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## Substance Use Disorder and COVID-19; Forensic Medicine and Pharmacology Perspectives: A Concise Narrative Review

اضطراب تعاطي المخدرات وكوفيد 19؛ من منظور الطب الشرعي وعلم الأدوية: مراجعة سردية موجزة



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### Abstract

Many investigations have confirmed the link between a substance use disorder (SUD) and the COVID-19 pandemic's increased risk of infection and consequences. This narrative review aims to understand these issues from a pharmacological standpoint, as well as the pandemic's impact on forensic medicine.

Research and review articles included in this review were selected through an extensive search of databases such as PubMed and the use of appropriate keywords e.g. "substance use disorder" and "COVID-19". Due to a weakened immune system and degeneration of the respiratory system's defense systems, SUDs have been shown to increase the risk of COVID-19 infection. Furthermore, some substances raise pro-inflammatory mediators, exposing the body to a cytokine storm. SUD frequently causes secondary comorbidities, such as the liver, lung and cardiovascular disease, complicating the treatment of COVID-19 infections. Some misused substances can compromise the treatment's effectiveness or safety.

This study also looked at the effects of the pandem-

**Keywords:** Forensic Science, COVID 19, SARS-COV-2, Alcoholism, Substance Use Disorder, Opioids, Smoking, Nicotine, Cannabinoids, Cocaine, Methamphetamine.

### المستخلص

أكدت العديد من الدراسات العلاقة الوثيقة بين اضطراب تعاطي المخدرات (SUD) وزيادة العدوى والمخاطر الناجمة عن وباء كوفيد 19. وتهدف الدراسة السردية إلى شرح هذه الظاهرة من مفهوم علم الأدوية وكذلك تأثير الوباء على الطب الشرعي.

استخدمت الدراسة منهجية البحث في قواعد البيانات الأكاديمية باستخدام الكلمات المفتاحية المناسبة ذات الصلة لتحقيق أهداف المراجعة.

أكدت الدراسات أن اضطراب تعاطي المخدرات. يزيد من احتمالية الإصابة بعدوى كوفيد 19 بسبب ضعف الجهاز المناعي، وتدهور آليات دفاع الجهاز التنفسي علاوة على ذلك، تزيد بعض المواد من العوامل المحفزة للالتهابات؛ مما يجعل الجسم عرضة لعاصفة السيتوكينات. وعادةً ما يؤدي اضطراب تعاطي المخدرات إلى أمراض مصاحبة أخرى مثل ضعف الكبد، مما يجعل علاج عدوى كوفيد 19 أكثر تعقيداً. يمكن

**الكلمات المفتاحية:** علوم الأدلة الجنائية، كوفيد 19، إدمان الكحول، اضطراب تعاطي المخدرات، المواد الأفيونية، التدخين، النيكوتين، القنب، الأفيون ومشتقاته، الكوكايين، الميثامفيتامين.

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ic on forensic medicine. It underlines the importance of developing safe forensic examination procedures and methodologies during pandemics. The use of narcotic substances was documented as one of the reasons for the increase in the frequency of COVID-19 and the severity of its repercussions.

## 1. Introduction

### 1.1 An overview

COVID-19 is an ongoing global pandemic illness, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of the 29th June 2021, more than 181 million cases have been confirmed, with more than 3.92 million confirmed deaths attributed to COVID-19 [1]. The angiotensin-converting enzyme 2 (ACE2) receptor, which is found in lung cells and other organs, allows SARS-CoV-2 to enter host cells. More details about transmission, symptoms and risk factors of COVID-19 are available in many reviews [2-4].

A substance use disorder (SUD) is a condition in which a person has a strong desire to use a certain substance or a combination of substances, such as alcohol, tobacco, or illegal drugs, to the point where their ability to function in daily life is harmed. Those addicts continue to use drugs despite their knowledge of their harm. Each addicting substance has its own set of toxic effects. The cardiopulmonary system is adversely affected by most abused drugs, particularly opioids, and most of these substances impair the immune system [5, 6].

According to the United Nations drug report (UNODC's), an estimated 271 million people (5.5% of the world's population, aged 15–64) took drugs in previous years [7]. In 2018, the prevalence of alcohol use disorder (AUD) in the adult population in Europe were 8.8% and 0.8 % in the Eastern Mediterranean [8]. Adolescents are more likely to use substances such as alcohol, cigarettes, and marijuana, are also more susceptible to traffic accidents.

أن تتداخل بعض المواد المخدرة مع الأدوية المستخدمة لعلاج كوفيد-19، كما عرض البحث المشاكل التي يسببها الوباء في الطب الشرعي. وتؤكد هذه الورقة أهمية تطوير إجراءات ومنهجيات آمنة لفحص الطب الشرعي أثناء الأوبئة، والتأكيد بأن تعاطي المواد المخدرة كان من أسباب زيادة وتيرة الإصابة بفيروس كوفيد 19 وخطورة تداعياته.

However; overdose, accidental injury, and suicide show similar incidence in all age groups [9].

COVID-19 and SUD are two health problems with synergistic negative impacts on the public [10]. The coronavirus pandemic and its economic distress on the public is likely to make people more vulnerable to drug abuse [11]. Illegal online activities and drug smuggling have increased, as has the increase in resorting to alcohol, sedatives, or more harmful adulterated substances [12,13].

### 1.2 Bidirectional Association between SUD and COVID-19

A significant risk of SUDs increases during lockdowns. Relapse and involuntary withdrawal are particularly serious for people with opiate use disorders. Years after the shutdown, a rise in SUD may be expected. During a COVID outbreak, those with SUD are at a higher risk of multimorbidity and mortality. [14-17]. Moreover, COVID-19 infection has been linked to both psychiatric disorders and SUD, with both acute and long-term effects. Social disturbances have also been recognized as a risk factor for the start of new diseases as well as the recurrence and worsening of existing ones [18].

For more details about the relationship of the pandemic and drug trafficking, its changing patterns, and the emergence of new materials, the reader is referred to this comprehensive United Nations publication [19]. To reduce the exacerbation of COVID-19 among addicted groups, a worldwide group of experts in addiction medicine provided a list of recommendations for managing COVID-19 in



people with SUDs (Table-1) [20]. However, the deleterious pharmacological consequences of SUDs, as well as the impact of COVID-19 on forensic medicine, must be underlined, and this is what this review attempts to address.

## 2. Objectives

The present narrative review aims to explain the pharmacological basis of the high risk of getting COVID-19 and worse outcomes among individuals with SUDs as well as the impact of the pandemic on the practice of forensic medicine.

## 3. Methods

In June 2021, PubMed was searched to explore the pharmacological basis of the role of substance use disorders and the risk of mortality and morbidity among COVID-19 patients. We used all relevant terms (COVID-19), substance use disorder, and commonly abused drugs. For the impact of COVID-19 on forensic medicine, key terms such as “post-mortem” or “forensic autopsies” and “COVID-19” or “SARS-COV-2” were used to search relevant publications via academic resources such as PubMed. The search was restricted to publications in English and availability of free full texts. Relevant pharmacological profiles about the narcotic substances were retrieved from updated review articles.

## 4. Findings

### 4.1 Impact of COVID-19 on Forensic Medicine

One of the challenges posed to the medical field during the COVID-19 pandemic was the lack of autopsies performed due to the lack of autopsy rooms deemed ‘safe’ enough to prevent the transmission of SARS-CoV-2. Hence, most COVID-19 related deaths are determined to be “death with COVID-19” as opposed to “death caused by COVID-19”, and

only with a proper post-mortem investigation can one be distinguished from the other [21].

A full autopsy can also help in the post-mortem investigation by identifying the presence of drugs of abuse by forensic toxicologists and whether they are at a fatal or non-fatal level in the body. A history of chronic use of drugs can exacerbate symptoms of COVID-19, therefore, identifying the presence of any drug of abuse can help explain the deceased’s demise. By providing comprehensive post-mortem autopsies or examinations, it will be easier to assess how existing comorbidities whether respiratory, cardiovascular, malignant, metabolic, etc. contributed to the cause of death alongside COVID-19 [21].

This also poses a problem for forensic purposes, in that a lack of an autopsy or proper post-mortem investigation could easily conceal criminal cases. For example, if a patient is critically ill with COVID-19 and is poisoned, the deceased will be presumed dead due to COVID-19. Without a proper autopsy or toxicology screen, the true cause of death could not be determined. Leaving the possibilities for criminal offences higher than usual. Therefore, the lack of autopsy data prevents the cycle of information that helps connect clinical care to forensic pathology practices in forensic medicine [22].

If the deceased’s history of alcohol abuse was not known, it could be difficult to detect in an autopsy investigation because ethanol can be produced naturally post-mortem [23]. Therefore, toxicological results can be misleading in suggesting that they played a role in the cause of death in addition to, or as a result of, COVID-19.

Salerno et al., (2020) argued that the lack of autopsies in COVID-19 deaths was a missed opportunity, in that having a full understanding of the pathophysiological insights provided by autopsies along with the useful clinical and epidemiologic data could help providing enhanced therapeutic tools



[24]. In their search, 50 articles were published at the time of their submission (and met their inclusion criteria) and only 7 of them reported data that were 'autopsy based. However, they found that only two complete autopsies were performed and only one of the two autopsies described the cause of death as COVID-19 [24].

Tozzo et al., (2020) argued that prisoners are a vulnerable group in the spread of infectious diseases, due to the prevalence of HIV, HCV, HBV and tuberculosis from the detainees who were put in prison as a result of their drug abuse [25]. They mentioned that the overcrowding in Italian prisons is because of the overrepresentation of drug addicts in the prison system [25]. It is no surprise that because of these underlying conditions in prisons, along with the poor health services, overcrowding and high-risk behaviors of prisoners, outbreaks of infections are common [26].

#### 4.2. SUDs and COVID-19

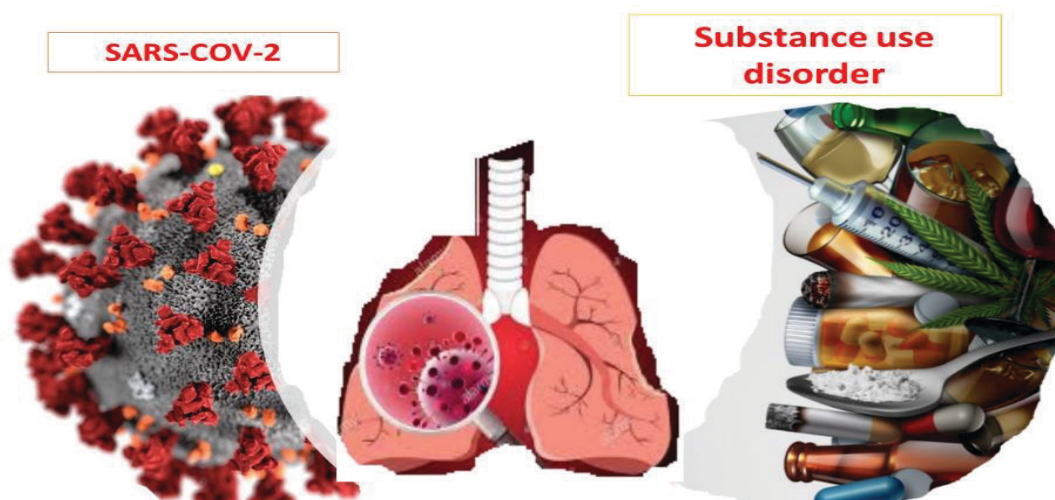
##### An Overview

A systemic review discussed COVID-19's pathogenesis and pathology, as well as potential risk

factors and problems for SUD patients. It gave information and suggestions for the management of the infection and its prevention in those high-risk patients [27]. However, few studies documented the impact of SUD as a risk factor for increased morbidity and mortality of COVID 19. In this context, in the USA, a retrospective case-control study using electronic health records (EHRs) of about 73 million patients found that about 12 thousand had COVID-19. The infection was substantially more common among patients who had been diagnosed with a SUD (within the last year). COVID-19 patients with a SUD had a considerably worse prognosis (hospitalization: 41.0%, mortality: 9.6% ) compared to COVID-19 patients without a SUD (hospitalization: 30.1%, death: 6.6 % ) [28].

The 2nd study in the USA revealed that patients with a history of SUDs showed higher risks of getting COVID-19, with the incidence being more predominant in the case of opioid use disorders [28].

In the 3rd study in the USA, which is a propensity score (PS)-matched double-cohort study (February 20 to June 30, 2020) the researchers included 54,529 adult patients diagnosed with COVID-19.



**Figure 1:** An illustration showing the increased risks from the confluence of the SUD epidemic with COVID-19 pandemic against human health.



The study demonstrated that patients having a history of SUDs are at high risk of hospitalization (odds ratio [OR]=1.84), ventilator use (OR=1.45), and mortality (OR=1.30) [29].

A study in New York City (January 1, 2020, to October 26, 2020) was implemented to assess the correlations between SUD history and clinical outcome of COVID-19. A total of 2.7% (n = 5,107) of the individuals who were confirmed patient of COVID-19 had a history of SUD out of (n = 188,653). The AORs for hospitalization due to cocaine and alcohol use were 1.78 and 6.68, respectively. Cocaine had a 0.64 (0.14–2.84) association with death. This study documented that patients with a history of SUD may have a higher risk of poor COVID-19 outcomes [30].

However, according to one center's reports in Barcelona, a limited percentage of patients with SUDs (median age of 56, major kind of substance use is alcohol, the majority were male) were hospitalized for COVID-19 [31].

### 4.3 Pharmacological basis for impact of SUD on COVID-19

Both the infection of vascular endothelial cells and COVID-19's pro-inflammatory immune responses are likely to be severe in patients with SUDs. Substance abuse has been shown to disrupt the blood-brain barrier (BBB) irreversibly [32] as well as impact the hypothalamus-pituitary-adrenal axis (HPA axis), and hence suppress the immune system [33]. For a deeper understanding of the negative effects of SUDs on immunity and exaggerated complications of COVID-19, we will discuss certain substances in detail. A summary of the pathological effects of addicting substances and their impact on COVID-19 complications are presented in Table-2 [27].

#### 4.3.1 Alcohol

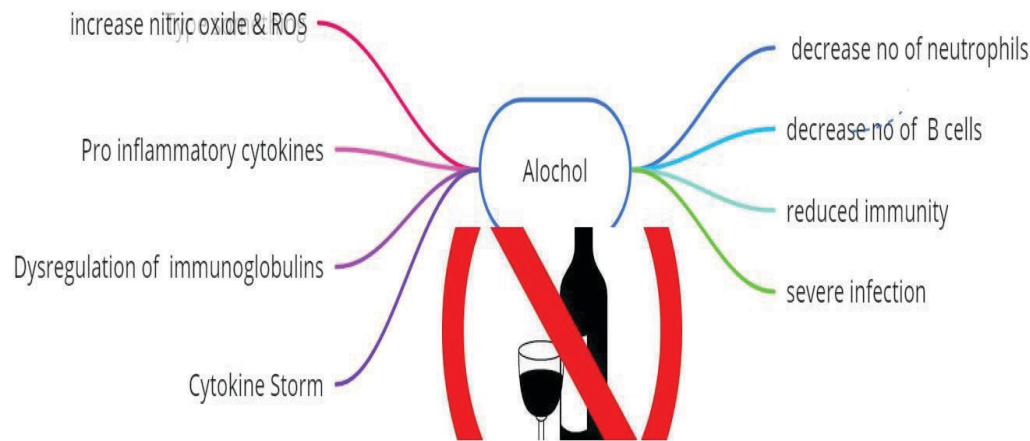
Alcoholism is a worldwide problem, which causes about three million deaths every year [34]. In the context of the COVID-19 pandemic, alcohol usage poses unique challenges, with worse implications for public health. It is also associated with an increase in the incidence of domestic violence during the pandemic [34]. Heavy drinking raises the chance of severe lung infections. Children's welfare may also be jeopardized. Alcohol is a known risk factor for depression and suicide which may be especially prominent during this period of social isolation. It's unlikely that drinking will accomplish any benefit against COVID-19, on the contrary, it leads to neglecting the rules of epidemic prevention [35].

Unfortunately, there are a lot of misconceptions regarding the alleged health benefits of alcohol. Widespread methanol poisonings were reported in Iran, (5,000 cases of which 700 persons died) [36]. Methanol poisonings were also reported in Azerbaijan and Turkey, due to consuming adulterated alcohol [37].

Chronic alcohol consumption is known to suppress immunity [38]. It also increases the risk of getting infections [39]. This was attributed to unfavorable alterations in the function of T and B cells along with alterations with the production of immunoglobulins [40]. Figure-2 illustrates the unfavorable impact of alcohol on the immune system and the risk for organ damage.

There is an association between alcohol consumption and upregulation of ACE2, particularly in the lungs. This increase is also present after four weeks of alcohol abstinence [41]. ACE2 receptors are the target for coronaviruses; alcohol consumption significantly increases the risk of contracting bacterial and viral lung infections (including COVID-19) [42]. Alcohol and its metabolites have a multisystemic effect, affecting the liver, heart, lungs,





**Figure 2-** *Impact of alcoholism on the immune system and inflammatory response.*

and other organs. In patients suffering COVID-19, alcoholism may raise the risk of cardiac injury, acute respiratory distress syndrome, pulmonary fibrosis, and liver damage, worsening disease prognosis and outcome [43].

Moreover, patients with AUD may have less scheduled time for non-alcohol-related activities because of social distancing during the pandemic. Patients may relapse if they do not participate in structured activities [44, 45].

#### 4.3.2 Opioids

Opioids, which are prescribed for pain management, have analgesic and CNS depressive properties, as well as the potential to generate euphoria. Misuse of prescribed opioid drugs diverted opioid medications or illicitly obtained heroin are all examples of opioid use disorders (OUD) which are linked to significantly higher rates of morbidity and mortality. In the USA OUDs were designated a national emergency in 2017 [46, 47].

Individuals with OUDs usually suffer from a variety of co-morbidities, social deprivation, and homeless-

ness [48, 49]. Putative pathophysiological reasons for potentially poor outcomes in COVID-19 infected patients with opioid use disorders (OUD) include respiratory depression which is likely to exaggerate hypoxemia from COVID-19 viral pneumonia [50] and the negative impact of opioids on the immune system.[48]. Opioid use by inhalation may exacerbate the "late hyper-inflammatory phase" or cause end-organ damage in COVID-19 patients [51].

Drug-drug interactions (COVID-19 drugs and opioids) can be more problematic in COVID-19 patients with OUD, especially if the meds cause cardiac adverse effects [52]. According to preliminary data, opioid-related overdose deaths increased after COVID-19 [53].

Furthermore, pandemic control measures such as quarantine or isolation, as well as a lack of health-care resources and staff, have put a burden on the most effective treatment for OUD, methadone or buprenorphine-based opioid agonist treatment (OAT) [54]. In many nations, getting OAT can be difficult [55]. These circumstances will cause OAT patients to drop out and stop taking their medicine, and the



accompanying opioid withdrawal will likely lead to a relapse among illicit opiate users [56, 57].

### 4.3.3 Amphetamine-type Stimulants and Cocaine

#### 4.3.3.1. Amphetamine-type Stimulants

Amphetamine-type stimulants include methamphetamine (METH) and amphetamine. Amphetamine is one of the most effective medications for the treatment of ADHD, along with methylphenidate. However, the varied pharmacological activities of these drugs are not only limited to their therapeutic efficacy but also associated with adverse events and the potential for recreational addiction [58]. Comprehensive details of adverse effects of amphetamine-type stimulants are available in these reviews [59, 60]. Increased severity and mortality of COVID-19 among METH users were documented in several publications [61, 62]. Hypertension, tachycardia, and congestive heart failure or cardiomyopathy among other cardiac abnormalities have been related to METH [63, 64]. Moreover, pulmonary oedema is frequently caused by METH-related heart diseases. Therefore, COVID-19 symptoms and a poor prognosis might be made worse by a reduction in lung capacity caused by fluid accumulation in the lungs and blood vessel constriction [65].

Amphetamine alter the expression of genes and proteins involved with the HPA axis in the brain, resulting in immunological suppression, [64] which could put its users at risk of viral infections and catastrophic consequences. METH has been demonstrated to have deleterious effects on the immune system in animal models, according to studies. [66] The innate immune system's activities, including phagocytosis and antigen presentation, have been demonstrated to be inhibited by METH [67]. Dendritic cells, natural killer cells, monocytes, and macrophages are among the immune system cells that

are reduced by METH [68]. METH also affects the adaptive immune system. It alters the production of antibodies and reduces the ability of highly specialized cells, known as lymphocyte T-cells, to fight off pathogens. It can also interfere with cytokines [69].

The effects of METH on both the innate and adaptive immune systems, when combined, can enhance vulnerability to a variety of infections, including COVID-19, however, the underlying mechanisms are still under investigations. While data from animal studies suggest that METH influences immunological function, further research is needed to corroborate these findings in humans. People who consistently use METH, however, may be more prone to infections and have more severe symptoms related with these infections, including COVID-19, due to its potential harmful impact on the immune system.

#### 4.3.3.2 Cocaine.

Cocaine, a powerful CNS stimulant, is primarily abused in Western countries. Cocaine usage is the largest cause of drug-abuse-related visits to emergency rooms, with the majority of these visits being due to cardiovascular complications many of which are fatal [70].

Vasoconstriction, endothelial dysfunction, and accelerated atherosclerosis are among the cocaine-induced cardiovascular problems, Cocaine's acute and chronic vascular effects are caused by a complex aetiology that includes hypertension, decreased homeostasis and platelet function, thrombosis, thromboembolism, and changes in blood flow [71]. Acute respiratory syndromes, known as "crack-lung", have been described in crack users up to 48 hours following free-base cocaine inhalation, with symptoms including pulmonary edema, interstitial pneumonia, diffuse alveolar hemorrhage, and



eosinophil infiltration on chest X-rays. Alveolar damage has been linked to the high temperature of volatilized cocaine, the presence of contaminants, and cocaine-induced local vasoconstriction [72]. These health problems of cocaine and crack on the heart and lungs undoubtedly make addicts more vulnerable to infection and exacerbation of COVID-19 [30].

#### 4.3.4. Cannabinoids

Cannabis usage unfavorably impacts almost all physiological and biochemical systems, including the immunological, cardiopulmonary/respiratory, hepatic, renal, endocrine, reproductive, and central neurological systems, as well as genetics and general health.[73]. Cannabis use has been shown to affect viral illnesses such as the human immunodeficiency virus (HIV), hepatitis C infection (HCV), and human T-cell lymphotropic type I and II virus (HTLV-I/II) in a variety of ways [74]. During the first three months of the pandemic, cannabis sales on illegal online markets exploded [75].

Regarding its impact on the COVID-19 pandemic, in a study, van Laar et al., (2020) performed a survey and found that of the over 1,500 participants, approximately 41% of them indicated they increased their use of cannabis during the pandemic as a result of the lockdown measures put in place by the government while only 6.6% of the responders indicated that they had used cannabis less often than before [76]. Since cannabis' most prevalent route of administration is smoking, whether with or without tobacco, it is suggested that it will result in worse COVID-19 outcomes due to the upregulation of the angiotensin-converting enzyme II-receptor, which are used by both SARS-CoV-2 and SARS-CoV to enter host cells [77-79].

Cannabinoids may have a potential for the inhibition of hyper inflammation leading to Cytokine

Release Syndrome (CRS). However, extensive evidence from pre-clinical and clinical trials are still missing [80]. Also, there are no evidence-based medicine guidelines to support the use of Cannabidiol (CBD) to treat COVID-19 associated mental health conditions or substance use disorders [81]. In contrast, multiple clinical risks were suggested [74, 82].

#### 4.3.5. Nicotine

Nicotine is a well-known component of tobacco, which also contains a variety of toxic chemicals. Smoking has been linked to many complications including thrombosis and atherosclerosis, pulmonary disease, and cancers [83, 84]. No study supports the view that smoking acts as a treatment intervention or prophylaxis to reduce the impact or ameliorate the negative health impacts of COVID-19. In contrast, many studies have confirmed the association between smoking and the exacerbation of COVID-19 [85-90].

E-cigarette aerosols have been shown in pre-clinical experiments to harm lung tissue, promote inflammation, and reduce the lungs' ability to respond to infection [91]. In this context, smoking is documented as a risk factor for poor COVID-19 prognosis, according to two meta-analyses [92, 93]. Other meta-analyses of 40 studies concluded that smoking, whether current or former smoking, significantly increases the risk of COVID-19 severity and death [94].

Cigarette smoking significantly increases the number of alveolar macrophages (AMs), which are innate immune cells in the lungs. These cells release elastase, a lysosomal enzyme that can damage lung connective tissue and parenchymal cells. Nicotine inhibits antibody responses and T-cell proliferation considerably. The immunological suppression caused by nicotine, notably the reduction





in CD8+ T-cells, suppress the ability of the lungs for clearance of infection [95, 96].

Nicotine causes oxidative stress, which can erode the BBB's integrity over time [97], increase its permeability [98], and lead to an increase in bacterial invasion of the brain [97]. In the brain microvessels, nicotine enhances gene expression of proinflammatory cytokines TNF- $\alpha$ , IL-1, and IL-18, as well as chemokines CCL2, CCL8, and CXCL1, while suppressing anti-inflammatory proteins Bcl6, IL-10, and CCL25 [99].

The serious impact of smoking on cardio-pulmonary health are well known [100], moreover, higher expression of type-2 angiotensin converting enzyme (ACE2) in lung cells of smokers enhanced SARS-COV-2 ability for entry into lung cells [101, 102].

#### 4. Conclusion

One of the reasons for the increase in the frequency of COVID-19 and the intensification of its consequences was the use of narcotic substances, and the wisdom of Islam may be seen in prohibiting these substances, particularly alcohol. A concerted effort is urgently needed to lower the danger of addiction. This review also emphasizes the significance of devising safe methods and methodologies for conducting forensic exams during pandemics.

#### List of abbreviation

Hepatitis B virus: HB; Blood-brain barrier: BBB; Alcohol use disorder: AUD; Adjusted odds ratio: AOR, Opioid use disorder: OUD, opioid agonist treatment: OAT; human immunodeficiency virus: HIV; hepatitis C virus : HCV; Cytokine Release Syndrome: CRS; Cannabidiol: CBD; alveolar macrophages: AMs; Respiratory distress syndrome: RDS; Hypothalamus pituitary-adrenal axis: HPA axis; Attention deficit hyperactivity disorder: ADHD; brain-microvascular en-

dothelial cells: BMVECs; Chronic Obstructive Pulmonary Disease: COPD; Myocardial infarction: MI; Interleukin-10: IL-10 ; Chemokine (C-C motif) ligand 2: CCL2; Chemokine (C-C motif) ligand 8: CCL8; Chemokine (C-C motif) ligand 25: CCL25; B-cell lymphoma 6 protein: Bcl6; Chemokine (C-X3-C motif) ligand 1 : CXCL1;

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