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Chemical Profiling of Hashish Resin and its Possible Role in Forensic Cases Involving Violence in Jazan, Saudi Arabia

التنميط الكيميائي لراتنج الحشيش ودوره المحتمل في القضايا الجنائية التي تنطوي على العنف في جازان، المملكة العربية السعودية

Mohammed Albeishy, Farid Abualsail, Mohammed Hakamei, Ahmad Maghfori, Mohammed Alarishi, Faridah Alagsam, Nuha Arishi, Lulah Ogdi, Wafa Qumayri, Magbool Oraiby, Ibrahim Khardali, Mohsen Fageeh and Ibraheem Attafi*

Poison Control and Medical Forensic Chemistry Center, Jazan Health Affairs, Ministry of Health, Jazan, Saudi Arabia.

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Abstract

Hashish resin is a narcotic prepared from a concentrated extract of cannabis flowers and leaves. It can cause confusion, anxiety, panic, paranoia, and even psychosis. This study's goal was to assess the hazards associated with abuse of hashish resin, its chemical composition and possible role in forensic cases involving violence in Jazan, Saudi Arabia. For this purpose, all forensic cases in Jazan, from January 2019 to December 2021 were retrospectively investigated. The data were collected from the OTARR electronic system using the data collecting form. Gas chromatography-mass spectrometry was used to analyze the chemical composition of seized hashish. The percentage of cases having positive results for hashish in fatal cases were 1, 2, and 5% and in crime cases these were 29, 26, and 31% in 2019, 2020, and 2021, respectively. Homicide and suicide were the major manners of death among fatalities involving hashish. More than one-third of the crimes were related to hashish use/abuse. Amphetamine and ethanol were most used drugs in combination with hashish. The average level of THC (the active compound in hashish) in

Keywords: Forensic Science, Fatalities, Crimes, Hashish, Suicide, Homicide, Violence, Postmortem. THC Level.

المستخلص

راتنج الحشيش هو مخدر محضر من مستخلص مركّز من أزهار وأوراق القنب. يمكن أن يسبب الارتباك والقلق والذعر وجنون الارتياب وحتى الذهان. وقد هدفت هذه الدراسة إلى تقييم المخاطر المرتبطة بتعاطي راتنج الحشيش وتكوينه الكيميائي ودوره المحتمل في القضايا الجنائية التي تنطوي على العنف في جازان بالمملكة العربية السعودية. ولذا تم التحقيق في جميع حالات الطب الشرعي في جازان، من يناير 2019 إلى ديسمبر 2021 بأثر رجعي. وتم جمع البيانات من نظام OTARR الإلكتروني باستخدام نموذج جمع البيانات. وتم استخدام كروماتوغرافيا الغاز - قياس الطيف الكتلي لتحليل التركيب الكيميائي للحشيش المضبوط. وكانت نسبة نتائج الحالات الإيجابية للحشيش في الوفيات 1 ، 2 ، و 5٪ وفي قضايا الجرائم كانت 29 ، 26 ، و31٪ في 2019 و 2020 و 2021 على التوالي. وكان القتل والانتحار من الأساليب الرئيسية للوفاة بين الوفيات المرتبطة بتعاطي الحشيش. كما أن أكثر من ثلث الجرائم كانت مرتبطة باستخدام/ تعاطي الحشيش. وكان الأمفيتامين والإيثانول أكثر الأدوية استخدامًا مع الحشيش.

الكلمات المفتاحية: علوم الأدلة الجنائية، الوفيات، الجرائم، الحشيش، الانتحار، القتل، العنف، التوزع ما بعد الوفاة، مستوى THC.

* Corresponding Author: Ibraheem M. Attafi, Ph.D
Email: iattafi@moh.gov.sa

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crimes and fatalities was determined. The relationships between chemical composition of seized hashish, mental diseases and violence were investigated and discussed.

وتم تحديد متوسط مستوى THC (المركب النشط في الحشيش) في الجرائم والوفيات. وتم التحقيق في العلاقات بين التركيب الكيميائي للحشيش المضبوط والأمراض العقلية والعنف ومناقشتها.

1. Introduction

Hashish is the common name for Cannabis sativa (C. sativa), and the most commonly used portions are flowers, leaves, and hashish resin that is produced from them. It is produced mostly in Morocco, Afghanistan, Lebanon, and Pakistan, and then exported to illegal markets in the Middle East [1]. In addition to its euphoric effects and mood elevation, hashish is used for the psycho activity and to mind escape from surrounding troubling environment. Hashish resin hazardous risks may result from its regular consumption either orally or through smoking. In this regard, frequent users of hashish resin are exposed to a higher risk of developing psychosis, violent behavior, and impaired driving ability, etc. [2, 3].

Its abusive use causes euphoria and mood elevation, manifested as excitement, intense happiness, increased friendliness, awareness, and exaltation, followed by central nervous system depression, manifested as decreased in motor activity, alertness, and conversely in some cases, anxiety, confusion, panic, sedation, and sometimes paranoia and psychosis [4-6]. Other effects include a decrease in intelligence and information processing [7], disturbance of time perception, impaired discriminative ability and avoidance responses [8]. The aggressive behavior was increased when it was administered or withdrawn in social seclusion wild mice [9] and during hashish withdrawal in former chronic hashish users [10].

In fact, acute administration of Δ9-Tetrahydrocannabinol (THC), the active constituent of hashish, suppresses the tendency for aggression and violence in experimental animals evidenced by inhibition of predatory attack and killing. However, the chronic THC induced-killing-behavior is a dose-dependent effect and was gradually increased over a considerably prolonged time period [11]. In addition, it also increased the aggressiveness and violent behavior under certain conditions such as individuals who are under stress or with psychiatric disorders [12, 13]. Moreover, an investigation of fatalities involving the use of illicit drugs found that hashish was detected in most of the suicidal deaths [14].

The above-described health consequences could be due to of hashish alone or in combination with other drug of abuse, and/or hashish adulterants or contamination. In this regard, seized hashish resin may be more likely adulterated or contaminated with aluminum, lead, formaldehyde, synthetic cannabinoids, and others [15-17]. Additionally, according to Oomen et al.(2021) cannabis products were adulterated with synthetic cannabinoid receptor agonist MDMB-4en-PINACA [17]. Adulteration of cannabis products with these compounds resulted in serious health consequences, with some individuals being hospitalized. Furthermore, they identified another method of adulterating cannabis products by adding tobacco, calamus, and other cholinergic compounds. According to McPartland, tobacco may alter the pharmacodynamics of THC, thereby amplifying its effects [18].

Based on previous studies [15-18], determining chemical profile of seized and adultrated/contaminatedd cannabis may help in identifying its impact on cannabis-associated social crimes and enable health care providers and policymakers in designiing new as well as realistic strategies in reducing its exposure to the general public. To the best of our knowledge, no previous study has been undertaken to investigate the chemical profile of seized hashish resin in Jazan region. It is hoped that results of the present study will enhance our efforts in identifying toxic adulterants in the seized cannabis and determining its toxicity, extent of social violence and crime associated with the use of seized cannabis. Moreover, present study will also a provide a baseline data for further research in evaluating social and toxic effects of seized and adulterated cannabis.

2. Materials and Methods

2.1 Chemical profile of hashish resin

The Poison Control and Medical Forensic Chemistry Center in Jazan routinely receives hashish resin seized and collected by Narcotics Control Administration in Jazan region for toxicological analysis. Al-Darb, Gizan, and Samtah in Jazan region were the cities where hashish resin was seized and collected for this study. Groups D, G, and S represent samples from Al-Darb, Gizan, and Samtah, respectively. Each group consists of 15 samples that were randomly selected.

The chemical composition of each of the 45 hashish resin samples was analyzed using a general screening Gas Chromatography-Mass Spectrometry (GC-MS, Agilent Technologies, USA) method. Each chemical component was identified using Wiley and NIST mass spectral libraries with more than 90% library score.

2.2 Analysis of forensic cases involving hashish

All crime and fatal forensic cases received in the Poison Control and Medical Forensic Chemistry Center in Jazan, Saudi Arabia, from the 1st of January 2019 to the 31st of December 2021 were retrospectively evaluated. The data were collected via a questionnaire through a unique electronic Online Traceable Authenticated Reliable Result (OTARR) system using a well-designed data collection form. All acquired data regarding toxicological analysis results, hashish associated deaths and the manner of death were analyzed. These data included crime and fatal cases involving hashish only or combined with other drugs of abuse. All the other criminal cases not involving hashish were excluded. The manner of death was classified as following: suicidal, homicidal, accidental, and undetermined. The toxicological analysis and quantification results including (GC-MS) data were collected and analyzed.

2.3 Sample preparation

For biological samples, 20 μL of a 5 μg/mL working internal standard (THC-COOH-D9, Lipomed, Switzerland) was added to 200 μL of 10N NaOH and 1.0 mL of sample. This mixture was Vortex for 30 seconds and then heated in a 60 ^{o}C water bath for 20 minutes. This mixture was allowed to cool before adding approximately 530 μL of 3N HCL to acidify the pH (2-3). Samples were extracted using solid phase extraction (SPE) method. Briefly, SPE cartridges (Clean Screen THC, UCT, Philadelphia, USA) were pre-conditioned by adding 3 mL methanol, 3 mL DW, and 1 mL 0.1 M HCL at high flow. Then, samples were loaded into the SPE cartridge and allowed to pass slowly (1 mL/min). The eluted fraction was washed with 3 mL DW followed by 2 mL 70:30 mixture of 0.1M HCL and Acetonitrile v/v, respectively. The washed fraction was dried under high nitrogen flow for 15 minutes. The dried fraction was mixed with 3 ml of a 50:50 mixture of hexane and ethyl acetate and eluted in a new tube at a flow rate of 1 mL/min. This fraction was evaporated to dryness under a nitrogen stream and then reconstituted by adding 50 μL ethyl acetate and vortexing for 30 seconds and finally adding 50 μL of BSTFA [bis (trimethylsilyl) trifluoroacetamide] containing

1.0% TMCS (Trimethylchlorosilane). The mixture was vortexed for another 30 seconds and then transferred to a GC-MS vial with a 150 μL glass insert. The cap was immediately caped and heated at 70 ^{0}C for 45 minutes.

For crude samples, Poison Control and Medical Forensic Chemistry department received hashish resins seized from different areas in the Jazan region. Each resin was assigned a unique number corresponding to a specific city or source. Each sample (50 mg) was manicured and transferred to a test tube, followed by the addition of 1 mL of extraction solution (methanol and chloroform in a 9:1 ratio). At room temperature, the sample and extraction solution were incubated for overnight. After the incubation, the samples were filtered and centrifuged at 1500g for 10 minutes. A 200 μL of clear supernatant was transferred to a new test tube and evaporated under nitrogen gas before redissolving in 150 μL methanol. The samples were then vortexed and transferred to GC-MS autosampler vials for GC-MS analysis.

2.4 Gas Chromatography-Mass Spectrometry (GC-MS) analysis

The hashish-related substances were fractioned using GC-MS analysis method (GC-MS Agilent Technologies, USA). Thermo Fisher Scientific (TR-5MS) separation column having a length of 30 m , Internal Diameter (ID) 0.25 mm and film thickness of 0.25 μm were used. Helium was used as the carrier gas with 1 ml/min flow rate. A total of 2 μL of each sample was injected into splitless mode at an injection port with a temperature of 260 ^{0}C.

Electron Ionization (EI) used as the ion source in MS and the source electron energy was 70 eV. The temperature of the ion source and transfer line was set at 230 ^{0}C. The analytical method was developed and validated in our lab and is used for the routine analysis of hashish related substances.

For biological samples, the MS was carried-out in selective ion monitoring (SIM) for m/z 371, 473, 488 for THC-COOH and m/z 380, 482 and 497 for THC-COOH-D9 internal standard. The GC initial temperature was 150 ^{0}C and gradually increased to the final temperature 300 ^{0}C at 30 ^{0}C/min rate and held for 4 min. The Data analysis was performed using MassHunter software (GC-MS Agilent Technologies, USA).

For hashish resin samples, the resin extract was evaluated using a general GC-MS screening (GC-MS Agilent Technologies, USA). The GC thermal program began at 80 ^{0}C and lasted 1.5 min, then increased the temperature at the start of the ramp to 210 ^{0}C at a rate of 30 ^{0}C/min, then slowed to 20 ^{0}C/min to achieve the final temperature of 320 ^{0}C. The total run time was 30 min. The chemical composition of the hashish resin extract was then determined using commercial mass spectrum libraries from Wiley and the National Institute of Standards and Technology (NIST).

2.5 Psychological disorders and hashish components

The file of chemical profile obtained from GC-MS analysis was uploaded into the Comparative Toxicogenomics Database (CTD: http://ctdbase.org/) analysis tool which identified the chemical-disease association via hypergeometric test with CTD direct evidence obtained from the published literature. In this context, CTD contains curated and inferred correlations between chemicals and diseases. CTD biocurators extract curated chemical–disease relationships from the published literature.

Using a tool for creating Venn diagrams (http://ctdbase.org/tools/myVenn.go), we identified the chemicals that were detected in all of the tested samples. Using CTD's 'Set Analyzer Query' tool (http://

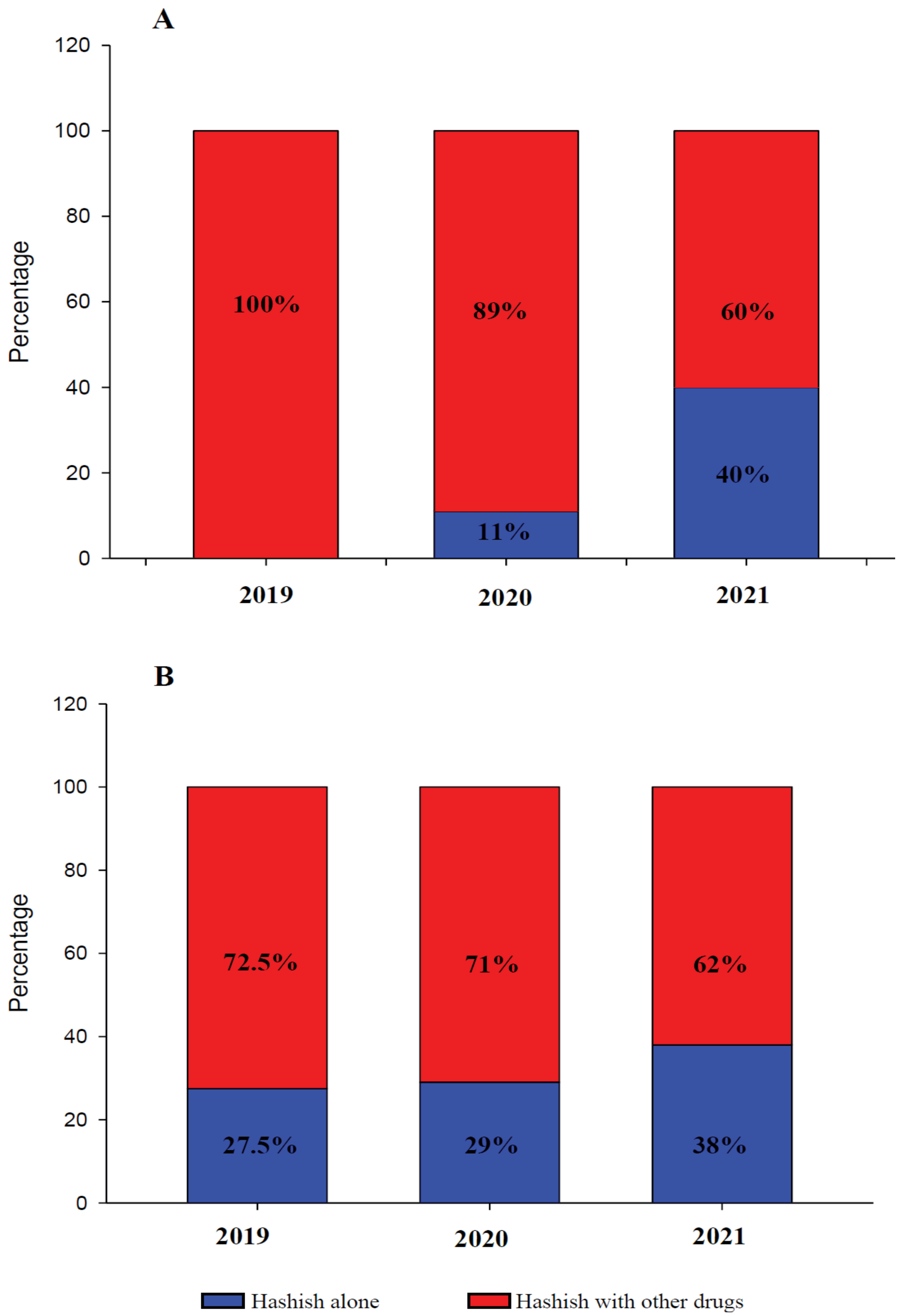

Figure 1- *Stacked bar chart of the abundance of Fatality (A) and Crime (B) involving hashish by year.*

Table 1- *Summary of toxicological analysis of forensic cases involving hashish*

Forensic cases	No. of Sample		THC concentrations mg/L					
			Brain	Liver	Kidney	Stomach	Blood	Urine
Crimes	545	Mean ± SEM						0.47 ±0.03
		Median						0.21
		10 – 90 Percentile						0.05 – 1.10
Fatal cases	18	Mean ±SEM	0.01 ±0.00	0.40 ±0.20	0.03 ±0.01	0.03 ±0.02	0.13 ±0.04	0.38 ±0.18
		Median	0.01	0.1	0.01	0.01	0.10	0.07
		10 – 90 Percentile	0.00 – 0.01	0.04 – 1.40	0.00 – 0.08	0.01 – 0.10	0.01 – 0.30	0.03 –1.20

ctdbase.org/tools/analyzer.go), we selected only the chemicals that overlapped and were associated with curated mental disordes. Briefly, selecting 'Chemicals' as the type of input, entering the list of chemical names, common in all three groups, and selecting 'Curated Diseases' as the output. Chemical-disease relationship was sorted by direct evidence for marker/mechanistic relationships among the respective chemicals and diseases. Default values were used for corrected p-values (threshold 0.01).

2.6 Statistical analysis

All variables were categorized and tabulated using descriptive statistics. Means, standard error of mean (SEM), median, and 10th – 90th percentiles were presented. All data were investigated and calculated using SigmaPlot 11 for Windows.

3. Results

The toxicological analysis of specimens consisting of urine, blood and postmortem tissues (stomach, liver, kidneys and brain) were collected from forensic cases involving hashish. The results are summarized in Table 1. The average urine concentrations of THC in hashish-associated crimes and fatalities were 0.47 and 0.38 mg/L, respectively. The 10th – 90th percentiles of THC urine concentration was 0.05 – 1.1 mg/L in criminal cases 0.03 –1.2 mg/L in fatal cases. These results shows that 90% of the hashish-associated criminal and fatal cases had a THC concentration of more than 0.05 and 0.03 mg/L, respectively. The highest postmortem average tissue concentration of THC was detected in liver (0.4 mg/L), followed by stomach (0.03 mg/L), kidney (0.03 mg/L), and the brain (0.01 mg/L).

The abundance of fatalities (A) involving hashish alone increased from 0.0 in 2019 of the total fatalities involving hashish to 11% in 2020 and 40% in 2021, respectively. In addition, the social crimes (B) involving hashish alone increased from 27.5%, to 29%, and to 38% in 2019, 2020, and 2021, respectively.

The percentage of forensic cases involving hashish is presented as a pie chart in the figure 2 which shows that 25% of forensic cases involved the use of hashish alone, whereas 75% of the cases involved the use of cannabis with other drugs of abuse as well; in 46% cases hashish plus amphetamine, 15% hashish plus ethanol and 14% hashish with other drugs. The relation between hashish-associated moralities and the manner of death is presented in the figure 3. The occurrence of homicidal intoxications was the most common manner of death among all forensic cases involving hashish

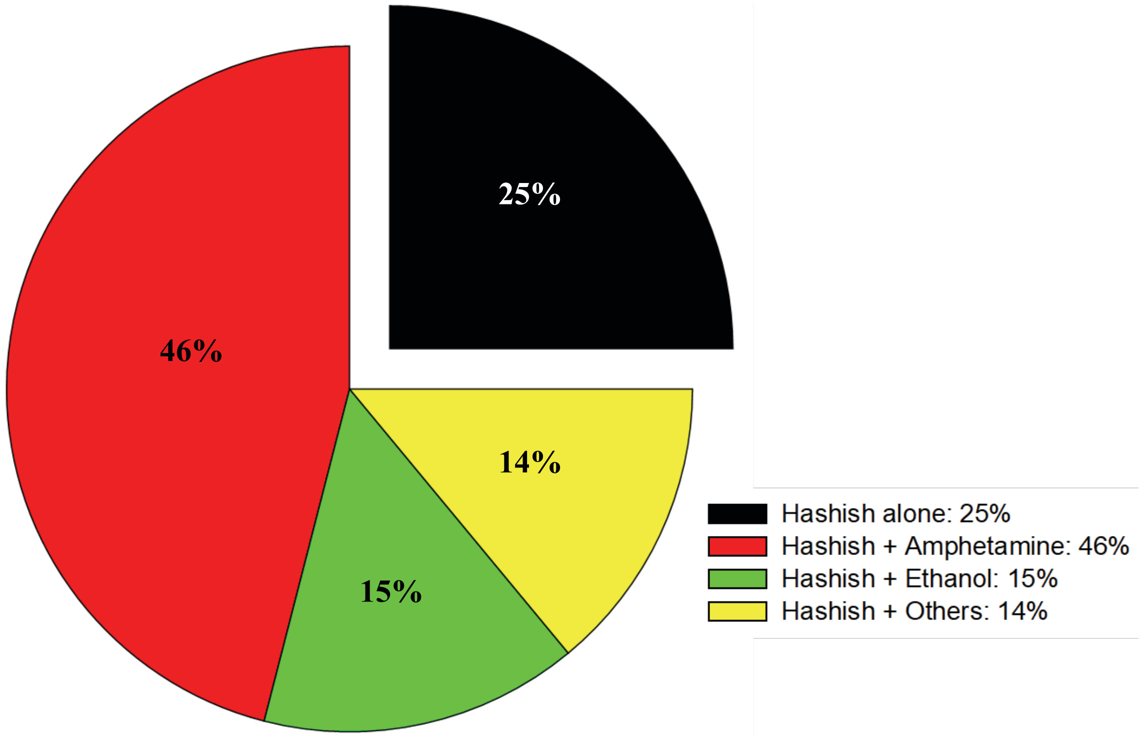

Figure 2- *Percentage of hashish alone and with other drugs in Forensic cases involving hashish.*

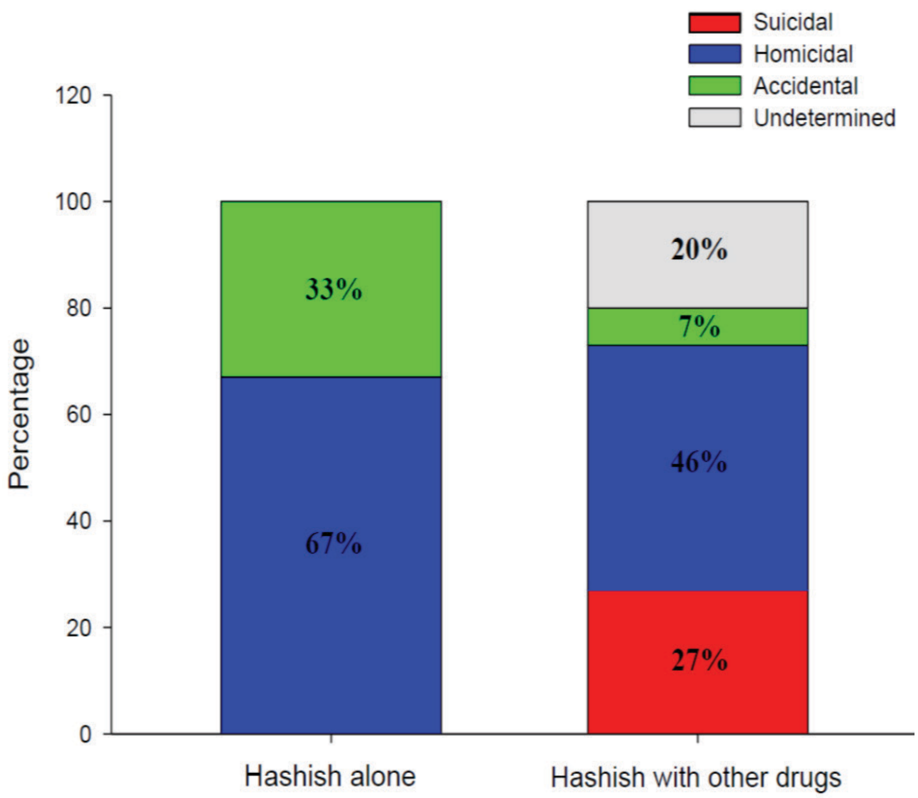

Figure 3- *Stacked bar chart of occurrence of the manner of death according to fatalities involving hashish alone or hashish with other drugs.*

alone (67%) and hashish with other drugs was 46%. In addition, the occurrence of homicidal intoxications in the form of accidental death was seen in 33% of the forensic cases involving hashish alone while the suicidal intoxication occurred in 27% of the forensic cases involving hashish with other drugs. In 20% of THC related cases the manner of death was undetermined while 7% of cases involved accidental deaths.

Based on the GC-MS organic profile of seized hashish resin, the three subdivided groups showed three distinct chemical groupings with some overlap. The degree to which these groups detect comparable chemicals is shown by a Venn diagram (Figure 4). The blue circle represents detected chemicals in hashish resins from Al-Darb (group D), the green circle represents detected chemicals from Gizan (group G), and the yellow circle represents detected chemicals from Samtah (group S). There were 11 overlapping chemicals found in the hashish resin samples from Al-Darb, Gizan, and Samtah. Bisabolol, cannabichromene, cannabidiol, cannabigerol, cannabinol, caryophyllene, caryophyllene oxide, delta 8-tetrahydrocannabivarin, dronabinol, guaiene, and himachalane were the detected chemicals.

Only dronabinol and cannabidiol were associated with curated disorders in the CTD database, out of 11 common overlapping chemicals. Dronabinol and cannabidiol overlap 27 diseases, according to the CTD's 'Set Analyzer Query' tool. Among the "curated" mental disorders were seizures, schizophrenia, psychosis, cognitive disorder, ataxia, and Alzheimer's disease.

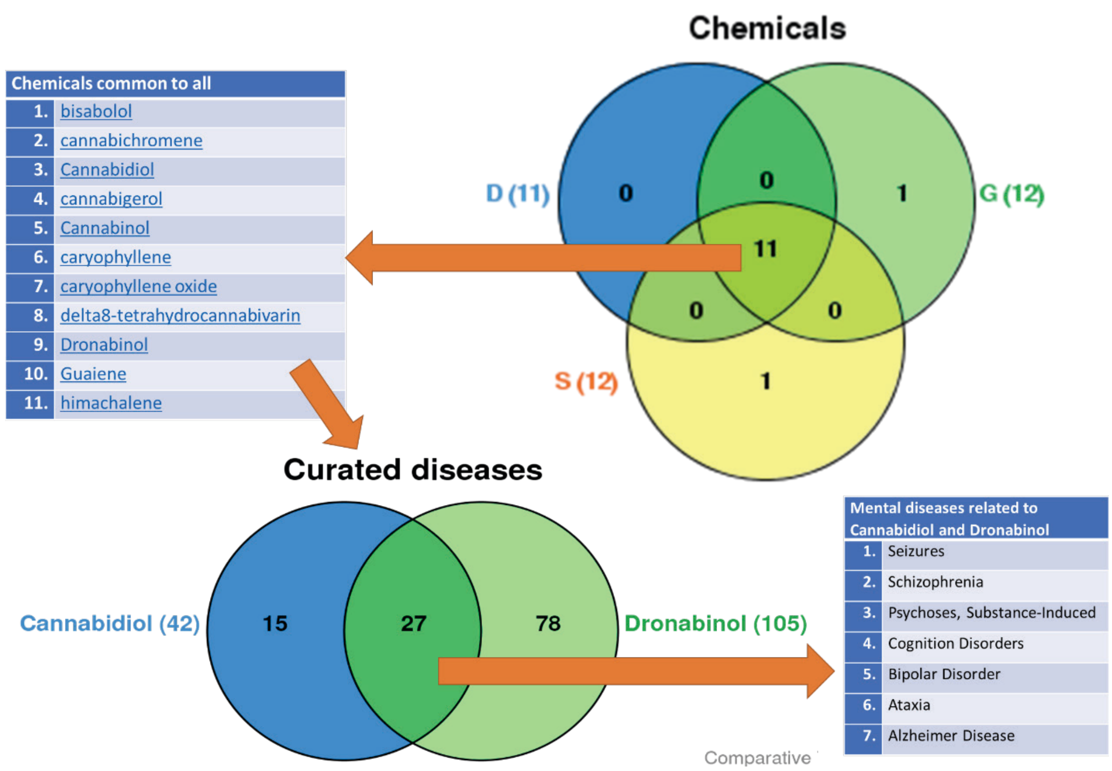

Figure 4- *Representative Venn diagrams for the integrated chemical composition profile of hashish seized from three different areas in Jazan region and its associated diseases using CTD database. The blue circle represents detected chemicals in hashish resins from Al-Darb (group D), the green circle represents detected chemicals from Gizan (group G), and the yellow circle represents detected chemicals from Samtah (group S).*

4. Discussion

According to the Global Burden of Disease Report [19], the number of fatalities from illicit drugs overdose, including cannabis, in Saudi Arabia was 570 deaths in 2012, which increased to 923 in 2019. Cannabis was the most commonly used illicit drug after amphetamines [20,21]. The present study aimed to collect retrospectively the data about forensic cases involving hashish-associated social crimes and fatalities, and also analyze the organic profile of seized hashish resins and identify the cases, risks and its possible role in social violence and death.

Schizophrenia, psychosis, and cognition disorder were the most commonly curated mental disorders linked with dronabinol and cannabidiol in the current study. In this respect, it has been shown that mental illnesses such as schizophrenia and depression are linked to an increased tendency to violence. Therefore, the relationship between hashish abuse and social violence cannot be ruled out. The current study also found that the percentage of crimes and fatal cases involving hashish alone were increased over the years. In addition, the homicidal intoxication was the most common manner of death among fatalities involving hashish alone in compared with fatalities involving hashish with other drugs. The relationship has been found between hashish abuse, homicide and suicide in several previously published studies [22-25]. In the Eastern region of Saudi Arabia, hashish abuse ranked the second illicit drugs among suicidal hanging in the period 2014 to 2019 [26].

The current study also found that the crimes involving hashish alone accounted for one third of all the crimes involving hashish, and this percentage increased over the time. Similarly, fatality involving hashish alone was dramatically increased from 0.0 (2019) to 11.0 (2020) and then to 40% (2021) of all fatality cases, respectively. Referring to the manner of death, homicidal was associated with two-third of fatal cases who tested positive only for hashish and approximately half of fatalities involved hasish with other drugs. Whereas, one-third of the total suicidal deaths were associated with hashish along with other drugs.

Our result implies that some of the organic profile components in hashish resin are responsible for majority of social violence in forensic cases in Jazan area. This is consistent with the findings of Grenyer, Solowij, and Barlow (1999), who found a relationship between hashish exposure and violent behavior [12]. Recent studies have reported that hashish abuse was associated with an increased risk of violence, psychosis, suicidal and homicidal ideations [27, 28]. In addition, besides dronabinol and cannabidiol, exposure to hashish principal component Δ-9-THC is associated with a risk of developing schizophrenia and psychotic behavior, and as a consequence violence may increase [29, 30]. However, further studies are required to investigate dose-dependent effect of hashish and establish a defined correlation between the Δ-9-THC levels and social violence.

The quantification results of THC in forensic cases show that urine average concentrations were closely similar in crimes and fatal cases. The postmortem blood average concentration of THC was 0.13 mg/L (median: 0.1). It was also detected in the brain, liver, kidney and stomach, and we found that the average concentrations of THC in the liver were the highest among postmortem tissues concentration, followed by stomach, kidney and brain. Therefore, liver tissue may be used as alternative to biological fluid postmortem samples. In addition to THC and other hashish metabolites, cannabidiol also can be used as evidence for hasish abuse in postmortem samples. According to Pettersen et al, cannabidiol (CBD) can be detected in various postmortem body matrices. Its concentration in pericardial fluid and cardiac blood similar to that of the peripheral blood. Moreover, its muscles concentration generally higher than those in the other postmortem matrices, whereas vitreous humor was not a suitable sample for detecting CBD [31].

Further study should be made to determine the violence effects for the exposure to hashish resin or their active components including dose-response study and explore the brain chemo-bioorganic signature in fatalities involving hashish alone. These will provide the professionals the necessary knowledge in the hashish resin exposure and their associated violence effects that help in decision making in clinical and forensic setting.

5. Conclusion

The present study raises awareness about the proportional increase in the percentages of social violence and forensic cases involving chronic use of hashish. Homicidal and suicidal cases were the most common manifestations of hashish addiction. More than one-third of the criminal cases were due to hashish. Amphetamine and ethanol are the most frequently used drugs in combination with hashish. The prolonged effect of hashish components, such as dronabinol and cannabidiol, on the mental health of drug addicts may be manifested in the form of schizophrenia, psychosis and cognitive problems. This study contributes to our understanding about a possible role of cannabis in social, suicidal and homicidal crimes. Moreover, our results highlight the presence of a potential correlation between various chemical components of hashish, social violence and other socio-psychological crimes.

Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval

This study has been reviewed and approved by Jazan Health Ethics Committee, Saudi Arabia (No. 2178).

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