articles, books, and conference papersinEnglish until 2017 from PubMed, Scopus, Google Scholar with keywords; Sulfur mustard, mustard gas, eye, lungs, pulmonary, cutaneous, skin, molecular, cellular, DNA damage, oxidative stress, inflammation, apoptosis, clinical signs, treatment, antidote and proteomics wereusedin this review.

Molecular mechanism of Sulfur Mustard Toxicity

SM reacts with different components of cells and causes cell damages. SM reacts with aqueous environment of the cells and leads to formation of hydrochloric acid [lynch, 1918]. Alkylation of intracellular and extracellular proteins and enzymes by SM impairs cellular metabolic functions and leads to cell damages [Kehe and Szinicz, 2005; Peters, 1947].

Apoptosis and DNA damage:

SM causes intermolecular cyclization in the cells. Highly reactive SM byproducts react with cellular proteins and nucleic acids. Alkylation of sulphydril and amino groups as well as DNA and RNA leads to impairments in cellular physiological and metabolic function culminating in cell death [Kehe and Szinicz, 2005; Wheeler, 1962].

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SM induces Apoptosis *via* different molecular and signaling pathways. It causes DNA damages that leads to cell death [Nourani et al., 2016]. Since SM is a highly reactive alkylating agent, it can react with DNA and forming Mono adducts, bi-functional adducts and double strands breaks [Kehe et al., 2009a]. Poly (ADP-Ribose) Polymerase activates in high dose of SM toxicity that leads to Nicotinamide adenine dinucleotide and adenine triphosphate deplretion in the cells and subsequently necrotic cell deaths [Pieper, 1999].

Impairment in calcium homeostasis and increase of intracellular calcium concentration is another consequence of SM exposure in molecular level. It is also results in activation of mitochondrial pathway of apoptosis by uprequlation of calmodulin, increase of nitric oxide synthetase, activation of endonuclease and therefore cell death [Mol and Smith, 1996; Sawyer and Hamilton, 2000].

SM activates both intrinsic and extrinsic apoptotic pathways [Nourani et al., 2016]. Alteration in mitochondrial membrane integrity and direct alkylation of mitochondrial DNA leads to swelling of mitochondria and thus release of cytochrome C, activation of caspase 9 and cell death. Extrinsic pathways of apoptosis activate by SM with stimulation of Fas receptor and death receptors that leads to activation of caspase 8 and subsequently caspase 3. This signaling pathway results in apoptosis [Ghabili et al., 2011; Kehe et al., 2009a; Nourani et al., 2016].

Inflammation and oxidative stress:

Inflammation and oxidative stress induce apoptosis following sulfur mustard exposure in body tissues [Balali-Mood and Hefazi, 2005; Ghabili et al., 2011]. Depletion of intracellular antioxidant such as gluthatione (GSH) leads to increase level of oxidative agents such as reactive oxygen and nitrogen species and cause cell damage [Steinritz et al., 2009]. Inflammation is a

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widespread response among body tissues after sulfur mustard exposure. SM activates different proteins and signaling pathways such as activate the activator protein-1 and Nuclear Factor kappa B (NF-κB) that leads to stimulation of cyclooxygenase-2 (COX-2) and matrix metalloproteinases. Stimulation of these enzymes results in increase of inflammatory mediators and cytokines. Therefore migration of inflammatory cells to body tissues occurred [Ghabili et al., 2011; Kehe et al., 2009a; Malaviya et al., 2010; Sabourin et al., 2003]. Expression of matrix metalloproteinases such as MMP-2 and MMP-9 is a major mechanism for the destruction of transmembrane proteins and vesication in the SM cutaneous injuries [Kehe et al., 2009b].

Pathological effects of Sulfur mustard

Sulfur mustard penetrated body organs and induces long term eye, skin, lung, gastrointestinal, urogenital damages and can cause carcinogenic and mutagenic consequences [Balali-Mood and Hefazi, 2006a; Firooz et al., 2010; Graham and Schoneboom, 2013a; Panahi et al., 2013d; Panahi et al., 2014a; Panahi and S., 2015; Panahi et al., 2017c].

Eyes:

Eye is one of the first organs that showed effects of SM exposure. Aqueous and mucosal characteristics of cornea and conjunctiva suspected the eyes to SM toxicity [Panahi et al., 2013e]. Ocular pain, foreign body sensation, burning, anterior uveitis, conjunctivitis, photophobia and temporary blindness are common acute ocular signs [Panahi et al., 2013e; Solberg et al., 1997].

Delayed ocular symptoms occur after a long asymptomatic period. Chronic inflammatory process, sulfur mustard byproducts and autoimmune reactions are responsible for these late

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ocular signs [Javadi et al., 2005; Panahi et al., 2012b; Panahi et al., 2017b; Panahi et al., 2016c; Solberg et al., 1997]. Neovascularization, Corneal opacification and ulceration, corneal dystrophy, limbal stem cell deficiency, corneal thinning, limbal ischemia, diminished tear meniscus layer are important delayed ocular symptoms [Javadi et al., 2005; Panahi et al., 2013e; Solberg et al., 1997].

Skin:

Twenty percent of SM after exposure penetrates and bounds to the epidermis and dermis, especially in cornified layer [Kehe et al., 2000].Sebaceous and sweat glands are also damaged by SM exposure[Hejazi et al., 2016]. Acute cutaneous damages caused by SM are characterized by erythema, itching, vesicle, bullae, blister, burn, pigmentation changes, scaling, urticaria, dry skin, fissure, purpura, ecchymosis, lichenification, and excoriation [Momeni, 1992].

Most of the skin lesions are presented firstly on armpits, axilla, genital area and the neck [Graham and Schoneboom, 2013a]. Chronic and long-term skin effects of SM described as atrophy, chronic urticaria, eczema, hypersensitivity to mechanical trauma, keloids, late onset vesication, local hair loss, pruritis, psoriasis, seborrheic dermatitis, telangiectasis, vitiligo, pigmentation change and xerosis [Balali-Mood and Hefazi, 2006b; Firooz et al., 2010; Momeni, 1992], and are associated with several biochemical and immunological imbalances [Panahi et al., 2013a; Panahi et al., 2013b; Panahi et al., 2013f].

Respiratory system:

Around 100,000 Iranian veterans were exposed to SM during the Iraq was against Iran. One-third of them have been diagnosed with long-term effect of SM injuries [Emad and Rezaian, 1997]. Short-term respiratory effects of SM are characterized as cough, sputum, dyspnea, pharyngitis,

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laryngitis, pseudo-membrane formation and bronchospasm, pneumonia, pulmonary hemorrhage, pulmonary edema and respiratory failure [Ghanei et al., 2005]. Chronic bronchitis, tracheobronchial stenosis, asthma, bronchiectasis, chronic coughs, chest pain, lung fibrosis, bronchiolitis, emphysema, airway stenosis and lung cancer are reported as long term consequences of SM exposure in Iranian veterans [Ghanei and Harandi, 2008; Sahebkar et al., 2015].

Other organs:

SM is absorbable *via* gastrointestinal tract after ingestion of contaminated water and foods [Balali-Mood and Hefazi, 2006a]. Nausea, diarrhea, abdominal pain, acute gastroenteritis, vomiting, loss of electrolyte and fluids, erosions, mucosal barrier destruction, necrotic colitis are reported gastrointestinal effects of patients with exposure to SM [Balali-Mood and Hefazi, 2006a; Balali-Mood et al., 2008].

Acute effects of SM on urogenital system reported as renal damages, decrease in androgen secretion and spermatogenesis impairment. One of the important reported long-term urogenital damages is infertility. It has been reported between 2.5 to 35 % in the SM-exposed patients. Loss of libido has been reported in 25-52 % of Iranian veterans post SM-exposure. Impaired spermatogenesis reported as one of the main long-term consequences of SM exposure [Ghanei et al., 2004; Panahi et al., 2013c; Soroush et al., 2008].

Effects of SM on central and peripheral nervous system and mental health of veterans have been reported [Balali-Mood and Hefazi, 2006b; Balali-Mood et al., 2008; Roshan et al., 2013]. In acute and high dose exposure to SM, seizure reported as the main consequences [Balali-Mood et al., 2008]. Neuropathic symptoms, headache, restlessness and lethargy have been reported as

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associated signs with nervous system involvement in the patients [Balali-Mood et al., 2008; Roshan et al., 2013; Thomsen et al., 1998]. Impairment in mental health also reported in SM exposed victims Incidence of hostility, obsessive compulsive disorders, depression and somatization were increased in SM-exposed victims in compare to unexposed patients [Roshan et al., 2013]. Decrease in quality of life in SM exposed victims and increase in mental and social problems such as insomnia, emotional problems, psychosis and post-traumatic stress disorders have been reported [Razavi et al., 2014].

Immune and hematopoietic systems also impaired by the effect of SM. Bone marrow suppression, leukocystosis, leukopenia, changes in blood cells morphology and nucleus. In high dose of SM exposurethese effects are severe and increase the mortality rate [Balali-Mood and Hefazi, 2006a; Balali-Mood and Hefazi, 2006c; Balali-Mood et al., 2008]. Increases in the level of immunoglobins are results of SM exposure in acute form of SM exposure, but dysfunction in humoral and cellular immune system was observed as delayed effects of SM [Balali-Mood et al., 2005; Ghotbi and Hassan, 2002; Mahmoudi et al., 2005; Panahi et al., 2016b]. Major clinical signs post SM exposure summarized in the **Table 1**.

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Treatment protocols in SM exposed victims

Currently there is no definitive treatment protocol for SM exposed patients. The goal of treatment is relieving the symptoms with fast healing rate and retrieval of damaged tissues to normal function and appearance in short period of time [Graham and Schoneboom, 2013a].The first approach for treatment of SM poisoning in the victims is decontamination. Removing and destroying contaminated clothes, wash out of contaminated skin and eye and transferring of the patients to medical sites are first essential aids [Balali-Mood and Hefazi, 2005; Chiesman, 1944].Patients should be examined and 500 mg sodium thiosulphate per kg should be administered with an antidotal effects. Other drugs such as cysteine, corticosteroids and vitamin E are also useful in the management of SM poisoning. Use of sodium thiosulphate before exposure is more effective. Use of pain killers and sedatives is another important part management in SM exposed patients [Callaway and Pearce, 1958; Connors, 1966; Connors et al., 1965; Foster et al., 1962; Willems, 1989].

In acute skin lesion, use of 0.2–0.3% chloramine-T solution is recommended. It's useful because of disinfectant properties.Reactive Skin Decontamination Lotion is another option for decontamination in sulfur mustard exposed patients [Balali-Mood and Hefazi, 2005; Balali-Mood and Hefazi, 2006a; Rejaei, 2010]. Silver sulfadiazine to prevent secondary bacterial infection and calamine or local steroids to reduce erythema and ameliorate the skin damage has been recommended [Dachir et al., 2002; Dachir et al., 2004; Graham et al., 2002; Poursaleh et al., 2011; Rice et al., 2000]. Sterile dressing, pain medication such as acetaminophen, morphine, antihistamines and sedatives, are recommended as other treatment protocols [Ghanei et al., 2010; Kehe and Szinicz, 2005; Weibrecht et al., 2012]. Debridement of large blisters is also suggested. The fluid should be removed and the blister topically treated with ointments [Dacre and

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Goldman, 1996; Marrs et al., 2007]. Skin grafting is recommended for large full thickness skin lesion [Graham et al., 2002; Rice et al., 2000]. To control of the itching, systemic antihistamines and topical corticosteroids were used regularly. With regards to side effects of corticosteroids some alternatives were recommended such as cetirizine, curcumin, capsaicin, doxepin, aloe vera/olive oil combination, hydroxyzine, phenol/menthol combination, Unna's Boot and pimecrolimus [Panahi, 2007; Panahi et al., 2008; Panahi et al., 2011a; Panahi et al., 2012a; Panahi, 2011; Panahi et al., 2009; Panahi et al., 2011b; Panahi et al., 2012c; Panahi et al., 2012d; Panahi et al., 2012e; Panahi et al., 2012f; Panahi et al., 2012g; Sahebkar, 2012; Shohrati et al., 2008a; Shohrati et al., 2008b; Shohrati, 2007].

Treatments of acute ocular lesions includeocular washings with normal saline, 1.5% or sodium bicarbonate, or 0.5% dichloramine-T, artificial tears and lubricants, topicalantibiotics, corticosteroids, mydriatic, antiglaucoma ophthalmic drops, corrective contact lenses, dark glasses [Babin et al., 2004; Balali-Mood and Hefazi, 2005; Graham and Schoneboom, 2013a; Hughes, 1942; Panahi et al., 2017c; Pleyer et al., 1999]. Management of delayed ocular symptoms is medical and surgical. These treatments are artificial tears and lubricants, anti-inflammatory drugs, immunomodulatory drugs, human blood-derived therapy, amniotic membrane transplantation, tarsorrhaphy, stem cell transplantationand corneal transplantation [Babin et al., 2004; Balali-Mood and Hefazi, 2005; Balali-Mood and Hefazi, 2006c; Jadidi et al., 2014; Javadi et al., 2005; Panahi et al., 2017c; Vidan et al., 2002].

Managements of respiratory symptoms are crucial in SM-exposed victims. Use of oxygen supplementation and humidify air is essential [Emad and Rezaian, 1997; Tang and Loke, 2012]. Patients should be hydrated to avoid thickening of mucus and secretions. Different drugs such as N-acetylcysteine, antibiotics, bronchodilators, curcuminoids and corticosteroids are

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recommended in the patients to manage respiratory symptoms [Balali-Mood and Hefazi, 2005; Ghanei and Harandi, 2008; Ghanei et al., 2005; Panahi et al., 2015; Panahi et al., 2016a; Panahi et al., 2014b; Panahi et al., 2017a]. In the managements of patients with respiratory symptoms, use of inhaled beclomethasone or combination of inhaled corticosteroids and long-acting β2-agonists such as fluticasone-salmeterol, immunosuppressive therapy and anti-cholinergic like ipratropium bromide is recommended [Graham and Schoneboom, 2013b; Poursaleh et al., 2012; Razavi et al., 2013; Shohrati et al., 2014].

Proteomics assessment of sulfur mustard exposed victims

Aslam et al. described proteomics as "*Proteomics involves the applications of technologies for the identification and quantification of overall proteins present content of a cell, tissue or an organism. Proteomics is crucial for early disease diagnosis, prognosis andto monitor the disease development.*" [Aslam et al., 2017].

Mol et al. (2008) in an *in vitro* study evaluated the proteomics in human epidermal keratocytes (HEK).They cultured HEK from mammary skin during cosmetic surgery [Mol et al., 2008]. The results showed that Partial breakdown of type I cytokeratins K14, K16 and K17 as well as the emergence of new charge variants of the proteins heat shock protein 27 and ribosomal protein P0. Also this study ascertained that probably type I cytokeratins breakdown by caspase-6 in HEK [Mol et al., 2008].

In 2009, Everley et al. showed that guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) were down-regulated by up to two folds in an *in vitro* study on

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human keratinocytes model after SM-exposure. However phosphorylated proteins showed up to 3-fold increases in the SM-exposed cells [Everley and Dillman, 2010].

Mehrani et al., (2009) evaluated proteomics of bronchoalveolar lavage fluid (BAL) from sulfur mustard exposed patients with lung diseases [Mehrani et al., 2009].

One of the major proteins involved in SM pathogenicity in the respiratory system are calcium-binding proteins. Two major calcium-binding proteins are calcyphosine and S100 calcium-binding protein A8 which are significantly decreased and increased in BAL of SM patients, respectively [Mehrani et al., 2009].

S100 proteins are involved in the immune response, enzyme activity and calcium hemostasis, and regulation of apoptosis and tissue remodeling [Foell et al., 2004]. It is noticeable that S100 A8 protein (calgranulin A) was only found in the patients with moderate to severe clinical signs post-SM exposure [Mehrani et al., 2009]. This protein is also found in the idiopathic pulmonary fibrosis patients but not in normal subjects and stimulates neutrophils chemotaxis and adhesion [Halayko and Ghavami, 2009].

In another study by Shahriary et al., on the proteome of neutrophils in SM-exposed patients with respiratory diseases, overexpression of S100 A8 and S100 A12 was reported [Shahriary et al., 2015].

Calcyphosine is another important calcium-binding protein which is important in cell growth, differentiation and regulation of cell functions [El Housni et al., 1997]. Therefore, decrease in the level of this protein in BAL fluid is a consequence of SM exposure [Mehrani et al., 2009].

Surfactant proteins are also reduced following SM exposure and because of the protective effects of this protein (clearance of microorganism, apoptotic and necrotic cells), reduction of the protein is correlated with the severity of lung dysfunction. Increase in the level of Apo A1 and

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haptoglobin isoforms have also been reported by Mehrani and colleagues in 2009. Apo A1 protein was expressed even in mild cases after SM exposure. [Mehrani et al., 2009]. Another protein change in the blood smear of patients exposed to SM was overexpression of protein disulfide isomerase (PDI), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and superoxide dismutase (SOD). Also proteins such as serpin B1, cronin 1A, actin isoforms, and coactosin have been found to be down-regulated in the neutrophils after SM exposure. Downregulation of these proteins is related to remodeling of the cells [Shahriary et al., 2015].

Researchers assessed the proteomics profile of sulfur mustard exposed patients with lung diseases with 2-dimensional gel electrophoresis from plasma revealed that α1 haptoglobin isoforms and Amyloid A1 isoforms are detected in plasma of the all SM exposed patients and lung disease patients in compare of healthy controls which have not detected [Mehrani et al., 2011]. Haptoglobin is a major protein involved in the defense against oxidative stress induced by hemoglobin [Varadi et al., 2013]. Amyloid A1 was found in the patients with severe form of respiratory diseases post-SM exposure. Tissue damages and remodeling leads to the increase of these two proteins (α1 haptoglobin and Amyloid A1) in the SM-exposed patients [Mehrani et al., 2011].

Pashandi et al., (2015) analyzed serum proteome of ten patients with history of severe SM exposurewith delayed ocular symptoms.The results of this study demonstrated that thirteen proteins including albumin, haptoglobin, andkeratin isoforms as well as immunoglobulin kappa chain upregulated whilsttransferrin and alpha 1 antitrypsin downregulated in patients in comparison to control group [Pashandi et al., 2015]. Alteration in protein profile in the patients post SM exposure summarized in **Tables 2** and **3**.

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Conclusion:

SM is a vesicating agent and its chronic toxic complications have affected both military and civilian population around the world. It is fortunate that the use of this warfare agents prohibited by OPCW, and countries do not use this agents, but it is always a potentiate threads. Great number of studies has been performed on the management of respiratory, cutaneous and ocular SM-induced damages. Currently Iranian researchers focused on delayed SM-induced damages and incidence of cancer or mutagenic process in the body of SM-exposed victims. Use of newly developed drugs to control of delayed tissue damages in the patients with the history SM exposure is currently perform as clinical trials or animal model studies. Small number of studied performed on the evaluation of proteomics profile in sulfur mustard exposed body tissues. Different proteins were known to be altered in the skin and lungs after SM exposure. Future studies are needed to define expressed genes, up-regulated and down-regulated proteins in the different body tissues in SM-exposed victims.

Conflict of interests

There is no competing interest to disclose.

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Table 1- Recommended treatments for the major complications in the sulfur mustard exposed patients

Organ	Treatment options	Refs.
Eye	Artificial tear 1.5% or sodium bicarbonate 0.5% dichloramine-T Topical antibiotics Corticosteroids Mydriatics antiglaucoma ophthalmic drops corrective contact lenses dark glasses immunomodulatory drugs tarsorrhaphy Stem cell and amniotic membrane and corneal transplantation Anti-vascular endothelial growth factor (VEGF) Keratectomy Keratoplasty	Babin et al., 2004; Balali-Mood and Hefazi, 2005; Balali-Mood and Hefazi, 2006a; Jadidi et al., 2014; Javadi et al., 2005; Panahi et al., 2017b; Vidan et al., 2002; Graham and Schoneboom, 2013b; Pleyer et al., 1999
Skin	0.1% benzalkonium bromide Chloramine-T solution Topical Antibiotics Local steroids Debridement Sterile dressing Pain medication Skin graft Systemic antihistamines Curcumin Doxepin aloe vera/olive oil combination Phenol/menthol combination Unna's Boot Pimecrolimus	Balali-Mood and Hefazi, 2005; Balali-Mood and Hefazi, 2006c; Rejaei, 2010; [Dachir et al., 2002; Dachir et al., 2004; Graham et al., 2002; Poursaleh et al., 2011; Rice et al., 2000; Ghanei et al., 2010; Kehe and Szinicz, 2005; Weibrecht et al., 2012; Dacre and Goldman, 1996; Marrs et al., 2007; Graham et al., 2002; Rice et al., 2000;
Respiratory system	Oxygen N-acetylcysteine Antibiotics Bronchodilators Corticosteroids combination of inhaled corticosteroids and long-acting β2-agonists immunosuppressive therapy anti-cholinergic drugs Cucuminoids Protease inhibitors Interferon Surfactant therapy Hypertonic saline Mannitol	Balali-Mood and Hefazi, 2005; Ghanei and Harandi, 2008; Ghanei et al., 2005; Panahi et al., 2015; Panahi et al., 2016a; Panahi et al., 2014b; Panahi et al., 2017a; Graham and Schoneboom, 2013a; Poursaleh et al., 2012; Razavi et al., 2013; Shohrati et al., 2014

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Table 2- Protein changes in the sulfur mustard exposed patients

Ref.	Method	Sample	Protein Changes
Hossein Mehrani et al., 2009	Identify differentially expressed proteins in BAL fluid of healthy and sulfur mustard-exposed lung disease	Human Patients N=30 Male patients with mild, moderate, and severe conditions (ten males in each group)	Significant increase in vitamin D binding protein isoforms, haptoglobinisoforms, and fibrinogen especially in exposed moderate and severe lung diseases patients. A significant decrease was noted in calcyphosine, surfactant protein A, and transthyretin in these patients. Apolipoprotein A1 was detected in all patients. S100 calcium-binding protein A8 was only detected in BAL fluid of moderateand severe groups.
Hossein Mehrani et al, 2011	Two dimensional SDS-PAGE; fractionated protein profiles of patients. Selected protein spots were successfully identified with MALDI TOF MS	Human Patients N=40 (20 healthy & 20 exposed patients with lung diseases)	α1haptoglobin isoforms were detected in plasma of the all lung disease patients. Amyloid A1 isoforms was also detected in plasma of the lung disease patients.
Alireza Shahriary et al, 2015	Two-dimensional gel electrophoresis followed by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI TOF MS)	Human Patients N= 30 (10 SM exposed and 10 COPD; a group of 10 healthy male)	In COPD & SM exposed group, the proteomes of PMN had overexpression of S100A8, S100A12, PDI, GAPDH, and SOD, and under-expression of serpin B1, cronin 1A, actin isoforms, coactosin, and Rho GDPDI
ZaiddodinePashandi et al, 2015	The western blotting was used to confirm the proteins that have been identified	Human Patients N=20 (10 exposed male patients with SM severe ocular effects & 10 control)	Thirteen proteins including albumin, haptoglobin, and keratin isoforms as well as immunoglobulin kappa chain which showed upregulation while transferrin and alpha 1 antitrypsin revealed downregulation in these patients.

HD: Sulfur Mustard; BAL: Bronchoalveolar lavage; HEK: Human Epidermal Keratinocytes; MALDI-TOF MS: matrix assisted laser desorption ionization-time of flight mass spectrometry; SDS-PAGE: sodium dodecyl sulfate polyacrylamide gel electrophoresis

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Table 3- In vitro and in vivo studies on Proteomics profile evaluated in the exposed tissues to Sulfur Mustard

Ref.	Method	Sample	Outcome
Marijke A.E. Mol et al., 2008	To investigate the role of Caspase 3 & 6 in HEK during 24 h after exposure to HD	HEK	Several type I and II cytokeratins, actin, stratifin (14-3-3σ) and galectin-7 were identified. Partial breakdown of type I cytokeratins K14, K16 and K17 as well as the emergence of new charge variants of the proteins heat shock protein 27 and ribosomal protein P0 were observed. Caspase-6 is probably responsible for the breakdown of type I cytokeratins in HEK.
Everley PA et al., 2009	Quantitative proteomic approach termed stable isotope-labeling with amino acids in cell culture combined with immobilized metal affinity chromatography to study the large-scale protein phosphorylation changes resulting from SM exposure	HEK	Characterization of over 2300 nonredundant phosphorylation sites, many of which exhibit altered levels in response to SM.

HD: Sulfur Mustard; BAL: Bronchoalveolar lavage; HEK: Human Epidermal Keratinocytes; MALDI-TOF MS: matrix assisted laser desorption ionization-time of flight mass spectrometry; SDS-PAGE: sodium dodecyl sulfate polyacrylamide gel electrophoresis

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