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Comparison between pediatric and adult acute natural cannabinoids toxicity: A 5-year retrospective study with special consideration of acute synthetic cannabinoids toxicity

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ABSTRACT

Acute cannabinoids toxicity is an alarming toxicological problem. The current study aimed to compare children and adults with acute natural cannabinoids toxicity and highlight cases with acute synthetic cannabinoids (SCs) toxicity. This retrospective cross-sectional study was conducted on patients with acute cannabinoids toxicity admitted to Tanta University Poison Control Center from January 2019 to December 2023. Socio-demographic, toxicological, clinical, and laboratory data were retrieved from patients' medical records. Patients were divided into a pediatric group (≤ 18 years) and an adult group (> 18 years). Out of 106 patients, 68 were children and 38 were adults. Impaired consciousness level and bradypnea were more significantly reported in children ($P < 0.001$, 0.007, respectively). Low oxygen saturation, tachycardia, hypokalemia, and leukocytosis were more significantly reported in adults ($P < 0.001$, for each). Delay time from exposure to medical intervention and potassium level were significantly valid to predict complications in children (Adjusted odds ratio: 1.393 and 4.139, respectively). Delay time to medical intervention and oxygen saturation were significant risk factors for prolonged hospital stay in children (Adjusted odds ratio: 1.255 and 0.677, respectively). Acute SCs toxicity was observed only in four cases presented mainly with seizures, tachycardia, hypertension, tachypnea, and hypoxemia. It could be concluded that natural cannabinoids toxicity is more prevalent than SCs. Presentation of acute natural cannabinoids toxicity exhibits variations between children and adults. Delay time to medical intervention, as well as potassium and oxygen saturation levels are significant risk factors for complications and prolonged hospitalization in children.

1. Introduction

Over the last decades, substance abuse has emerged as a significant health issue that strongly affects all countries. As defined by the World Health Organization (WHO), substance abuse is the hazardous use of psychoactive substances, including alcohol and illicit drugs with substantial risk of morbidity and premature death [1].

As other countries, Egypt is witnessing increasing rates of substance abuse while the exact prevalence is unavailable, most probably due to substantial social stigma and underreporting [2]. Some reports highlight the magnitude of the problem; in 2016, about 6.8 % of Egyptians aged above 15 years were involved in substance abuse [3]. Furthermore, in 2022, the Egyptian Ministry of Social Solidarity estimated that about 5.9 % of the total population consumed illicit drugs [4].

Globally, cannabis ranks third among abused substances after alcohol and tobacco as it is widely cultivated and trafficked with an ancient history of both medicinal and recreational uses [5,6] . The annual prevalence rate of cannabis consumption has been estimated to

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be nearly 2.5 % of the global population [7]. In Egypt, different reports are available considering the prevalence of cannabis abuse. For example, it was reported that more than 9 % of Egyptian students are using bango and 3 % are depending on hashish [8].

Despite the fact that recreational cannabis use is known to be associated with a low risk of acute toxicity, recent reports indicate an increase in the potency of cannabis preparations, potentially leading to more visits to poison control centers due to accidental acute toxicity [9]. Furthermore, accidental ingestion of cannabis by children is also reported even in developed countries especially with legalization of medical and recreational marijuana [10]. Although it is an alarming toxicological problem, data regarding acute cannabis toxicity is still limited [11].

It is worth mentioning that the term cannabinoid refers to chemical substances that interact with cannabinoid receptors, producing effects similar to those of the Cannabis plant [12]. Depending on the source of production, cannabinoids are divided into endocannabinoids, phytocannabinoids and synthetic cannabinoids. The first group (endocannabinoids) is produced by mammalians while the second group (phytocannabinoids) is extracted from the cannabis plant and includes the most psychoactive Δ9-tetrahydrocannabinol (Δ9-THC) and non-psychoactive component cannabidiol. The third group involves a number of synthetic cannabinoids (SCs) which are sold for recreational use [13].

Toxicity from natural cannabinoids (marijuana) including hashish and bango can result from inhalation, smoking, or ingestion [14–16]. Manifestations are diverse depending on the patient's age, cannabis potency, route of exposure, and combination with other psychoactive substances [17].

Basic treatment of acute cannabis toxicity is mainly supportive to keep a patent airway with adequate ventilation and circulation. Children presented with apnea and risk of aspiration need to be intubated and mechanically ventilated. However, those who are presenting with lethargy, rapid electrolytes and arterial blood gases, as well as random blood sugar measurement is considered. For patients with mild toxicity, benzodiazepine may be enough to control anxiety and agitation [18].

Regarding SCs, they are designer drugs with variable structure and potencies that mimic the psychoactive properties of Δ9-THC. In Egypt, they are traded under different names including strox and voodoo [16]. In 2014, they were added to Schedule No. 1 of the Egyptian Drugs Act [19]. Synthetic cannabinoids acquired their popularity because they are easily manufactured, so they are more accessible at low prices compared to cannabis. Additionally, they are not detected by standard toxicology screening for natural cannabis [15].

Despite the cannabomimetic effects of SCs, their side effects cannot be expected and may be more serious than the natural cannabis [20]. Acute toxicity could be due to Δ9-THC and additives like anticholinergic agents and ketamine [21]. However, acute strox intoxication is manifested by visual and auditory hallucinations, fright, speech impairments, and paranoia leading to aggressive behavior [15,22]. It may also cause loss of concentration, delirium, vomiting, and fainting, as well as extreme fear of death and fatal convulsions [23]. Pupillary dilatation, tachycardia, flushed dry skin, and other anticholinergic toxidrome were also reported. In severe cases, lethal cardiovascular collapse and deep coma could occur [24]. Supportive and symptomatic care is the main line considered in the treatment of acute strox toxicity [25].

Considering that age could affect the characteristics of acute toxicity and the introduction of SCs into the market of substance abuse, this study aimed to compare clinical and laboratory findings of acute natural cannabinoids toxicity in the adults and pediatric group, together with highlighting cases presented with acute SCs toxicity.

2. Patients and methods

2.1. Study design and settings

The current retrospective cross-sectional study was conducted on all patients with acute cannabis or SCs toxicity who were admitted to Tanta University Poison Control Center (TUPCC) throughout five years from January 2019 to December 2023.

2.2. Ethical considerations

The current study was approved by our institution's ethics committee (approval code: 36264PR708/5/24) and followed the declaration of Helsinki. To secure confidentiality, patients' data were coded for anonymous statistical analysis. The requirement for written informed consent was waived due to the retrospective nature of the study.

2.3. Eligibility criteria

All patients, males and females, with acute cannabis or SCs toxicity were included in the study. Diagnosis was based on definite history as reported from the patients or witnesses besides clinical assessment of the attending physician and urine screening test [26]. On the other hand, patients with known medical illnesses such as cardiovascular or neuropsychological diseases, renal or hepatic impairment, respiratory disorders such as asthma or chronic obstructive pulmonary disorders, and diabetes were excluded. Additionally, the current study excluded patients with mixed intoxication or those who received medical intervention before admission. Pregnant and lactating females were also excluded.

2.4. Data collection

The following variables were extracted from the medical records of each patient:

1. Socio-demographics: age, sex, and residence.
2. History of pre-existing medical disorders.
3. Toxicological data: name of substance, route, manner, and place of exposure, and delay time from exposure to medical intervention.
4. Findings of clinical examination:

- Vital signs: systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (PR), respiratory rate (RR), temperature, and oxygen (O_2) saturation.
- Level of consciousness using the Glasgow Coma Scale (GCS).
- Systemic examination: head & neck, neurological, chest, abdomen, skin, and extremities examination
- Electrocardiographic (ECG) findings

1. Results of laboratory investigations:

- Arterial blood gases (ABG): pH, partial arterial carbon dioxide pressure ($PaCO_2$), partial arterial oxygen pressure (PaO_2).
- Serum electrolytes: serum sodium (Na) and potassium (K) levels
- Serum random blood glucose level
- Glucose potassium (Glu/K) ratio was obtained by dividing serum random blood glucose level over serum potassium level
- Renal functions: blood urea nitrogen and serum creatinine.
- Liver enzymes: aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

2. Outcome measures: mortality, intensive care unit (ICU) admission, and duration of hospital stay.

Patients were treated according to guidelines including emergency

and supportive measures if indicated. Patients were divided according to their age into two groups: the pediatric group included patients whose age was 18 years or less and the adult group where the age of patients was above 18 years.

2.5. Statistical analysis

All data were tabulated and analyzed by the statistical package for the social sciences software program, IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, N.Y., USA). Categorical data were presented as numbers and percentages, while numerical data were first tested for normality by the Shapiro-Wilk test. Normally distributed numerical data were expressed as the mean ± standard deviation, while skewed numerical data were represented as median and interquartile range (IQR: 25th −75th percentiles). Comparisons between the studied groups were done by applying Pearson's Chi-Square test for categorical data. When more than 20 % of cells have expected count of less than 5 Fisher's Exact and Fisher-Freeman-Halton Exact tests was adopted instead of Pearson's Chi-Square test. Normally distributed numerical data were compared by the Independent Samples T-test. Alternatively, Mann-Whitney *U* test was performed to compare skewed data. For determining risk factors of complicated outcome and prolonged hospital stay among the studied children group, univariable and multivariable logistic regression analyses were performed. As regards multivariable logistic regression, all variables that showed significant results in the bivariate analysis were selected as covariates. Results were presented as adjusted odds ratio (AOR) and 95 % confidence interval. $P < 0.05$ was considered statistically significant.

3. Results

A total of 165 patients with acute natural cannabinoids poisoning were admitted to TUPCC from the start of January 2019 till the end of December 2023. Fifty-nine patients did not meet the inclusion criteria where 22 patients had incomplete medical files, 20 patients had mixed drug ingestion, 15 patients had systemic comorbidities, and two patients had previous medical treatment before admission to the hospital. The current study enrolled 106 patients with acute natural cannabinoids toxicity who met the eligibility criteria during the study duration. Patients ranged in age from 9 months to 45 years. The pediatric group included 68 participants (64.2 %) with a median age of 1.5 years (IQR 1.5–2.5). The adult group included 38 participants (35.8 %) with a median age of 33 years (IQR 22–35) (Fig. 1).

Table 1 provides a summarized overview of socio-demographics and exposure characteristics of the studied patients. It could be noticed that the majority of included patients were males and from urban areas (76.4 % and 69.8 %, respectively). Although males significantly contributed to both pediatric and adult groups (67.6 % and 92.1 %, respectively), they had significantly higher percentages in the adult group compared to the pediatric group. Additionally, females

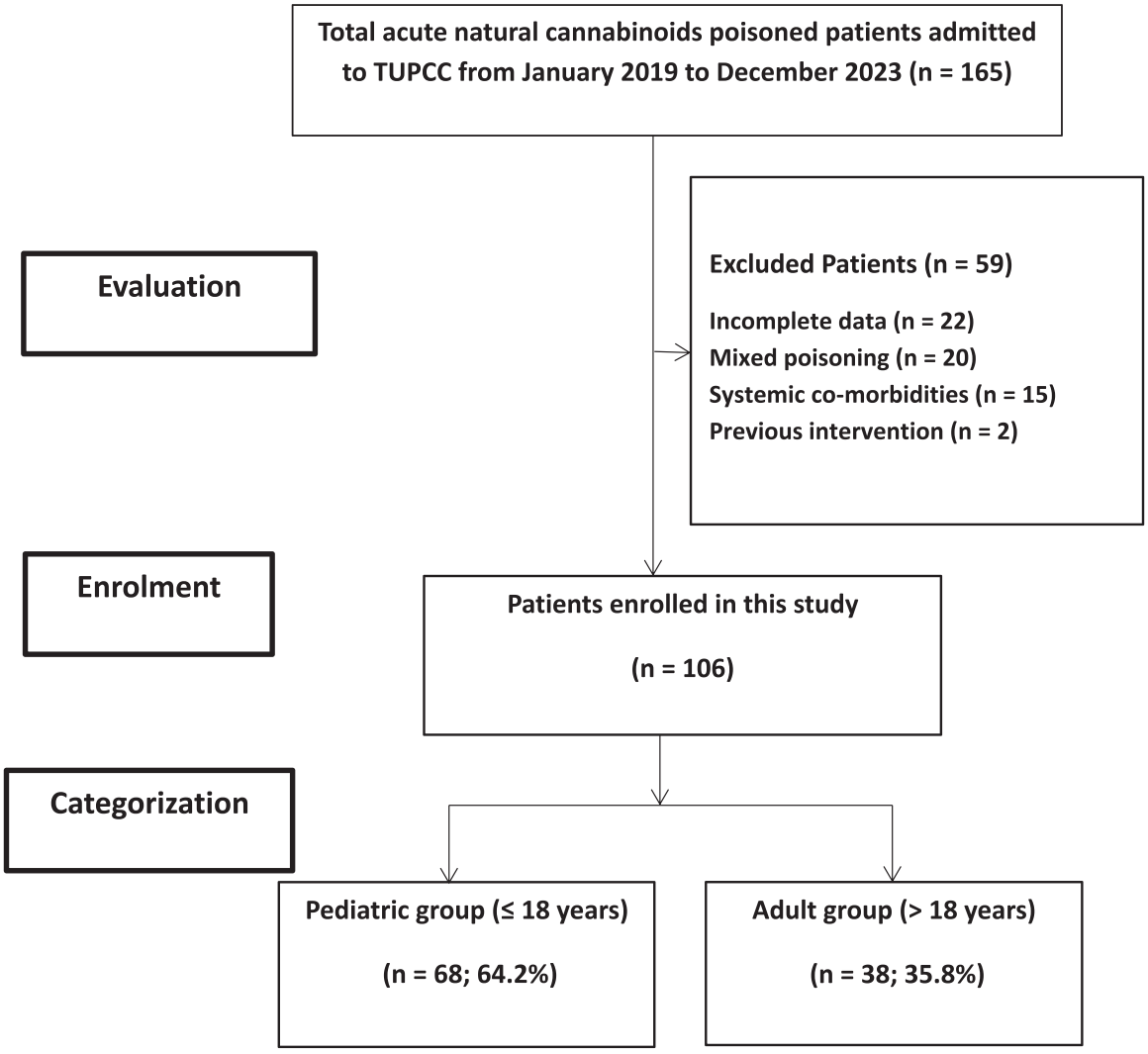

Fig. 1. Flowchart of the recruited acute natural cannabinoids poisoned patients.

Table 1
Socio-demographics and exposure characteristics of acute natural cannabinoids poisoned patients (n = 106).

Variables		Groups				Total n = 106 (100 %)		Chi-Square test
		Children ≤ 18 years- old n = 68 (64.2 %)		Adults > 18 years- old n = 38 (35.8 %)				
		N	%	N	%	n	%	P-Value
Gender	**Male**	46	67.6 %	35	92.1 %	81	76.4 %	0.004*
	Female	22	32.4 %	3	7.9 %	25	23.6 %	
Residence	**Urban**	42	61.8 %	32	84.2 %	74	69.8 %	0.016*
	Rural	26	38.2 %	6	15.8 %	32	30.2 %	
Place of exposure	**Indoors**	64	94.1 %	28	73.7 %	92	86.8 %	0.003*
	Outdoors	4	5.9 %	10	26.3 %	14	13.2 %	
Route	**Ingestion**	66	97.1 %	6	15.8 %	72	67.9 %	< 0.001*
	Inhalation	2	2.9 %	32	84.2 %	34	32.1 %	
Intent of exposure	**Unintentional (accidental)**	66	97.1 %	0	0.0 %	66	62.3 %	< 0.001*
	Intentional (abuse)	2	2.9 %	38	100.0 %	40	37.7 %	
Delay time	**≤ 2 hours**	34	50.0 %	22	57.9 %	56	52.8 %	0.435
	> 2 hours	34	50.0 %	16	42.1 %	50	47.2 %	

* Significant at P < 0.05; n: number

significantly contributed to the pediatric group (32.4 %) than the adult group (7.9 %) (P = 0.016). Patients from urban areas had a significantly higher percentage in both groups and they more significantly contributed to the adult group in comparison with the pediatric group (84.2 % and 61.8 %, respectively) whereas patients from rural areas had a significantly higher percentage in the pediatric group than the adult group (P = 0.016). Indoor exposure was reported in 86.8 % of the cases and it was significantly higher in both groups compared to outdoor exposure (P = 0.003). Ingestion was the main route of exposure in the pediatric group (97.1 %) and it was more significantly reported compared to the adult group (15.8 %). On the other hand, inhalation was significantly observed in the adult group rather than the pediatric group (84.2 % and 2.9 %, respectively). Unintentional (accidental) poisoning was reported in 97.1 % of the pediatric group, while all adults were cannabis abusers with significant difference between the two groups (P < 0.001). No significant difference was observed between the two groups regarding the delay time to medical intervention.

Initial clinical assessment of the studied groups is demonstrated in Table 2. Regarding the level of consciousness, the majority of adult patients were fully conscious (97.4 %), meanwhile, 55.9 % of children were conscious and the remaining 44.1 % were unconscious where mild, moderate, and severe unconsciousness were reported in 6, 12, and 12

Table 2
Initial clinical assessment of acute natural cannabinoid poisoned patients (n = 106).

Variables		Groups				Total n = 106 (100 %)		Chi-Square and Exact tests
		Children ≤ 18 years- old n = 68 (64.2 %)		Adults > 18 years- old n = 38 (35.8 %)				
		n	%	N	%	n	%	P-Value
Level of consciousness	**Conscious**	37	54.4 %	37	97.4 %	74	69.8 %	< 0.001*
	Mild unconsciousness	7	10.3 %	1	2.6 %	8	7.5 %	
	Moderate unconsciousness	12	17.6 %	0	0.0 %	12	11.3 %	
	Severe Unconsciousness	12	17.6 %	0	0.0 %	12	11.3 %	
Oxygen saturation	**Normal**	58	85.3 %	14	36.8 %	72	67.9 %	< 0.001*
	Low (< 95 %)	10	14.7 %	24	63.2 %	34	32.1 %	
Pulse rate	**Normal**	38	55.9 %	0	0.0 %	38	35.8 %	< 0.001*
	Tachycardia	28	41.2 %	38	100.0 %	66	62.3 %	
	Bradycardia	2	2.9 %	0	0.0 %	2	1.9 %	
Blood pressure	**Normal**	56	82.4 %	30	78.9 %	86	81.1 %	0.960
	Hypertension	10	14.7 %	8	21.1 %	18	17.0 %	
	Hypotension	2	2.9 %	0	0.0 %	2	1.9 %	
Respiratory rate	**Normal**	47	69.1 %	32	84.2 %	79	74.5 %	0.007*
	Tachypnea	2	2.9 %	6	15.8 %	8	7.5 %	
	Bradypnea	19	27.9 %	0	0.0 %	19	17.9 %	
Temperature	**Normal**	60	88.2 %	30	78.9 %	90	84.9 %	0.295
	Hyperthermia	6	8.8 %	6	15.8 %	12	11.3 %	
	Hypothermia	2	2.9 %	2	5.3 %	4	3.8 %	
Pupil size	**Normal**	57	83.8 %	37	97.4 %	94	88.7 %	0.120
	Mydriasis	4	5.9 %	0	0.0 %	4	3.8 %	
	Miosis	7	10.3 %	1	2.6 %	8	7.5 %	
Vomiting	**Yes**	8	11.8 %	5	13.2 %	13	12.3 %	0.999
	No	60	88.2 %	33	86.8 %	93	87.7 %	
ECG	**Normal**	60	88.2 %	31	81.6 %	91	85.8 %	0.346
	Abnormal	8	11.8 %	7	18.4 %	15	14.2 %	
ECG abnormalities	**Sinus tachycardia**	6	8.8 %	5	13.2 %	11	10.4 %	0.518
	Supraventricular tachycardia	2	2.9 %	0	0.0 %	2	1.9 %	0.536
	Depressed ST segment	0	0.0 %	2	5.3 %	2	1.9 %	0.126

* Significant at P < 0.05; n: number; ECG: electrocardiography

patients, respectively. Low O_2 saturation was detected in 32.1 % of the participants representing 34 patients; of them 24 were adults and 10 belonged to the pediatric group. For PR, 55.9 %, 41.2 %, and 2.9 % of the pediatric group had normal pulse rate, tachycardia, and bradycardia, respectively while all adult patients had tachycardia. Most of the participants had normal blood pressure (81.1 %) while hypertension and hypotension were reported in 17 % and 1.9 %, respectively. Normal RR, tachypnea, and bradypnea were observed in 69.1 %, 2.9 %, and 27.9 % of the pediatric group and in 84.2 %, 15.8 %, and 0 % of the adults, respectively. Regarding body temperature, normal temperature was the most prominent and found in 84.9 % of the participants. The majority of patients (94 patients; 88.7 %) had normal pupil size and vomiting was reported in 12.3 % of the participants. Abnormal ECG findings were detected in only 15 patients representing 14.2 % of the enrolled participants. Significant differences were observed between children and adults regarding level of consciousness and O_2 saturation, as well as the distribution of both pulse and respiratory rates.

Table 3 shows the results of laboratory investigations of the studied patients. The mean value of serum K level was significantly lower and the Glu/K ratio was significantly higher among the adults compared to the pediatric group ($P < 0.001$ for each). Furthermore, leukocytosis was more significantly reported in the adult group ($P < 0.001$). However, no significant difference was observed between the two groups regarding ABG status, the platelets count, as well as, serum sodium and random blood sugar levels. Serum creatinine, blood urea nitrogen, and liver enzymes were within the normal values.

Table 4 depicts the outcome of the studied groups. All adult patients improved while 6 children showed complications in the form of dysrhythmia and pneumonia (4 and 2 patients, respectively). Furthermore, the pediatric group exhibited a significantly prolonged length of hospital stay compared to the adults ($P = 0.013$). Mortality and ICU admission were not reported among the studied cases.

As revealed in Table 5, the delay time to medical intervention significantly contributed to the prediction of complicated outcome among the studied pediatric group ($P = 0.018$). For every hour increase in the delay time, there was 1.393 times increased risk of complicated outcome (AOR: 1.393). Regarding serum K level, each one-unit increase in the K level by mmol/L was significantly associated with 4.139 times increased risk of complicated outcome ($P = 0.041$, AOR: 4.139). The overall model showed an accuracy of 94.1 % for the prediction of complicated outcome.

Using multivariate logistic regression, delay time to medical intervention and O_2 saturation were significantly valid to predict prolonged length of hospital stay (1–2 days) in children ($P = 0.036$ and $= 0.015$, respectively). For every hour increase in the delay time, there was a 1.255-fold increase in the risk of prolonged hospital stay (AOR: 1.255). Regarding O_2 saturation, the negative beta coefficient (- 0.391) indicates the inverse relationship between O_2 saturation and hospital stay. This relationship was further supported by the AOR of 0.677, which indicated that for every one-unit decrease in O_2 saturation (%), there was a 0.677-fold increase in the risk of prolonged hospital stay. Table 6 illustrates that the overall model showed an accuracy of 88.2 % for the prediction of prolonged hospital stay.

During the study duration, our center managed 4 cases of acute SCs toxicity (strox), all occurring in 2020; no cases were registered prior to or after this year. Because of their small number, it was not possible to be entered in the overall case statistics. This summary presents data collected from these four cases:

All cases were adult males belonged to urban areas with indoor intentional inhalation exposure. Delay time from exposure to medical intervention ranged from 2 to 4 hours after smoking 2–3 of strox usually during the night on the street. Three patients presented with seizures and one patient exhibited hallucination. For vital signs, tachycardia and hypertension were observed in all cases with the exception of one case that was normotensive. Tachypnea was documented in all cases except one patient had a normal respiratory rate. Two cases had a normal body temperature while hyperthermia was observed in two cases. Oxygen saturation was below the normal level in all cases. All cases had leukocytosis, metabolic acidosis, hypokalemia, hyperglycemia, and elevated creatinine. The hospital stay ranged from 21 to 30 hours.

4. Discussion

Cannabinoids are a distinct group of chemicals that act as agonists on cannabinoid receptors and contain Δ9-THC. Besides, endogenous cannabinoids that originated within the body, natural cannabinoids are plant-derived from Sativa and Indica species of Cannabis while SCs are artificially synthesized [27,28]. Because of the high prevalence of the cannabis use, it has a significant impact on the public health with a wide range of acute toxicity manifestations [29]. However, not much data is

Table 3
Comparison of the laboratory investigations between the studied groups of acute natural cannabinoids toxicity (n = 106).

Variables		Groups				Total n = 106 (100 %)		Chi-Square and Exact tests
		Children ≤ 18 years- old n = 68 (64.2 %)		Adults > 18 years- old n = 38 (35.8 %)				
		n	%	n	%	n	%	P-Value
Acid-base status	**Normal**	50	73.5 %	34	89.5 %	84	79.2 %	0.180
	Respiratory alkalosis	12	17.6 %	4	10.5 %	16	15.1 %	
	Metabolic acidosis	4	5.9 %	0	0.0 %	4	3.8 %	
	Respiratory acidosis	2	2.9 %	0	0.0 %	2	1.9 %	
Serum sodium level (mmol/L)	**Mean ± SD**	138.8 ± 6.2		140.6 ± 4.0		139.5 ± 5.5		0.080
Serum potassium levels (mmol/L)	**Mean ± SD**	4.3 ± 0.7		3.1 ± 0.1		3.9 ± 0.8		< 0.001*
Random blood glucose levels (mg/dL)	**Median [IQR]**	100.0 [91.0–114.0]		110.0 [85.0–150.0]		100.0 [90.0–124.0]		0.384
Serum Glu/K ratio	**Mean ± SD**	24.98 ± 6.4		39.92 ± 14.4		30.34 ± 12.3		< 0.001*
Serum creatinine	**Normal**	68	100 %	38	100 %	106	100 %	NA
Blood urea nitrogen	**Normal**	68	100 %	38	100 %	106	100 %	NA
AST	**Normal**	68	100 %	38	100 %	106	100 %	NA
ALT	**Normal**	68	100 %	38	100 %	106	100 %	NA
White blood cells count	**Normal**	62	91.2 %	0	0.0 %	62	58.5 %	< 0.001*
	Leukocytosis	6	8.8 %	38	100.0 %	44	41.5 %	
Platelets count	**Normal**	62	91.2 %	38	100.0 %	100	94.3 %	0.086
	Thrombocytosis	6	8.8 %	0	0.0 %	6	5.7 %	

* Significant at $P < 0.05$; SD: standard deviation; Glu/K ratio: glucose potassium ratio; NA: Not applicable; AST: aspartate aminotransferase; ALT: alanine aminotransferase

Table 4
Evaluation of the outcome of the studied patients with acute natural cannabinoids toxicity (n = 106).

Variables		Groups				Total n = 106 (100 %)		Chi-Square and Exact tests
		Children ≤ 18 years- old n = 68 (64.2 %)		Adults > 18 years- old n = 38 (35.8 %)				
		n	%	N	%	N	%	P-Value
Outcome	**Improved**	62	91.2 %	38	100.0 %	100	94.3 %	0.086
	Complicated	6	8.8 %	0	0.0 %	6	5.7 %	
Complications	**Dysrrhythmia**	4	5.9 %	0	0.0 %	4	3.8 %	0.294
	Pneumonia	2	2.9 %	0	0.0 %	2	1.9 %	0.536
Length of hospital stay	**< 1 day**	58	85.3 %	38	100.0 %	96	90.6 %	0.013*
	1–2 day	10	14.7 %	0	0.0 %	10	9.4 %	

* Significant at P < 0.05.

Table 5
Multivariable logistic regression analysis for determining risk factors of complicated outcome among the studied children group.

Variable	Beta coefficient	AOR	95 % CI	P-Value	Accuracy	P-value Model
Delay time (hours)	0.331	1.393	1.058–1.833	0.018*	94.1 %	0.006*
Serum potassium level	1.420	4.139	1.060–16.152	0.041*		
Constant	−10.433	0.000		0.000*		

* Significant at P < 0.05; AOR: adjusted odds ratio; CI: confidence interval

Table 6
Multivariable logistic regression analysis for determining risk factors of prolonged length of hospital stay (1–2 days) among the studied children group.

Variable	Beta coefficient	AOR	95 % CI	P-Value	Accuracy	P-value Model
Delay time (hours)	0.227	1.255	1.015–1.551	0.036*	88.2 %	< 0.001*
Oxygen saturation	- 0.391	0.677	0.494–0.926	0.015*		
Constant	34.901	1436.0		0.023*		

* Significant at P < 0.05; AOR: adjusted odds ratio; CI: confidence interval

available about the difference between adults and children regarding the clinical manifestations and laboratory investigations of acute natural cannabinoids toxicity. Hence, the current study aimed to compare the clinical and laboratory parameters of acute natural cannabinoids toxicity between adults and children with description of cases presented with acute SCs toxicity.

In the current study, children accounted for more than half of the included patients (64.2 %). Literature revealed inconsistent results; according to Noble et al. [26] and Mohammed et al. [17], 44.7 % and 92.5 % of their patients were below 18 years. Differences may be related to socio-demographic characteristics and eligibility criteria. However, Sánchez Artiles et al. [30] and Kelly and Nappe [31] concluded frequent cannabis toxicity in the pediatric population and adolescents.

The present study revealed that males (92.1 %) contributed more significantly to the adult group than females (7.9 %). This finding supports previous reports that men have higher rates and frequencies of cannabis use [32,33]. Similarly, males outnumbered females in the pediatric group with a significant difference. Young boys tend to be more courageous and less obedient, so they are at a greater risk for accidental poisoning than girls [34]. Furthermore, male adolescents are more frequent to display cannabis use than female adolescents [35].

Regarding residence, patients from urban areas were more significantly presented than those from rural areas. In accordance, Coughlin et al. [36] reported that cannabis use was more predominant in urban areas. It could be explained by the increased accessibility of all cannabis products which are designed to be given by various routes of administration like edible and vaped together with customs and traditions of rural society as strong social and family bonds discourage substance abuse in rural areas [16].

Safe places like homes and private places are the most preferred for abusers to consume substances. Furthermore, the conservative nature of Egyptian society discourages outdoor drug intake [16]. This could justify the significant indoor exposure reported in this study. This is also enforced by Egyptian law which has forbidden the use of cannabis since 1925 and any custom will be considered an illegal use [37] The same result was recorded by Cheng et al. [38]. In contrast, Kaur et al. [39] found that 86.5 % of subjects of Punjab in India were using substance in open areas such as agricultural fields and old buildings. Indoor exposure (94.1 %) was significantly higher in the pediatric group than outdoor exposure (5.9 %). Similarly, Tweet et al. [40] observed that 97.7 % of cannabis toxicity among children below 6 years occurred in a residential setting. Children usually take cannabis accidentally at the same residence as their families.

The effect of cannabis is substantially delayed with oral ingestion. Additionally, oral forms are easily ingested without any pleasure during preparation [41]. Accordingly, the current study revealed that inhalation was more significantly reported in the adult group. In line with our findings, Noble et al. [26] concluded that intentional inhalation of cannabis was the most common in adults. In contrast, unintentional ingestion (97.1 %) was significantly higher in the pediatric group. In the same line, Mohammed et al. [17] reported that all preschool children accidentally ingested cannabis products. Packaging of cannabis preparations usually simulates sweets, beside hand to mouth habits predispose to accidental ingestion of cannabis in children.

No significant difference was observed between the two groups regarding the delay time to medical intervention; easy transportation to our center and its situation in Tanta city allow the rapidity of seeking medical care by patients from Gharbia and the nearby governorates.

The active ingredient of natural cannabinoids, Δ9-THC, has the ability to bind to different receptors and shows high selectivity for

Cannabinoid 1 (CB1) and 2 (CB2). Specifically, CB1 receptors are mainly distributed in the cardiovascular system including peripheral vasculature, as well as the central nervous system [42]. This could explain distinct neurological and cardiovascular manifestations detected in this study. However, differences were observed between the enrolled adults and children.

Regarding the level of consciousness, statistical analysis of the current study revealed that it significantly differed in the pediatric group compared to the adult participants. Noticeably, immaturity of brain synapses, as well as the ingested dose of cannabis per kilogram body weight could substantially affect the toxicity in young children. Disturbed level of consciousness up to coma is commonly observed in acute cannabis-poisoned children whose age is below 6 years [11]. In this context, Carstairs et al. [43] reported a case of a 14-month-old comatose child after hashish ingestion did not regain consciousness for more than 48 hours.

In the current study, low O_2 saturation below 95 % was significantly observed in the adult group. Central nervous system and respiratory depression may be predisposing factors [44]. Furthermore, cannabis smoke irritates the bronchial tree interfering with sufficient air entry [45].

Although tachycardia was observed in all adult patients, it was reported in 41.2 % of the pediatric group with an observed significant difference between the two groups. Furthermore, hypertension was detected in 14.7 % and 21.1 % of the pediatric and adult patients, respectively. In acute cannabis toxicity, THC is expected to trigger dose-dependent hypertension and tachycardia [42]. On the other hand, bradycardia is an occasional finding of acute cannabis toxicity and seems to occur due to dose-dependent inhibition of central sympathetic tone [46]. This could explain the finding of the current study that bradycardia was not observed in adult patients and only 2.9 % of the pediatric group (2 patients) had bradycardia.

It is noteworthy that the cardiovascular effects of cannabis are substantially linked to its biphasic effect on the autonomic nervous system. The low-moderate doses are found to stimulate and inhibit sympathetic and parasympathetic activity, respectively. As a result, tachycardia, hypertension, and increased cardiac output occur. Conversely, at higher doses, sympathetic activity is inhibited so bradycardia and hypotension predominate [47].

It was observed that bradypnea was significantly reported in the pediatric group; this could be explained by the significantly impaired consciousness level in children. Meanwhile, tachypnea was reported in 7.5 % of the participants which may be related to the severity of cannabis toxicity as documented by Mohammed et al. [17] in their study on preschool children. They also reported that most of the patients (68 %) had normal body temperature, while a minor percentage had hyperthermia. They attributed hyperthermia to the cannabis anti-cholinergic effect as heat dissipation is reduced by impaired sweating. In the current study, 84.9 %, 11.3 %, and 3.8 % had normal body temperature, hyperthermia, and hypothermia, respectively. Hypothermia may be attributed to CNS depression.

The effect of cannabis on pupil size is controversial [48]. In the current study, mydriasis was observed in 5.9 % of the pediatric group while it was not detected in adults. According to Mattimoe et al. [11], children below the age of 6 years are more commonly presenting with altered sensorium with dilated sluggish pupils compared to elder patients. In this context, another study included children less than 6 years who ingested cannabis products revealed that 11.4 %, 1.4 %, 2.5 %, 0.9 %, 5.9 %, and 0.5 % of them had tachycardia, bradycardia, hypotension, hypertension, mydriasis, and miosis, respectively, while the highest percentage (70 %) was for CNS depression [40].

In the present study, vomiting was reported in 12.3 % of the studied patients. In this context, Elhelaly and Salah Eldin [49] documented vomiting in 7 % of their studied acute natural cannabinoids poisoned patients. Vomiting may be caused by central or peripheral mechanisms. Activation of CB1 receptors reduces gastric motility and delays gastric emptying with subsequent emesis [50]. Furthermore, cannabinoids receptors are numerous in the gastrointestinal tract and their stimulation, can lead to the process of vomiting [51].

Transient ECG abnormalities are among the cardiovascular effects of cannabis. Sinus tachycardia was detected in 10.4 % of the studied patients, while supraventricular tachycardia and depressed ST segment were equally distributed (1.9 % for each). Mugnai et al. [47] reported a case of cannabis smoking presented with sinus tachycardia and negative T waves. They considered sympathetic activation and increased oxygen demand due to tachycardia and hypertension with decreased oxygen supply as risk factors for ECG changes.

In the current study, 73.5 % of the pediatric group and 89.5 % of the adult group had normal ABG (79.2 %) with no significant difference between the two groups. In partial agreement, Mohammed et al. [17] reported that 59 % of preschool children had normal ABG however they recorded a significant association between abnormal ABG findings and the severity of poisoning.

The current study revealed no significant difference between the two groups regarding serum Na level. However, Bui et al. [52] discussed lower serum Na in chronic marijuana users. Cannabis has been concerned with modifying the membrane fluidity and also bound directly to Na channels which could be the possible mechanism for hyponatremia [53]. On the other hand, serum K level was significantly lower in the adult group. According to Singh et al. [54], cannabis modulates K receptors and inhibits adenylate cyclase. Furthermore, Hermanns-Clausen et al. [55] explained K loss through the kidneys or excessive diarrhea, K shifts into cells, and binge-eating.

The current study revealed no significant difference between the children group and the adult group regarding random blood sugar level. Considering the significantly lower K level in the adult group, the Glu/K ratio was significantly higher in the adult group. Glucose/potassium ratio has materialized as a biomarker in numerous pathophysiological disorders [56]. In the toxicological field, it could be used as a simple tool to predict the severity of many acute poisoning. Elmorsy et al. [57] concluded that a high Glu/K ratio could predict the severity of acute theophylline toxicity. Furthermore, Sharif and Fayed [58] recommended Glu/K ratio for early prediction of intermediate syndrome following acute anticholinesterase poisoning.

In agreement with Elhelaly and Salah Eldin [49], we found that blood urea nitrogen and serum creatinine, as well as liver enzymes were within the normal values. Furthermore, it was observed that leukocytosis was more significantly prominent among the adults. It could be explained according to Rodriguez-Olaverri et al. [59] who stated that leukocytosis can be related to the heavy marijuana inhalation; marijuana smoke is a pro-inflammatory chemical which could trigger systemic inflammation generating leukocytosis.

Cannabis toxicity in children seems to be more concerning. The relatively small body weight of the children in relation to the ingested amount of cannabis may predispose to the development of complications. As revealed in the current study that 8.8 % of the pediatric group developed complications while none of the adult patients had complications. Furthermore, impaired consciousness level could predispose to aspiration and subsequently contributed to pneumonia developed among the pediatric group. As recommended by Wong et al. [18], cannabis intoxication should be suspected in afebrile children who had no prior medical history and presented with neurological impairment without focal neurological signs.

Treatment of cannabis toxicity depends mainly on symptomatic and supportive care. Accordingly, most adult patients improve spontaneously and require only observation and limited interventions. However, admission is usually not required. On the other hand, pediatric patients may require longer observation and support, as well as the involvement of social services to assure safety in the home [42]. This could justify the significant difference between the pediatric group and the adult patients regarding the duration of the hospital stay. Substantially, the development of complications among the pediatric group could also explain the

significantly prolonged hospital stay in children.

Complications and prolonged hospital stay were recorded in the pediatric group; accordingly, multivariate logistic regression was applied to identify risk factors. Delay time and hyperkalemia were significantly contributed to the prediction of the development of complications while delay time and low O_2 saturation were significant predictors for prolonged hospital stay. Similarly, Abdelkader et al. [60] found significant association between the pre-hospitalization period and development of complications in pediatric patients presented with acute poisoning. Additionally, Sam et al. [61] recognized pre-hospitalization period as a significant predictive parameter for the severity of poisoning. Prolonged pre-hospitalization period predisposed to the development of complications and so prolonged hospital stay. Timely supportive measures and good oxygenation will eliminate hypoxia and reduce morbidity and mortality rates [62].

As a major intracellular cation, K plays a significant role in maintaining normal heart functions. Elevated extracellular K (hyperkalemia) could lower the resting cardiac membrane potential leading to life-threatening conduction blocks and tachyarrhythmias or bradyarrhythmia [63,64].

Although we reported only four cases of acute strox intoxication, Hashem et al. [65] enrolled 448 patients presented with acute SCs poisoning of them 325 were strox poisoning in Poison Control Center of Ain Shams University hospitals in Egypt from January 2018 to June 2019. Discrepancies in the number of presenting cases may be related to regional availability which could affect the pattern of substance use, the practice of reporting and seeking medical help, especially for mild cases and differences in the eligibility criteria. Furthermore, Slima and Azab [16] observed a declining rate of SCs presentation to Menoufia poisoning and dependence control center in 2020 and following years. They attributed their findings to the significant adverse effects of SCs.

However, the clinical presentations of patients included by Hashem et al. [65] were more or less similar to ours. They reported metabolic disturbance as the most predominant findings followed by gastrointestinal manifestations (epigastric pain and vomiting) and neurological manifestations (confusion, hallucination, agitation, generalized convulsion, and deep coma). They also observed respiratory insufficiency and cardiac dysrhythmia. Adverse effects of SCs are related to their strong affinity to cannabinoid receptors, as well as inclusion of some additives like atropine, ketamine, and xylene beside other unidentified mind-altering agents [26,15,24].

4.1. Strengths and limitations

The current study addressed the prevalence of cannabinoids toxicity both natural and synthetic over a period of five years. Furthermore, the study highlighted the significant difference between acute pediatric and adult natural cannabinoids toxicity regarding socio-demographics, toxicological characteristics, and clinical manifestations, as well as laboratory parameters. To the best of the authors' knowledge, this is the first study to explore risk factors for development of complications and prolonged hospital stay in children acutely intoxicated with natural cannabinoids; the identified risk factors are simple and easily obtained. The main limitations of this study were its uni-centered and retrospective nature. Furthermore, while we acknowledge that adolescents whose ages range between 13 and 18 years may exhibit distinct physiological and toxicological responses compared to younger children who are less than 13 years old, our study was limited by a small sample size, with only two patients in the 13–18 age range. Due to this constraint, we opted to maintain a unified category for pediatric patients under 18 years of age to enhance statistical power and validity of the results. Besides, synthetic cannabinoids were not detected in standard urine tests. Therefore, further prospective multicenter studies including children and adolescents are recommended to evaluate the results of the current work.

5. Conclusion

Based on previous findings, it could be concluded that acute natural cannabinoids toxicity is more prevalent than synthetic cannabinoids. Furthermore, ingestion was the most common route of exposure among children while inhalation was the main route of poisoning in adults. Children with acute natural cannabinoids toxicity are commonly presented with impaired consciousness level and bradypnea while tachycardia and hypokalemia are more common in the adult group. Children with acute natural cannabinoids toxicity are more liable to develop complications compared to adults. In the pediatric group, prolonged delay time, and hyperkalemia could be determined as risk factors for complicated outcomes while delay time together with low O_2 saturation are associated with prolonged hospital stay.

Recommendations:

- More awareness should be raised about the serious health problems related to natural and synthetic cannabinoids through wide-scale educational programs.
- Physicians should stratify children presented with acute natural cannabinoids toxicity for complications and prolonged hospital stay using delay time and potassium and oxygen saturation levels.
- Physicians must train to deal professionally with acute intoxicated patients with acute natural and synthetic cannabis.
- Modification of the law is essential to include all substances that have cannabis-like action.
- Further studies are needed to clarify the effects of synthetic cannabinoid to identify their harmful effects.

CRediT authorship contribution statement

Ghonem Mona M.: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Elmansy Alshaimma Mahmoud:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Hodeib Aliaa A.:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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