

Exposure To Organic Solvents in Covid-19 Time: A Possible Vulnerability

Guzmán DC¹, Brizuela NO¹, Herrera MO², Mejía GB², Peraza AV¹, Soto MP³ and Olguín HJ^{*3}

¹Laboratory of Neuroscience, Instituto Nacional de Pediatría (INP). Mexico City

²Laboratory of Experimental Bacteriology, INP, Mexico City

³Laboratory of Pharmacology, INP and Dept of Pharmacology, Faculty of Medicine, Universidad Nacional Autónoma de Mexico

*Corresponding author: Olguin HJ, Pharmacology Laboratory, National Institute of Pediatrics, Mexico City, Mexico. Tel: 5255 5585 7644, E-mail: juarezol@yahoo.com

Received Date: March 18, 2022 Accepted Date: April 18, 2022 Published Date: April 20, 2022

Citation: Guzmán DC, Brizuela NO, Herrera MO, Mejía GB, Peraza AV et. al., (2022) Exposure to Organic Solvents in Covid-19 Time: A Possible Vulnerability. J Pharmacol Drug Metab 5: 1-12.

Abstract

It is very important to identify and control risk factors of Covid-19 in susceptible subjects for successful treatment and prevention. Both voluntary and involuntary toxic solvent inhalations are becoming an increasing concern in the Covid-19 pandemic, with possible interactions of toxic solvents exposure and covid-19 drugs treatment or synergic effects on oxidative damage parameters within tissues of young or adults vulnerable. These toxic chemicals induce oxidative stress in the skin and other tissues as well as DNA damage, inflammation, skin barrier dysfunction and immune dysregulation; thus, increasing the sensibility of this population.

Key Words: Addiction, Covid-19, Thinner, Antiviral, Ivermectine, Gasoline station attendants

Introduction

Children are highly susceptible to environmental contaminants as their physiology and some metabolic pathways differ from those of adults. Street children, working at busy intersections, are significantly exposed to chemical solvents that are associated with oxidative stress [1].

According to the National Addiction Survey, both voluntary inhalation of industrial solvents and involuntary exposure to them have increased in an important form [2]. In a study conducted by Chiara et al. [3] on occupational exposure to the vapor of common organic solvents showed that all individuals are exposed to certain chemical, physical, biological and environmental organic solvents. The author found methylhyppuric acids (MHIPPs, xylenes metabolite), phenylglyoxylic and mandelic acid (PGA, MA ethylbenzene metabolites) as well as S-benzylmercapturic acid (SBMA, toluene metabolite) in the urine of workers, such as painters in shipyard industry, gasoline station workers etc.

Likewise, Renata et al. [4] found S-Phenylmercapturic acid (SPMA, benzene metabolite) in the urine of subjects working in these areas, while Rizk et al. [5] reported lower levels of antioxidant enzyme activities and trace metals in his study.

On the other hand, volatile organic compounds (VOCs), such as cyclohexane, toluene, acetaldehyde, formaldehyde and acetone, have potentially harmful effects on the skin.

Evidence suggests that proteasome; a major intracellular proteolytic system involved in a broad array of processes such as cell cycle, apoptosis, transcription, DNA repair, protein quality control and antigen presentation; is a VOC target. Proteasome inactivation after VOC exposure is accompanied by apoptosis, DNA damage and protein oxidation. Low protease, which degrades oxidized, dysfunctional and misfolded proteins in the mitochondria, is also a VOC target [6]. Higher incidence of cancer is suspected in subjects exposed to organic solvents. These solvents are characterized by reactive metabolic intermediates that induce oxidative damage on liver, kidney and hematopoietic system [7,8].

Solvent Toxicity

The adverse effects of certain toxicant solvents, such as benzene; toluene, which directly affect hormonal impairments; molecular alterations; oxidative stress and DNA methylation

have been reported [9]. Moreover, Liu et al. [10] (2010) found that the direct associations between polycyclic aromatic hydrocarbon (PAH), benzene and toluene (BT) metabolites decreased lung function.

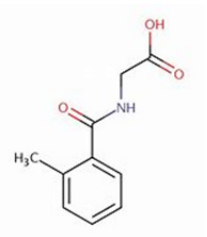
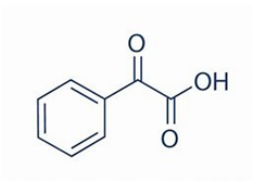
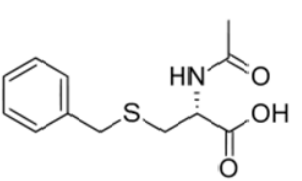
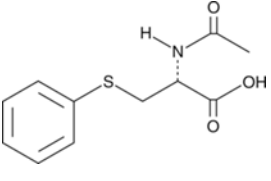
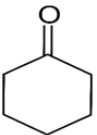
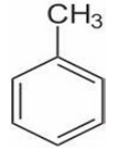
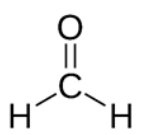
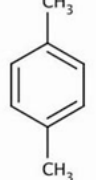
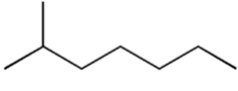
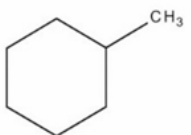
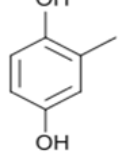
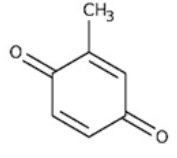
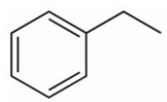

On the other hand, PAHs and BTs exposure could increase the risk of asthma in children. Some results have shown that asthmatic children have higher levels of malonaldehyde (MDA) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) compared with healthy children [11].

Additive use of inhalants is second place in children, adolescents and adults of all addictions (Table 1). In Mexico, COVID-19 pandemic has led to an increase in the number of people and frequency of inhalation of solvents in the population [12]. Among the most used solvents of abused is thinner [13]. The major compounds identified in the thinner, with peak area >2%, were p- xylene 6%, toluene 4%, 2,4-dimethylheptane 3%, 2-methylheptane 2%, methylcyclohexane 2.75%, cyclohexanone 2.6% and nonane 2.1%.

The main damage caused by these substances is due to their high content of toluene (60-70% thinner) [14]. This psychotropic component is considered in the morbidity associated with this addiction [15]. Inhalation of toluene vapor generates psychotropic effects [16] and may induce male reproductive dysfunctions and carcinogenicity for its ability to decrease epididymal sperm counts and serum concentrations of testosterone [17]. In addition, its toxicity decreases albumin, uric acid and urea levels; and increases creatinine, triglyceride, cholesterol and glucose levels. Simultaneous exposure to these substances brings about an increase in the activities of glutathione peroxidase (GPX), malondialdehyde dismutase (MDA) and superoxide dismutase (SOD) levels; and a massive tubular degeneration, tubular cell vacuolization, glomerular disorganization, congestion and glomerular cell shrinkage in the kidney tissue [18]. Likewise, it increases the levels of TBARS, GSSG, GST, SOD, COX-2 and caspase-3 activity, and considerably decreases GSH, GR and GPx. In fact, the brain (cortex and cerebellum) is the most affected organ in this addiction [19].

The damage of DNA genes by minor metabolites of toluene, methylhydroquinone and methylbenzoquinone suggests the formation of 8-oxo-7 and 8-dihydro-2'-deoxyguanosine by metabolites of toluene, whose concentration increases in the presence of Cu (II) and NADH.

Table 1: Organic solvents and metabolites use to voluntary or involuntary inhalation

		
Methylhyppuric acid	Phenylglyoxylic acid	S-Benzylmercapturic acid
		
S-Phenylmercapturic acid	Cyclohexane	Toluene
		
Formaldehyde	Xylene	2, -methylheptane
		
Methylcyclohexane	Methylhydroquinone	Methylbenzoquinone
		
Ethylbenzene	Benzene	

Generation Of Free Radicals

UV-visible and ESR spectroscopies have been used to detect the generation of O (\cdot -) (2) and semiquinone radicals [20]. Another process, which is used to establish contact with chemical solvents, is the chemical oxidation with hydroxyl radical (HO \cdot) and sulfate radical (SO $_4^{\cdot-}$). These radicals are often used to treat water contaminated with aromatic compounds, ethylbenzene, toluene, benzene and xylene.

The initial phase of the oxidation process involves radical addition; hydrogen abstraction or one-electron transfer to the ring followed by reaction with O $_2$. The hydroxycyclohexadienylperoxy radical produced in this reaction can eliminate hydroperoxyl radical (HO $_2^{\cdot}$) to produce a phenolic compound, or it can rearrange to form a bicyclic peroxy intermediate that subsequently undergoes ring cleavage [21]. Recent studies with toluene and xylene showed that the concentrations of metabolites are individuated, miR-589-5p, miR-941, miR-146b-3p and

miR-27a-3p, with well-known implications in oxidative stress and inflammation processes [22], and cause adverse effects on pulmonary function in occupationally exposed workers [23]. These workers show reduction of forced expiratory volume in 1 s (FEV₁), FEV₁/forced vital capacity (FVC), and forced expiratory flow at 25-75% of FVC.

Inhalants are widely used as recreational drugs and toluene is the main chemical compound present in them. This substance is responsible for inducing redox imbalance at the neuronal level. It has been documented those alterations in oxidative balance could represent an intermediate signaling pathway in the cascade of effects induced by toluene [24].

Tissue Damage Targets

Toluene is highly lipophilic in nature and this makes it potentially harmful to the nervous system [25,26]. This solvent, in acute dose, modifies the composition of lipids and interacts with membrane lipids by increasing significantly Na⁺, K⁺-AT-Pase activity [27], thus increasing the intracellular Na⁺. The increase in the intracellular Na⁺ leads to an increase in Na⁺/Ca²⁺ exchange. Also, increased Na⁺ concentration produces electrical disturbance, which may result in arrhythmia. In addition, increased Ca²⁺ may affect proteases and may help in the conversion of xanthine dehydrogenase to xanthine oxidase; thus, leading to increased production of super oxide radicals. Another important effect of toluene is its accumulation in the cell membrane, which impedes transport of ions and solutes through it. In addition, toluene leads to the formation of oxygen radical, which reacts with unsaturated fatty acids and proteins in erythrocytes and provokes lipid peroxidation and protein breakdown as well as increase osmotic fragility [28]. Oxidation of plasma membrane lipids leads to autocatalytic chain reactions, which eventually alter the permeability of the cell [29].

In vivo exposure to high concentrations of toluene generates a dose-dependent elevation of oxygen reactive species in different organs by significantly increasing protein carbonyls in both the frontal cortex and cerebellum. Moreover, toluene exposure induces oxidative stress in the brain and this may be a component of an adverse outcome pathway for some of the neurotoxic effects [30]. In summary, toluene leads to the generation of free radicals and increases lipoperoxidation. In addition, it leads to the formation of antioxidant enzymes such as total antioxidant substances (TAS), superoxide dismutase (SOD), γ -glutamylcysteine synthetase (γ -GCS), glutathione transferase (GST), glutathione peroxidase (GPX) and glutathione reductase (GRD) [31].

Likewise, PFT- μ and PFT- α provide neuroprotective actions through regulation of oxidative stress and neuroinflammation [32].

Human toluene exposure increases CYP2E1 mRNA and modifies its activity in leucocytes as key factors for unraveling the sub cellular mechanisms of toxicity exerted by oxidative stress [33].

Addiction to this substance and to the solvents, in general, mainly affects the less favored classes of the society that have some degree of malnutrition [34], and implies a persistent oxidant load [35]. Individuals with different immunogenetic backgrounds have different sensitivities to toxic chemical exposure and have allergic stimulation that may influence the threshold for toluene sensitivity due to the modulation of neurotrophin-related genes [36]. Following exposure to the aromatic compounds, the expression level of COX-2 increases markedly. In addition, prostaglandin E (2) (PGE (2)) and prostaglandin F(2 α) (PGF(2 α)), major products of the COX enzyme, were found to be upregulated in response to toluene [37]. The author suggests that toluene induces the production and secretion of PGE (2) and PGF(2 α) in lung epithelial cells via p38 MAPK and COX-2 activation in a redox sensitive manner.

Vulnerability To Alter Immune Response

Gasoline station workers, abundant in all the countries, have shown elevated protein carbonyl (PCO) levels and pro-inflammatory cytokines, decreased expression of CD80 and CD86 in monocytes, and reduced glutathione S-transferase (GST) activity. In other areas of work, the influence of organic solvents on the immunological, inflammatory and oxidative stress biomarkers has been demonstrated [38]. In fact, humans can be exposed to organic solvents by occupational exposure or by intentional inhalation for addiction or due to COVID-19 pandemic by the multiple and frequent use of disinfecting solvents.

The global impact of the new coronavirus, has been evident in the last months for the unprecedented socioeconomic disruption and for more than 3.4 million deaths, which it caused in the world and which has registered a toll of more than 284,000 deaths in Mexico [39]. Coronavirus disease 2019 (COVID-19) is a kind of viral pneumonia whose unusual outbreak started in Wuhan, China, and later found to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Its rapid and global spread led to overwhelming inundation of hospitals with patients. In the course of researches to combat the infection,

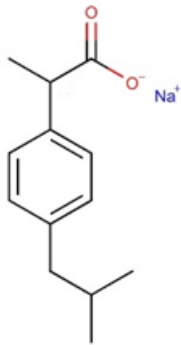
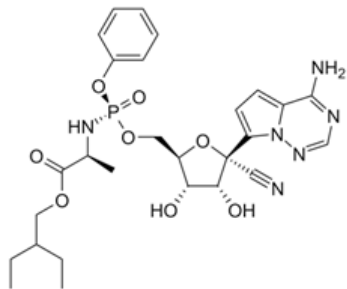
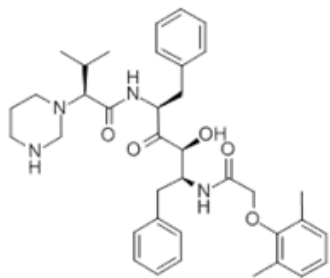
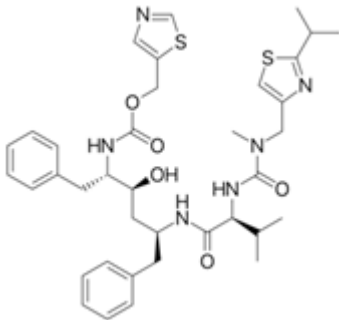
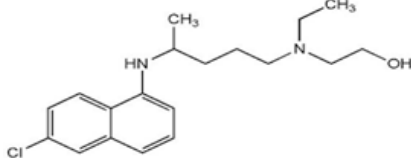
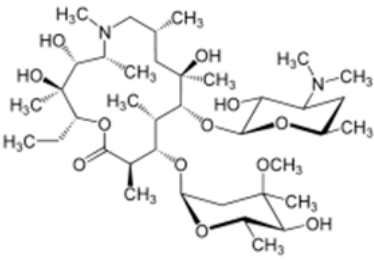
FDA approved remdesivir for the treatment of the infection. Other off-label medications used in combating the infection include chloroquine and hydroxychloroquine, tocilizumab, lopinavir/ritonavir, favipiravir, convalescent plasma therapy, azithromycin, vitamin C, corticosteroids, interferon and colchicine [40].

Antivirals And Other Drugs Used

Currently, there is no licensed antiviral treatment to prevent human CoV infection. In the case of COVID-19, cli-

nicians have identified its impacts on multiple organ systems, including gastrointestinal, renal, cardiovascular, pulmonary, immunological and hematological systems [41]. It is very important to identify and control risk factors of Covid-19 in susceptible subjects for successful treatment and prevention (Table 2). Based on these findings, the following drug therapies have been employed for its management:

Table 2: Drugs use to Covid-19 treatment

 <p>Na-Ibuprofenate</p>	 <p>Remdesivir</p>	 <p>Lopinavir</p>
 <p>Ritonavir</p>	 <p>Hydroxychloroquine</p>	 <p>Azithromycin</p>

Na-Ibuprofenate

Na-Ibuprofenate, has an amphipathic molecule capable of inserting into the bilayer membranes of the virus to destabilize its structure, alter its biological properties and prevent its duplication or infection. Its ant virucidal activity on Covid-19 leads to considerable reduction in local inflammation in the airways by inhibiting cyclooxygenase enzyme and by markedly diminishing reactive oxygen species (ROS). Its effectiveness in the treatment of COVID-19 infection suggests that reorganization of the actin filaments is a key step in lung inflammation induced by systemic

inflammatory responses caused by SARS-CoV-2, and that the interaction between actin proteins and S1 is involved in the 2019-nCoV infection and pathogenesis [42].

Remdesivir

Remdesivir is an adenosine analogue that can target the RNA-dependent RNA polymerase and block viral RNA synthesis. The active metabolite of remdesivir interferes with the action of viral RNA-dependent RNA polymerase and evades proof-reading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production. RNA-Dependent RNA Polymerase of

SARS-CoV-2 arrest of RNA synthesis occurs after incorporation of three additional nucleotides [43]. Remdesivir supplementation suppresses the systematic and hepatic inflammation by reducing inflammatory cytokines and by blocking nuclear factor κ B (NF- κ B) signaling [44]. However, neither antiviral nor immunomodulatory therapy in patients with SARS-CoV-2 infection/COVID-19 or pre-exposure prophylaxis against SARS-CoV-2 has proved to be effective [45].

3CLpro is a major CoV protease that cleaves the large replicase polyproteins during viral replication and can be targeted by the protease inhibitor lopinavir/ritonavir. In particular, several cases of recovered patients have been reported after being treated with lopinavir/ritonavir, which is widely used to treat Human Immunodeficiency Virus (HIV) infection in combination with the anti-flu drug oseltamivir [46].

Chloroquine (Cq)/Hydroxychloroquine (Hcq)

These drugs have the capacity to impair the replication of SARSCoV-2 by multiple mechanisms and their immunomodulatory properties could ameliorate clinical manifestations that are mediated by immune reactions [47].

HCQ activates the innate immune signaling pathways of IFN- β , AP-1 and NF κ B. It knocks down mitochondrial antiviral signaling protein (MAVS), inhibits TANK binding kinase 1 (TBK1)/inhibitor- κ B kinase (IKK) and blocks type I IFN receptor that reduces the efficiency of HCQ against DENV-2 infection. Furthermore, HCQ significantly induces cellular production of reactive oxygen species (ROS) associated with host defense system. Suppression of ROS production attenuates innate immune activation and anti-DENV-2 effect of HCQ [48]. On renal dysfunction, HCQ markedly reduces macrophage and neutrophil infiltration, pro-inflammatory cytokine production and NLRP3 inflammasome activation, inhibiting it by down-regulating I/R or H/R-induced NF- κ B signaling [49].

Chloroquine (CQ) and Hydroxychloroquine (HCQ) share similar chemical structures and mechanisms of action. CQ is widely used to treat malaria [50]. These authors found that COVID-19 infections are highly pandemic in countries where malaria is least pandemic and are least pandemic in nations where malaria is highly pandemic. Thus, putting forward their hypothetical benefits as efficacious means to treat COVID-19 infections. However, CQ and HCQ have the potential to cause harm as well as induce a broad range of adverse events that include serious cardiac side effects when combined with other

agents. For patients with COVID-19, the impact of HCQ on cytokine production and suppression of antigen presentation may have immunologic consequences that hamper innate and adaptive antiviral immune responses [51].

Azithromycin (AZ)

Some hospitals have begun to use AZ in combination with HCQ or CQ for the treatment of COVID-19. The doses commonly employed in this regard are 500 mg of AZ on day 1 followed by a daily dose of 250 mg for the next four days + 200 mg of HCQ administered three times per day for ten days [52]. Azithromycin and hydroxychloroquine perform similar action as an acidotropic lipophilic weak base, capable of penetrating into cells, and inducing mild adverse events [53,54]. However, both drugs were not found to have association with survival benefit among hospitalized COVID-19 patients. Nonetheless, it is suggested that the combination of Zn supplement with CQ in the treatment of COVID-19 yields favorable result. This is because chloroquine enhances the effectiveness of Zn, since it acts as an ionophore for Zn, which, once inside an infected cell, stops SARS-CoV-2 replication [55].

Tocilizumab (Tcz)

This drug is a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that is used as pro-inflammatory cytokine and represents a major breakthrough for the treatment of immune-mediated disorders [56]. The immune activation responsible for high remission rates is also responsible for the unique treatment-related toxicity of cytokine release syndrome (CRS). The clinical signs of CRS include fever, hemodynamic instability, and capillary leak associated with T-cell activation and elevated cytokine levels. Tocilizumab, an anti-IL-6 receptor antagonist, provides control of severe CRS without being directly T cell toxic [57]. The drug has demonstrated to have a trend association towards reducing the mortality rate among ICU patients [58]. However, a large clinical trial is needed to confirm tocilizumab's clinical efficacy and safety on COVID-19 patients.

Ivermectine

Ivermectine is an antiparasitic drug that has shown effective pharmacological activity towards various infective agents, and which has been recommended for COVID-19 treatment [59]. Its drug has been reported to cause cell death in cancer cell lines by inducing PAK1-mediated cytostatic autophagy, caspase-dependent apoptosis and immunogenic cell death

(ICD) through the modulation of some pathways, including the WNT-T cell factor (TCF), Hippo and Akt/mTOR pathways. Moreover, it affects the growth and proliferation of cancer cells. In addition, it plays several different roles, such as RNA helicase function, small-molecule mimetic of the surface-induced disso- ciation (SID) peptide, an activator of chloride channel receptors, an inducer of mitochondrial dysfunction and oxidative stress [60].

Oxidative Stress and Viral Infection

The SARS-CoV-2/COVID-19 pandemic is one of the largest challenges in medicine and health care worldwide. In the absence of a vaccine and specifically designed drugs, the medical community has proposed the use of various previously available medications in order to reduce the number of patients requiring prolonged hospitalizations, oxygen therapy and mechanical ven- tilation; and to decrease the high mortality rate resulting from the disease [61]. SARS-CoV-19 infection is accompanied by se- vere pneumonia, pulmonary alveolar collapse and detention of oxygen exchange. Excess oxygen induces free radicals (FR). Free radicals promote cytotoxicity that leads to cell injury. In addi- tion, they trigger mechanism of inflammation by mediating the activation of NFkB and induce transcription of cytokine pro- duction genes. Release of cytokines enhances the inflammatory response. Oxidizing agents come from phagocytic leukocytes such as neutrophils, monocytes, macrophages and eosinophils that invade the tissues. Oxidative stress (OS) represents an im- balance between the production and manifestation of reactive oxygen species therefore; the inability of the biological system to readily detoxify the reactive intermediates or repair the resulting damage [62] may enhance this stress. OS is elevated during crit- ical illnesses and this contributes to organ failure. In COVID-19 disease, there is an intense inflammatory response known as a cytokine storm that could be mediated by oxidative stress [63]. Reactive oxygen species (ROS) play physiological roles as sec- ond messengers, but can also exert detrimental modifications on DNA, proteins and lipids when they are originated from en- hanced generation or reduced antioxidant defense (oxidative stress). Formation and resolution of venous thrombus (DVT) are influenced by ROS through modulation of the coagulation, fibrinolysis, proteolysis and the complement system, as well as the regulation of effector cells such as platelets, endothelial cells, erythrocytes, neutrophils, mast cells, monocytes and fibroblasts [64].

Immune cells, particularly neutrophils, protect the humans against pathogens; such as bacteria, fungi and viruses; through increased generation of free radicals or oxidants and neutrophil extracellular traps (NETs) that ensnare pathogens, killing them extracellularly. NET levels increase during pro-in- flammatory diseases. It is found that depending on disease se- verity, COVID-19 patients exhibit elevated NET levels. Probably drugs inhibiting oxidant formation, such as vitamin supple- ments, could decrease NET formation in animal models of in- flammation [65]. Therapeutic potential of vitamins A, C, D, E supplement and micronutrients in COVID-19 ameliorate the in- flammation and oxidative stress associated with the disease [66].

Vitamin B3 or niacin is one of the most important com- pounds of the B-vitamin complex, which performs a number of pivotal functions that ensure homeostasis. This role can be at- tributed to the gut microflora and its ability to shape human be- havior and development by mediating the bioavailability of me- tabolites. This fact may be the possible interconnection between the novel coronavirus and commensal bacteria and explains how the gastrointestinal deficiencies displayed by SARS-CoV-2-in- fected patients arise [67].

A healthy diet may be considered a reliable tool for maintain- ing and optimizing our key internal parameters and could help SARS-CoV-2 patients.

Ozone Therapy

Systemic ozone therapy (OT) could be potentially use- ful in the clinical management of several complications second- ary to SARS-CoV-2. It is highly effective for decreasing organ damage mediated by inflammation and oxidative stress. Ho- meostasis of the free radical and antioxidant balance by OT are associated with its ability to modulate NF-κB/Nrf2 balance and the expression of IL-6 and IL-1β [68]. Therefore, ozone thera- py could mitigate SARS-CoV-2-induced complications and de- crease mortality.

Expectations

Since the recovery/death ratio of SARS-CoV-19 infec- tion has significantly increased in different nations of the world in the last weeks, it becomes clear that the experimental antiviral therapy together with antioxidant drugs, oxygen and dietary sup- port, and the availability of intensive care unit beds in hospitals with rigorous government control measures, all play an import- ant role in dealing with this lethal virus. In fact, it is very import-

ant to identify and control the risk factors of COVID-19 in susceptible subjects. This would guarantee success in the treatment of the disease and its prevention, as well as reduce the voluntary and involuntary exposure to toxic solvents that are abundantly and widely present today, both at home and work places, as an effort to prevent the infection, or avoid unexpected sequelae of the COVID-19 pandemic. With the global COVID-19 pandemic, this exposure has become an increasing concern to the health sector worldwide.

Declarations

Funding: This research received no specific grant from any funding agency in the public, commercial, private, or not-for-profit sectors.

Acknowledgements

We thank Dr. Cyril Ndidi Nwoye Nnamezie, an expert translator whose native language is English, for his help in preparing this manuscript. The authors express their profound gratitude to the National Institute of Pediatrics (INP) for the support in the publication of this article, following format PRISMA.

Conflict of interest: The authors declare that they have no conflict of interest.

Authors' contributions

DCG^{a,b,c,d}, NOB^{b,c,d}, MOH^{b,c,d}, GBM^{b,c,d}, AVP-
b,c,d, MPS^{b,c,d}, HJO^{b,c,d}

(a) Contributed to conception. (b) Critically revised the manuscript for important intellectual content. (c) Drafted manuscript. (d) Gave final approval. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

References

- Rafiee A, Delgado-Saborit JM, Sly PD, et al. (2021) Exploring urinary biomarkers to assess oxidative DNA damage resulting from BTEX exposure in street children. *Environ Res* 203:111725.
- National Survey of Addictions. Ministry of Health. National Council Against Addictions [Encuesta Nacional de Adicciones. Secretaría de Salud (SSA). Consejo Nacional contra las Adicciones (CONADIC). Instituto Nacional de Salud Pública (INSP). México. 2017
- Costa C, De Pasquale R, Silvari V, et al. (2006) In vitro evaluation of oxidative damage from organic solvent vapours on human skin. *Toxicol In Vitro* 20:324-31.
- Sisto R, Cavallo D, Ursini CL, et al. (2020) Direct and oxidative DNA damage in a group of painters exposed to VOCs: dose-response relationship. *Front Public Health* 8:445.
- Rizk AA, El-Wahab EWA, El-Marakby FA, et al. (2020) Assessment of oxidative stress among refueling workers in an Egyptian setting. *Environ Sci Pollut Res Int* 27:18099-108.
- Dezest M, Bechec ML, Chavatte L, et al. (2017) Oxidative damage and impairment of protein quality control systems in keratinocytes exposed to a volatile organic compounds cocktail. *Sci Rep* 7:10707.
- Pilger A, Rüdiger HW. (2006) 8-Hydroxy-2'-deoxyguanosine as a marker of oxidative DNA damage related to occupational and environmental exposures. *Int Arch Occup Environ Health* 80:1-15.
- Mueller S, Dennison G, Liu S. (2021) An assessment on ethanol-blended gasoline/diesel fuels on cancer risk and mortality. *Int J Environ Res Public Health* 18: 6930.
- Kumar S, Sharma A, Kshetrimayum C. (2019) Environmental and occupational exposure and female reproductive dysfunction. *Indian J Med Res* 150:532-45.
- Liu Y, Zhou Q, Xie X, et al. (2010) Oxidative stress and DNA damage in the earthworm *Eisenia fetida* induced by toluene, ethylbenzene and xylene. *Ecotoxicology* 19:1551-9.
- Kuang H, Liu J, Zeng Y, et al. (2020) Co-exposure to polycyclic aromatic hydrocarbons, benzene and toluene may impair lung function by increasing oxidative damage and airway inflammation in asthmatic children. *Environ Pollut* 266:115220.
- INEGI. (2021) Statistics for the purpose of the international day of the fight against drug misuse and trafficking (june 26) press release [Estadísticas a propósito del día internacional de la lucha contra el uso indebido y el tráfico de drogas (26 de junio) comunicado de prensa] Num. 358/21-25 de junio de 2021.
- Martínez-Alfaro M, Alcaraz-Contreras Y, Cárabez-Trejo A. et al. (2011) Oxidative stress effects of thinner inhalation. *Indian J Occup Environ Med* 15:87-92.
- Pajaro-Castro N, Caballero-Gallardo K, Olivero-Verbel J. (2019) Toxicity and expression of oxidative stress genes in *Tribolium castaneum* induced by toluene, xylene, and thinner. *J Toxicol Environ Health A*. 82:28-36.
- Gerasimov MR, Collier L, Ferrieri A, et al. (2003) Toluene inhalation produces a conditioned place preference in rats. *Eur J Pharmacol* 477:45-52.
- Yamawaki S, Segawa T, Sarai K. (1982) Effects of acute and chronic toluene inhalation on behavior and (3H)-serotonin binding in rat. *Life Sci* 30:1997-2002.
- Nakai N, Murata M, Nagahama M, et al. (2003) Oxidative DNA damage induced by toluene is involved in its male reproductive toxicity. *Free Radic Res* 37:69-76.
- Abouee-Mehrizi A, Rasoulzadeh Y, Mesgari-Abbasi M, et al. (2020) Nephrotoxic effects caused by co-exposure to noise and toluene in New Zealand white rabbits: A biochemical and histopathological study. *Life Sci* 259:118254.
- El-Nabi Kamel MA, Shehata M. (2008) Effect of toluene exposure on the antioxidant status and apoptotic pathway in organs of the rat. *Br J Biomed Sci* 65:75-9.
- Murata M, Tsujikawa M, Kawanishi S. (1999) Oxidative DNA damage by minor metabolites of toluene may lead to carcinogenesis and reproductive dysfunction. *Biochem Biophys Res Commun* 261:478-83.
- Van Buren J, Prasse C, Marron EL, et al. (2020) Ring-cleavage products produced during the initial phase of oxidative treatment of alkyl-substituted aromatic compounds. *Environ Sci Technol* 54:8352-61.
- Sisto R, Capone P, Cerini L, et al. (2020) Occupational exposure to volatile organic compounds affects microRNA profiling: Towards the identification of novel biomarkers. *Toxicol Rep* 7:700-710.

23. Yoon HI, Hong YC, Cho SH, et al. (2010) Exposure to volatile organic compounds and loss of pulmonary function in the elderly. *Eur Respir J* 36:1270-6.
24. Montes S, Yee-Rios Y, Páez-Martínez N. (2019) Environmental enrichment restores oxidative balance in animals chronically exposed to toluene: Comparison with melatonin. *Brain Res Bull* 144:58-67.
25. Mattia CJ, Ali SF, Bondy SC. (1993) Toluene-induced oxidative stress in several brain regions and other organs. *Mol Chem Neuropathol* 18:313-28.
26. Peshin SS, Gupta YK. (2018) Poisoning due to household products: A ten years retrospective analysis of telephone calls to the National Poisons Information Centre, All India Institute of Medical Sciences, New Delhi, India. *J Forensic Legal Med* 58:205-11.
27. Calderón-Guzmán D, Hernández-Islas JL, Espitia-Vázquez IR, et al. (2005) Effect of toluene and cresols on Na⁺, K⁺-ATPase and serotonin in rat brain. *Regul Toxicol Pharmacol* 41:1-5.
28. Karabulut I, Balkanci ZD, Pehlivanoglu B, et al. (2009) Effect of toluene on erythrocyte membrane stability under in vivo and in vitro conditions with assessment of oxidant/antioxidant status. *Toxicol Ind Health* 25:545-50.
29. Srivastava SK, Ansari NH, Liu S, et al. (1989) The effect of oxidants on biomembranes and cellular metabolism. *Mol Cell Biochem* 91:149-57.
30. Rao P, Kodavanti S, Royland JE, et al. (2015) Affiliations expand. Acute and subchronic toxicity of inhaled toluene in male Long-Evans rats: Oxidative stress markers in brain. *Neurotoxicology* 51:10-9.
31. Rao P, Kodavanti S, Royland JE, et al. (2011) Toluene effects on oxidative stress in brain regions of young-adult, middle-age, and senescent Brown Norway rats. *Toxicol Appl Pharmacol* 256:386-98.
32. Yang LY, Greig NH, Tweedie D, et al. (2020) The p53 inactivators pifithrin- μ and pifithrin- α mitigate TBI-induced neuronal damage through regulation of oxidative stress, neuroinflammation, autophagy and mitophagy. *Exp Neurol* 324: 113135.
33. Jiménez-Garza O, Baccarelli AA, Byun HM, et al. (2015) CYP2E1 epigenetic regulation in chronic, low-level toluene exposure: Relationship with oxidative stress and smoking habit. *Toxicol Appl Pharmacol* 286:207-15.
34. Prasad C. (1998) Food, mood and health: a neurobiological outlook. *Braz J Med Biol Res* 21:1517-27.
35. Boza JJ, Moënnos D, Vuichoud J, et al. (1999) Food deprivation and refeeding. influence growth nutrient retention and functional recovery of rats. *Nutr Metab* 1340-46.
36. Laio TY, Chen CC, Tsou HH, et al. (2019) Acute and chronic exposure of toluene induces genotoxicity in different regions of the brain in normal and allergic mouse models. *Neurotox Res* 36:669-78.
37. Mögel I, Baumann S, Böhme A, et al. (2011) The aromatic volatile organic compounds toluene, benzene and styrene induce COX-2 and prostaglandins in human lung epithelial cells via oxidative stress and p38 MAPK activation. *Toxicology* 289:28-37.
38. Moro AM, Sauer E, Brucker N, et al. (2019) Evaluation of immunological, inflammatory, and oxidative stress biomarkers in gasoline station attendants. *BMC Pharmacol Toxicol* 20:75.
39. Meczyki PL, Meczyki TV. (2021) Mexico added 284,000 deaths from COVID, including 1,413 infections a day. Meczyki.Net published date: october 19, 2021.
40. Bilbul M, Paparone P, Kim AM, et al. (2020) Psychopharmacology of COVID-19. *Psychosomatics* May 18.
41. Uzunova K, Filipova E, Pavlova V, et al. (2020) Insights into antiviral mechanisms of remdesivir, lopinavir/ritonavir and chloroquine/hydroxychloroquine affecting the new SARS-CoV-2. *Biomed Pharmacother* 131:110668.
42. García NH, Porta DJ, Alasino RV, et al. (2020) Ibuprofen, a traditional drug that may impact the course of COVID-19 new effective formulation in nebulizable solution. *Med Hypotheses* 144:110079.
43. Gordon CJ, Tchesnokov EP, Woolner E, et al. (2020) Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *J Biol Chem* 295:6785-97.
44. Li YN, Su Y. (2020) Remdesivir attenuates high fat diet (HFD)-induced NAFLD by regulating hepatocyte dyslipidemia and inflammation via the suppression of STING. *Biochem Biophys Res Commun* 526:381-88.

45. Blaess M, Kaiser L, Sauer M, et al. (2020) COVID-19/SARS-CoV-2 infection: lysosomes and lysosomotropism implicate new treatment strategies and personal risks. *Int J Mol Sci* 21:4953.
46. Costanzo M, De Giglio MAR, Roviello GN. (2020) SARS-CoV-2: Recent reports on antiviral therapies based on lopinavir/ritonavir, darunavir/umifenovir, hydroxychloroquine, remdesivir, favipiravir and other drugs for the treatment of the new coronavirus. *Curr Med Chem* 27:4536-41.
47. Sinha N, Balayla G. (2020) Hydroxychloroquine and COVID-19. *Postgrad Med J* 96:550-55.
48. Wang LF, Lin YS, Huang NC, et al. (2015) Hydroxychloroquine-inhibited dengue virus is associated with host defense machinery. *J Interferon Cytokine Res* 35:143-56.
49. Tang TT, Lv LL, Pan MM, et al. (2018) Hydroxychloroquine attenuates renal ischemia/reperfusion injury by inhibiting cathepsin mediated NLRP3 inflammasome activation. *Cell Death Dis* 9:351.
50. Meo SA, Klonoff DC, Akram J. (2020) Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19. *Eur Rev Med Pharmacol Sci* 24:4539-47.
51. Meyerowitz EA, Vannier AGL, Friesen MGN, et al. (2020) Rethinking the role of hydroxychloroquine in the treatment of COVID-19. *FASEB J* 34:6027-37.
52. Million M, Lagier JC, Gautret P, et al. (2020) Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. *Travel Med Infect Dis* 35:101738.
53. Choudhary R, Sharma AK. (2020) Potential use of hydroxychloroquine, ivermectin and azithromycin drugs in fighting COVID-19: trends, scope and relevance. *New Microbes New Infect* 35:100684.
54. Sauvat A, Ciccocanti F, Colavita F, et al. (2020) On-target versus off-target effects of drugs inhibiting the replication of SARS-CoV-2. *Cell Death Dis* 11:656.
55. Rahman MT, Idid SZ. (2020) Can Zn be a critical element in covid-19 treatment? *Biol Trace Elem Res* 1-9.
56. Sheppard M, Laskou F, Stapleton PP, et al. (2017) Tocilizumab (Actemra). *Hum Vaccin Immunother* 13:1972-88.
57. Frey N. (2017) Cytokine release syndrome: Who is at risk and how to treat. *Best Pract Res Clin Haematol* 30:336-40.
58. Ip A, Berry DA, Hansen E, et al. (2020) Hydroxychloroquine and tocilizumab therapy in COVID-19 patients-An observational study. *PLoS One* 15(8): e0237693.
59. Rizzo E. (2020) Ivermectin, antiviral properties and COVID-19: a possible new mechanism of action. *Naunyn Schmiedebergs Arch Pharmacol* 393:1153-56.
60. Liu J, Zhang K, Cheng L, et al. (2020) Progress in understanding the molecular mechanisms underlying the antitumour effects of ivermectin. *Drug Des Devel Ther* 14:285-96.
61. Ibáñez S, Martínez O, Valenzuela F, et al. (2020) Hydroxychloroquine and chloroquine in COVID-19: should they be used as standard therapy? *Clin Rheumatol* 39:2461-65.
62. Yang J, Yang X, Zou H, et al. (2016) Oxidative stress and treg and th17 dysfunction in systemic lupus erythematosus. *Oxid Med Cell Longev* 2526174.
63. Soto ME, Guarner-Lans V, Soria-Castro E, et al. (2020) Is antioxidant therapy a useful complementary measure for covid-19 treatment? an algorithm for its application. *Medicina (Kaunas)* 56:386.
64. Gutmann C, Siow R, Gwozdz AM, et al. (2020) Reactive oxygen species in venous thrombosis. *Int J Mol Sci* 21:1918.
65. Kalyanaraman B. (2020) Do free radical NETWORK and oxidative stress disparities in African Americans enhance their vulnerability to SARS-CoV-2 infection and COVID-19 severity? *Redox Biol* 37:101721.
66. Sahebnaasagh A, Saghafi F, Avan R, et al. (2020) The prophylaxis and treatment potential of supplements for COVID-19. *Eur J Pharmacol* 887:173530.
67. Doroftei B, Ilie OD, Cojocariu RO, et al. (2020) Mini-review exploring the biological cycle of vitamin b3 and its influence on oxidative stress: further molecular and clinical aspects. *Molecules* 25:3323.
68. Martínez-Sánchez G, Schwartz A, Donna VD. (2020) Potential cytoprotective activity of ozone therapy in SARS-CoV-2/COVID-19. *Antioxidants (Basel)* 9:389.

Submit your manuscript to a JScholar journal and benefit from:

- ¶ Convenient online submission
- ¶ Rigorous peer review
- ¶ Immediate publication on acceptance
- ¶ Open access: articles freely available online
- ¶ High visibility within the field
- ¶ Better discount for your subsequent articles

Submit your manuscript at
<http://www.jscholaronline.org/submit-manuscript.php>