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Captagon: A comprehensive bibliometric analysis (1962–2024) of its global impact, health and mortality risks☆

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ABSTRACT

Captagon is a synthetic stimulant combining amphetamine and theophylline. Initially introduced in 1961 as a treatment for hyperactivity, depression, and narcolepsy, Captagon was later classified as a Schedule 1 controlled substance due to its addictive and hallucinogenic properties. Despite its global prohibition in 1986, the trade of counterfeit products is widespread, especially in south-east Europe and far-east Asia, with its production being on the rise in Middle Eastern regions. This paper presents a quantitative data-driven bibliometric analysis of the existing literature on Captagon up to July 2024. It aims to delineate the structure and development of knowledge surrounding the substance, including key contributing countries, authors, prominent sources, and recurring thematic keywords. The quantitative and data-driven results were then used to guide the narrative discussion on Captagon. Findings indicate that current research predominantly focuses on Captagon's use and impact in conflict zones, often exploring its interaction with other substances used by civilians and militias. Results also show a growing trend in Captagon research, with Saudi Arabia, Jordan, and Iraq emerging as main contributors to the literature. Despite the attention in specific regions, a considerable gap remains in understanding the mechanisms of action of Captagon (particularly regarding its metabolism, toxicology, mortality risk), and in developing protocols for its discontinuation. Additionally, the drug's inconsistent composition requires further analyses to better predict risks and establish effective management strategies. Addressing these gaps will be crucial for the development of novel interventions and policies to mitigate the adverse effects of Captagon and improve public health systems worldwide.

1. Introduction

Fenethylline (IUPAC name: (R,S)-1,3-dimehtyl-7-[2-(1-phenyl-propan-2-ylamino) ethyl]purine-2,6-dione; (Katselou et al., 2016)), also referred to as amphetaminoethyltheophylline and amfetyline, is a synthetic stimulant composed of amphetamine and theophylline (AL-Imam et al., 2017; Wu et al., 2019). It is marketed as a psychostimulant under the brand names Captagon, Biocapton, and Fitton (AL-Imam et al., 2017). Other common names include "chemical courage", "Abu Hilalain'" (meaning "father of two crescents" in Arabic), Jihadi Drug, among others (AL-Imam et al., 2017; Katselou et al., 2016; Keup, 1986; Pergolizzi et al., 2024; Wu et al., 2019). Captagon was first reported as a potential treatment for hyperactivity, depression, and narcolepsy in 1961 (Pergolizzi et al., 2024; Pothmann et al., 1988; Wu et al., 2019). However, it was also found to have addictive and hallucinogenic side effects, especially when associated with sleep deprivation (Shalaby et al., 2022; Twark and Suzuki, 2017). Due to its addictive and hallucinogenic properties, Captagon was never approved for medical use and was classified as a Schedule 1 controlled substance in the United States, indicating a high potential for abuse. As a result, it became illegal to buy or sell in most countries by 1986 (AL-Imam et al., 2017; Pergolizzi et al., 2024). Since then, its illegal production and distribution have become a profitable business leading to varying levels of purity and the presence of harmful adulterants, which have increased the risk of fatal and other adverse reactions (Alabdalla, 2005).

While Captagon's production is mostly located in Southern Europe

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and Turkey, its use and production in Middle Eastern regions is on the rise (AL-Imam et al., 2017; Tobaiqy and Al-Asmari, 2024; Wazaify et al., 2020), where it has caused numerous fatalities due to its increased usage by militant combatant groups and civilians in conflict zones (Steenkamp, 2024). Amid its ongoing civil war, Syria has emerged as a key country for Captagon production, consumption, and export (Herbert, 2014; Katselou et al., 2016; Steenkamp, 2024). Lebanon and Yemen, both affected by ongoing conflict, play crucial roles in the production and trafficking of the drug, while Iran is involved in supporting smuggling operations through militias and organized crime networks (Ardabili et al., 2022; EMCDDA, 2019; Ganor and Halperin Wernli, 2013; Rose, 2023). Overall, conflict and organized crime continue to drive the production and distribution of Captagon in these regions. For soldiers, Captagon suppresses pain, boosts endurance, aggression, and alertness, and induces euphoria and a sense of invincibility, while exacerbating violence and lethality of conflicts (AL-Imam et al., 2017). For civilians facing pervasive hopelessness or helplessness, Captagon offers a temporary escape from their circumstances and helps them cope with food insecurity (Al Atom, 2018; Pergolizzi et al., 2024; Wu et al., 2019). For affluent Middle Eastern youth, it has been used for recreation or as a concentration aid for studying (Pergolizzi et al., 2024; Steenkamp, 2024).

Due to its potent psychoactive effects, cases of psychosis, severe anxiety, and suicidal tendencies, which can result in fatalities either directly or indirectly, have been reported (Al-Imam and Michalak, 2024; Shalaby et al., 2023). Captagon, like other amphetamines, can also lead to fatal overdoses. Overdosing on Captagon can cause severe cardiovascular complications, hyperthermia, and multi-organ failure. However, no case of direct Captagon-associated mortality has been reported thus far (Dagres, 2023).

Fenethylline exhibits a combined stimulatory effect from both amphetamine and theophylline, but it also has distinct characteristics (Katselou et al., 2016). For instance, fenethylline is less potent than amphetamine in terms of increasing blood pressure, possibly due to the opposing vasodilatory effects of theophylline (Katselou et al., 2016). Furthermore, fenethylline does not exhibit the same level of euphoria and appetite suppression seen with amphetamine, nor does it impair fine motor skills, as amphetamine does (Katselou et al., 2016). Additionally, fenethylline's lipophilicity allows it to access the brain more rapidly, potentially prolonging its activity compared to amphetamine (Nickel et al., 1986).

Moreover, while amphetamine is known for its acute toxicity and potential for abuse, fenethylline has been considered less toxic and better tolerated (Nickel et al., 1986). Animal studies suggest that fenethylline reduces some of amphetamine's toxic effects, such as amphetamine-induced enhancement of ethanol's effects (Nickel et al., 1986). These differences in pharmacological and toxicological profiles suggest that fenethylline acts as a distinct entity and not solely as a prodrug for amphetamine (Katselou et al., 2016; Nickel et al., 1986).

Attention has recently been given to its illegal trade in a review by Pergolizzi et al. (2024), which also considers future implications for its use. The current work aims to expand the review from Pergolizzi et al. (2024), which relies on data published on PubMed until December 2023. This is relevant because our preliminary Scopus analysis, conducted up to July 2024, revealed that 5 documents on Captagon have already been published. This makes 2024 the second-highest year for Captagon-related publications, following 2022, which had a total of 6 documents. This suggests that the literature and research on Captagon is gaining *momentum*. To better understand the reasons behind such growing interest in the substance, we conducted an in-depth quantitative data-driven analysis of the literature (as in Carollo et al. (2024); Fong et al. (2023)) to outline the structure and the development of knowledge around Captagon over time in terms of most involved countries, most productive authors, most interested sources, most influential documents, and most recurring keywords. Keyword analysis will also be used to identify frequent thematic domains and potential research gaps in the literature to discuss in the current work.

2. Methods

Data for the present work was collected from the Scopus database on 22 July 2024. Scopus was chosen as the primary database due to its extensive coverage of indexed journals (Neoh et al., 2023). A total of 53 documents published between 1962 (i.e., Börger (1962)) and 2024 were retrieved using the search string "TITLE-ABS("captagon")". The retrieved datasets consisted of 45 articles, 2 book chapters, 1 conference paper, 2 letters, 1 note, 1 review, and 1 short survey. The *bibliometrix* package for R (Aria and Cuccurullo, 2017) was implemented to outline the structure of knowledge in the literature on Captagon and to analyze co-occurrence patterns of document keywords to reveal the main themes in Captagon research.

3. Results from the bibliometric analysis

The bibliometric analysis indicates that the literature on Captagon grew from 1962 to 2024 at an annual growth rate of 5.92% documents per year. Documents in the dataset received an average of 5.96 citations and an average of 0.641 citations per year. In descending order, the top three most highly cited manuscripts were authored by Al-Husseini et al. (2018) (total citations on Scopus = 33; total citations per year = 4.71), Alabdalla (2005) (total citations on Scopus = 32; total citations per year = 1.60), and Al-Hemiary et al. (2014) (total citations on Scopus = 31; total citations per year = 2.82, see Table 1). In particular, Alabdalla (2005) analyzed one hundred and twenty-four seized batches of illicit Captagon to identify the chemical composition of counterfeit tablets and found that they lacked fenethylline, suggesting that what is sold and marketed as Captagon in Jordan may have different origins and compositions and this, therefore, could be a factor in causing health risks and potential fatalities. Differently, the study by Al-Hemiary et al. (2014) focused on analyzing recent data from Iraqi law enforcement and customs officials and the Iraqi Ministry of Health. The authors found rising substance use, with alcohol, hashish, and prescription drugs being most common, while new drugs like Captagon, crystal methamphetamine, and tramadol are emerging, highlighting the need for continued monitoring and public health strategies to address substance use disorders.

When focusing on the documents' authors, a total of 151 authors conducting research on Captagon were identified. The top three most productive authors were Wazaify M ($n = 3$ documents), Al-Imam A ($n = 2$ documents), and Alshehri MH ($n = 2$ documents; see Table 1).

The analysis of the corresponding author's affiliations revealed the

Table 1
Main summary of the results from the bibliometric analysis.

Item	Frequency
Most cited documents	
Al-Husseini et al. (2018)	33 citations
Alabdalla (2005)	32 citations
Al-Hemiary et al. (2014)	31 citations
Most productive authors	
Wazaify M	3 documents
Al-Imam A	2 documents
Alshehri MH	2 documents
Most involved countries	
Saudi Arabia	6 documents
Jordan	4 documents
Iraq	3 documents
Main sources	
Medizinische Welt	2 documents
Psychopharmacology Bulletin	2 documents
Substance Use and Misuse	2 documents
Most frequent keywords	
Captagon	14 documents
Fenethylline	5 documents
Jordan	4 documents

countries from which the documents in the dataset were published as well as the rate of international collaborations in terms of single-country publications (SCP) and multiple-country publications (MCP). Most of the publications about Captagon were published in Saudia Arabia ($n = 6$ documents; SCP $= 2$; MCP $= 4$), Jordan ($n = 4$ documents; SCP $= 3$; MCP $= 1$), and Iraq ($n = 3$ documents; SCP $= 3$; MCP $= 0$; see Table 1). From the results, the Middle East appears to be the world region that is mostly involved in Captagon research, with low rates of international collaborations.

The most relevant sources of the articles were *Medizinische Welt* ($n = 2$ documents), *Psychopharmacology Bulletin* ($n = 2$ documents), and *Substance Use and Misuse* ($n = 2$ documents; see Table 1).

A total of 111 keywords were identified from the 54 retrieved documents. The 10 most relevant keywords were *captagon* ($N = 14$ articles), *fenethylline* ($N = 5$ articles), *jordan* ($N = 4$ articles), *addiction* ($N = 3$ articles), *amphetamine* ($N = 3$ articles), *syria* ($N = 3$ articles), *abuse* ($N = 2$ articles), *conflict* ($N = 2$ articles), *drugs* ($N = 2$ articles), and epidemiology ($N = 2$ articles; see Table 1). From these keywords, we notice the interest in Captagon's properties (e.g., *addiction*, *abuse*), in the world regions (e.g., *Jordan*, *Syria*) most impacted by Captagon production, trafficking, and use (AL-Imam et al., 2017; Herbert, 2014), as well as the role of Captagon in fueling conflict (e.g., *conflict*). A co-occurrence analysis identified three clusters of commonly occurring keywords in the Captagon literature (see Fig. 1).

4. Discussion: narrative review from the identified research clusters

As shown in Fig. 1, three research clusters emerged from the co-occurrence analysis on the keywords commonly used in the literature on Captagon. The formation of the clusters demonstrates three main overarching themes that frequently occur in the current literature on Captagon. These three themes can be broadly summarized as (i) the connection between substance use (e.g., alcohol, stimulants, sedatives, cannabis) and its role in conflict zones, particularly in the Middle East and Syria; (ii) Captagon, its production, trafficking, and consumption, specifically in Jordan and the broader Middle East, and its role in fueling regional conflicts; and (iii) various drugs (heroin, tramadol, methamphetamine, cannabis) and their connection to neuroscience (neurotransmitters), with an additional emphasis on green chemistry and organizations like NEMI and ESA. In the subsequent sections, we will discuss and provide a narrative review of the literature on Captagon, starting with the keyword co-occurrence clusters and expanding to current research status and trends. Specifically, subsection 4.1 addresses the co-use of Captagon with other drugs of abuse, subsection 4.2 examines the chemical synthesis of captagon and the role of other additive substances, subsection 4.3 focuses on Captagon-related toxicities, and subsection 4.4 explores the role of customs in detecting different types of Captagon.

4.1. Co-use of Captagon with others drugs of abuse

The blue cluster in Fig. 1 pertains to documents that focus on the use and abuse of various substances (e.g., alcohol, hypnotics, stimulants, tobacco, cannabis) by both civilians and militias in conflict zones, particularly in the Middle East (e.g., Abazid (2022)). The interest in multiple substances is relevant in Captagon research as Captagon is often taken together with other drugs, either intentionally or unintentionally (Pergolizzi et al., 2024). Captagon is often used in combination with tramadol, methadone, alcohol, hashish/marijuana, and benzodiazepines, with many health policies recommending to treat Captagon abuse with the latter (Abdulfattah et al., 2024; AL-Imam et al., 2017; Albals et al., 2022; Alshenguity et al., 2019; Ardabili et al., 2022; Pergolizzi et al., 2024; Yasin et al., 2021; Yasin et al., 2020; Wazaify et al., 2020; Wazaify et al., 2024b).

The keywords of this cluster also suggest an interest in the literature regarding the motivation behind Captagon use (e.g., Alkhudhairy et al. (2024); Wazaify et al. (2024a)). For instance, in the university

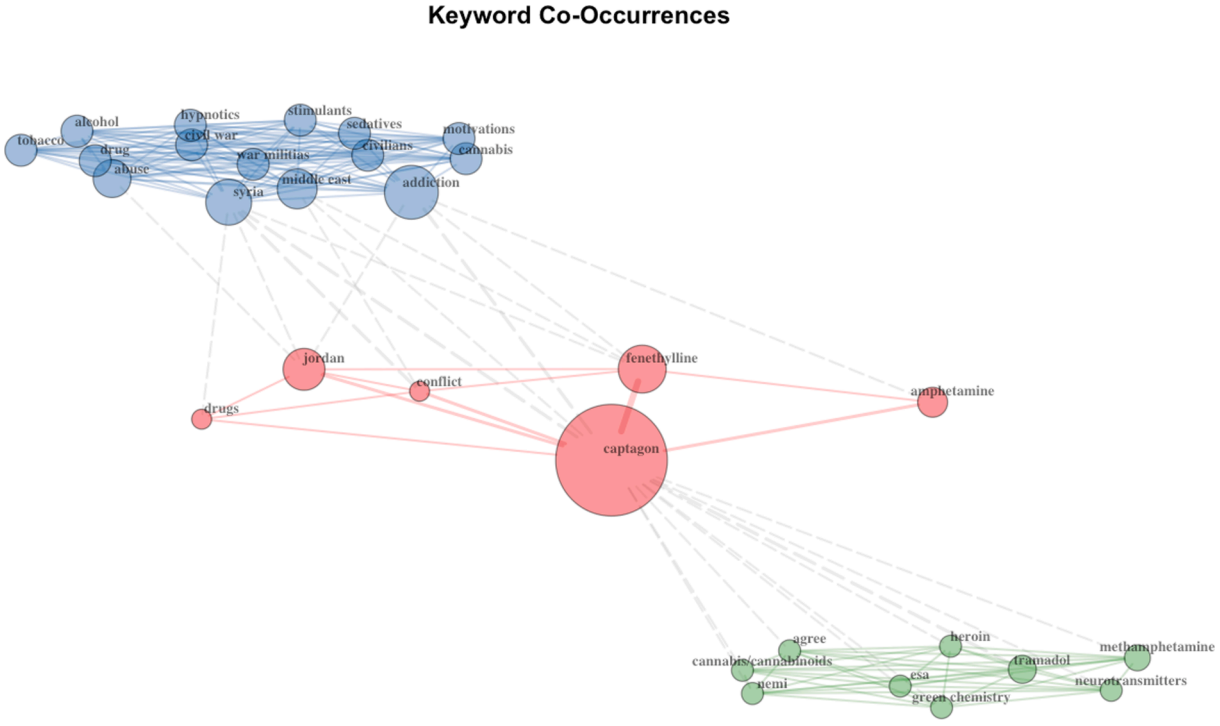

Fig. 1. Resulting co-occurrence analysis on the keywords in the literature on Captagon. In the network, keywords are depicted as individual nodes, with their size corresponding to their degree. Solid links represent co-occurrences of keywords within the same cluster, while dashed links indicate co-occurrences across different clusters. The thickness of these links reflects the frequency of co-occurrence. Utilizing the *bibliometrix* package for R (Aria and Cuccurullo, 2017), three clusters of keywords were automatically identified based on these co-occurrence patterns and are depicted in the figure in red, blue, and green.

population, Captagon is used to overcome life challenges such as academic and personal stress (Al Omari et al., 2022). Abdulfattah et al. (2024) found that the nonmedical usage of Captagon was prevalent among senior high school and university students in Jordan. However, the increased rates of Captagon use seem particularly linked to the outbreak of national conflicts in Middle Eastern regions, a theme that also appears in the red cluster of Fig. 1. For instance, Abazid (2022) argues that drug abuse is increasing in Syria, especially after the outbreak of the Syrian war in 2011. During the Syrian war, drug demand increased in the general population, especially among soldiers, who became new drug customers. Moreover, during the conflict, drug selling became a way to finance the purchase of new weapons. For these reasons, Syria has become a major producer of new drugs, including Captagon. However, the impact of Captagon on the Syrian conflict and its relations with bordering regions is often overlooked (Pergolizzi et al., 2024; Steenkamp, 2024; Van Hout and Wells, 2016). For instance, Steenkamp (2024) discusses how Captagon trafficking from Syria to the Arabian peninsula via Jordan has contributed to increasing the usage of Captagon in Jordan.

With respect to treatment programs, Binnwejim et al. (2021) found that cognitive-behavioral therapy combined with pharmacotherapy was more effective in treating Captagon use disorder and preventing relapse than either treatment alone, particularly in reducing cravings. Cognitive-behavioral therapy was also found to be more effective than pharmacotherapy in addressing the psychological aspects of addiction, such as automatic thoughts, depression, and negative health beliefs. Further research is needed to understand how treatment outcomes have been impacted by the evolution of Captagon addiction treatments over time and how current policies might continue to improve upon past practices.

Table 2 provides summaries of documents pertaining to the co-use of Captagon with other drugs of abuse.

Table 2
Summary table for documents regarding the "Co-use of Captagon with other drugs of abuse".

Reference	Summary
Abazid (2022)	The work examines the rising issue of drug abuse in the Middle East. It focuses on Syria, where the war has intensified drug production, trafficking, and addiction.
Abdulfattah et al. (2024)	The study conducted a cross-sectional survey of senior high school and university students in Jordan to assess the prevalence and correlates of nonmedical use of stimulants.
Al-Imam and Michalak (2024)	This letter to the editor emphasizes the urgent need for research on the rising issue of suicidal ideation among users of Iraqi crystal methamphetamine.
Al Omari et al. (2022)	Through in-depth interviews, this study explored the experiences of Jordanian university students who misuse Captagon.
Albals et al. (2022)	This study reviewed psychoactive substance use in Jordan from 2014 to 2018 based on data from the Anti-narcotic Department.
Alkhudhairy et al. (2024)	This study investigated drug use among young people in Al-Najaf Governorate, Iraq, between November 2021 and February 2022, surveying 112 users aged 10 to 29.
Alshenguity et al. (2019)	This study examined the socio-demographic characteristics and patterns of Captagon use among 98 patients at Alamal Mental Health Complex in Saudi Arabia between 2016 and 2017.
Ardabili et al. (2022)	This review examined substance use in the Eastern Mediterranean Region, where geopolitical conflicts have contributed to increased drug production and trafficking. Based on research from 2015 to 2021, the study focuses on the emerging drugs of concern in the region, particularly tramadol, Captagon, and khat.
Binnwejim et al. (2021)	This study assessed the therapeutic efficacy of cognitive behavior therapy and pharmacotherapy in treating Major Captagon Dependence among 41 male outpatients (mean age of 34.58 years).
Pergolizzi et al. (2024)	This study examined the history, production, and patterns of abuse of Captagon, detailing its rise as a prominent drug in the Eastern Mediterranean Region.
Steenkamp (2024)	This study investigated the relationship between Captagon trafficking and the ongoing civil war in Syria. It emphasizes how the drug trade has increased violence and influenced domestic consumption in Jordan.
Van Hout and Wells (2016)	This letter discusses how Captagon is contributing to the Syrian conflict by serving as both a source of funding for armed groups and a means for individuals to cope with the violence and trauma associated with the war.
Wazaify et al. (2024a)	This study explored the experiences of 27 individuals using Captagon and their therapists in Jordan. Through semi-structured interviews, the authors analyze addiction severity, withdrawal symptoms, and the drug's impact on quality of life.
Wazaify et al. (2024b)	This study investigated the impact of COVID-19 on substance use and Substance Use Disorders among 17 addiction treatment centers patients in Jordan through semi-structured interviews.
Wazaify et al. (2020)	This qualitative study examined the experiences of healthcare and educational professionals working with Palestinian families affected by substance use in two UNRWA camps in Jordan.
Yasin et al. (2021)	This study evaluated the impact of clinical pharmacist interventions on patients in addiction rehabilitation centers in Jordan.
Yasin et al. (2020)	This study examined patterns of substance use among 93 patients at two public addiction rehabilitation centers in Amman.

4.2. Chemical synthesis of captagon and the role of other additive substances

First synthesized by Chemiewerk Homburg to investigate its effects on physiological functions (e.g., pulmonary, cardiovascular, and central nervous systems) (Dahl, 2015; Katselou et al., 2016; Kristen et al., 1986; PillReports, n.d.), Captagon tablets are known to contain amphetamines conjugated with theophylline via an alcohol chain (Ellison et al., 1970; Katselou et al., 2016; Nickel et al., 1986; Pergolizzi et al., 2024). Such products are produced in two steps, that include the amphetamine synthesis and the tableting, which are often realized in different locations and countries for avoiding detection or because different equipment and skills are required (EMCDDA, 2023). Recent evidence and results from some forensic analyses realized in Europe have shown that 32 milligrams of amphetamine sulfate, the main ingredient, are present in a captagon tablet (EMCDDA, 2023). However, tablets also contain other substances, such as theophylline, piracetam, paracetamol, N-formylamphetamine, lidocaine and diphenhydramine, caffeine (EMCDDA, 2023). Such substances might be involved in some health issues as the presence of contaminants in Captagon might increase the risk of safety hazards linked to its use. Moreover, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reports that fenethylline has not been legally produced since 2009, with the International Narcotics Control Board (INCB) confirming that all remaining stocks were exhausted by the end of that year (EMCDDA, 2023; Board, 2011). Therefore, what is sold or trafficked today as Captagon likely does not contain fenethylline. Instead, current Captagon tablets are often a mixture of various substances, commonly including amphetamine, which mimics the effects of fenethylline.

Summaries of documents related to the chemical synthesis of Captagon and the role of other additive substances have been included in Table 3.

4.3. Captagon-related toxicities

Even though previous findings suggested that Captagon has few adverse side effects compared to amphetamine (Katselou et al., 2016; Kristen et al., 1986) and evidence on Captagon's toxicity is still quite limited to case reports (Katselou et al., 2016; Pergolizzi et al., 2024), it is undeniable that its use can determine addiction (Wu et al., 2019), withdrawal, and some safety issues potentially related to its main metabolites (amphetamine and theophylline) (Alabdalla, 2005; EMCDDA,

Table 3
Summary table for documents regarding the "Chemical Synthesis of Captagon and the Role of Other Additive Substances".

Reference	Summary
Dahl (2015)	This article provides an overview of Captagon and its usage. It explains the drug's history, effects, and the rise of its production and trafficking in the Syrian region. The article also discusses the implications of Captagon's prevalence for public health and security in the area.
Ellison et al. (1970)	The study investigated the metabolic fate of fenethylline in four male volunteers using tritium-labeled forms and compared it with the metabolism of d-amphetamine.
EMCDDA (2023)	This technical report examines Captagon trafficking and its implications for Europe. It discusses the growing production and distribution of Captagon, particularly from the Middle East, and highlights the increasing demand and risk factors associated with its use in Europe.
Board (2011)	This report on psychotropic substances presents statistical data for 2009, detailing the global production, consumption, and trafficking of various drugs, including their impact on public health and safety.
Katselou et al. (2016)	This study provides a comprehensive review of Captagon, detailing its chemistry, synthesis, pharmacology, and toxicology.
Kristen et al. (1986)	This paper evaluates fenetylline's medical therapeutic applications alongside its potential for misuse and addiction
Nickel et al. (1986)	This study investigated the pharmacological profile of fenetylline. It utilized high-pressure liquid chromatography (HPLC) to analyze fenetylline's metabolic patterns and their relationship to its pharmacodynamic effects.
Pergolizzi et al. (2024)	This study examined the history, production, and patterns of abuse of Captagon, detailing its rise as a prominent drug in the Eastern Mediterranean Region.
PillReports (n.d.)	The page provides a user-generated report on Captagon and its characteristics.

2023; Katselou et al., 2016; Pergolizzi et al., 2024; Wazaify et al., 2022). Based on the limited available data, these include visual distortions, seizures (Pergolizzi et al., 2024), cardiovascular damages (e.g., heart failure and cardiomyopathy (Elasfar et al., 2014), inferior myocardial infarction (AMI), acute coronary syndrome, premature atherosclerosis, tachycardia and electrocardiogram changes like in the congenital Brugada syndrome) (Elasfar, 2015; Gokdemir and Giden, 2019; Gresnigt et al., 2023; Gul et al., 2023; Katselou et al., 2016; Uluçay et al., 2012), liver and renal issues (Dakil and Hasan, 2024); malnutrition (Pergolizzi et al., 2024) and Ophthalmological alterations (e.g., hemorrhagic central retinal vein occlusion) Al-Ghadyan et al. (2009), and psychiatric manifestations. These include dissociative symptoms in case of intoxication (Preve et al., 2017) and others more frequent in case of chronic use, such as depression, insomnia, severe anxiety, suicidal thoughts, irritability and impatience (Al-Imam and Michalak, 2024; Shalaby et al., 2023; Katselou et al., 2016), and psychotic symptoms (e.g., hallucinations and delusions of jealousy and persecutory) (Shalaby et al., 2023; Twark and Suzuki, 2017), often in the context of the so called Amphetamine Induced Psychosis (Shalaby et al., 2023; Shalaby et al., 2022; Shufman and Dickman, 1999). Moreover, anecdotal findings suggest other side effects in regular users (e.g., vertigo, gastrointestinal symptoms, joint pain, muscle pain or cramping (Katselou et al., 2016). Overdoses and risky intoxications (Adebahr et al., 1979) should also be mentioned especially in case of contaminants and the consumption of counterfeit captagon tablets often containing ephedrine, procaine, quinine, caffeine, acetaminophen, and metronidazole, which are linked to higher risks of toxicities (Alabdalla, 2005; DEA, 2003; Katselou et al., 2016; Nevešćanin et al., 2008; Nichols and Kravitz, 2015; Pergolizzi et al., 2024; U.N.O., 2012).

Additionally, recent documents, such as the one authored by Dakil and Hasan (2024), are reporting the health impact of amphetamine and Captagon abuse on liver and renal function. Specifically, Dakil and Hasan (2024) show that drug users had significantly higher liver and renal impairment than non-drug users, with older drug users having more severe dysfunction. This suggests a compounded effect resulting from sustained use of amphetamines or Captagon over time.

Table 4 provides summaries of documents concerning Captagon-related toxicities.

4.4. Role of customs in detecting different types of Captagon

The cluster, depicted in green in Fig. 1, highlights recent innovations in green analytical chemistry for safe pharmaceutical analysis of commonly abused drugs (e.g., National Environmental Method Index (NEMI), Analytical eco-Scale assessment (ESA), and Analytical Greenness metric (AGREE)), including Captagon (Alharthy et al., 2022).

Several strategies have been developed over the years in forensic analysis for identifying captagon and its metabolites in biological samples, or to screen for adulterants in tablets (Goenechea and Brzezinka, 1984; Slechtova and Chundela, 1972; Aljohar et al., 2019). Considering that Captagon is metabolized into amphetamine and theophylline following ingestion, it is not so easy for forensic evaluation to determine the consumption of the substance (EMCDDA, 2023). The main strategies in the past included chromatographic methods such as the gas chromatograph-mass spectrometry (GC-MS) for hair analysis (Alabdalla, 2005; Kikura and Nakahara, 1997; Rücker et al., 1988), which remains a valid instrument up-to-date (Aljohar et al., 2019). Other methods include the Gas–Liquid Chromatography (GLC) combined with a Nitrogen Flame Ionization Detector (N-FID) (Iffland, 1982), the fluorescence polarization immunoassays (FPIA) (De La Torre et al., 1996) and techniques like the Thin-Layer Chromatography (TLC), the Ultraviolet (UV) and the Infrared (IR) and the Nuclear Magnetic (NMR) Spectroscopy (Katselou et al., 2016; Shimamine et al., 1992). Aside from the aforementioned methods, more recent approaches have emerged. For example, screening methods using a portable quadrupole-based GS/MS (FLIR Griffin™ G510) have been considered potentially useful for identifying drugs of abuse and adulterants in seized material including fenethylline (Fiorentin et al., 2020) and one-Step Derivatization–Extraction Method for Rapid Analysis of oral fluid has been applied (Mohamed, 2017). Although the body of evidence on methods specifically for forensic evaluation of Captagon is not extensive, these available instruments are used today to discriminate different shapes, colors, and mixtures of Captagon and for screening of adulterants (Aljohar et al., 2019). This is relevant as captagon tablets in both Eastern and Western countries might often present a variable content of adulterants. These adulterants are predominantly theophylline and caffeine, but also include other substances (e.g., allopurinol, paracetamol) and heavy metals (e.g., nickel and zinc) (EMCDDA, 2023; Katselou et al., 2016).

Summaries of documents that are relevant to the role of customs in detecting different types of Captagon have been included in Table 5.

5. Limitations

This paper has some limitations. First, the results of the bibliometric analysis depend on the database chosen for data collection as well as the key terms used in the search string. We chose Scopus as the only reference database for collecting the sample to use in the bibliometric analysis as it provides higher coverage of relevant journals and to avoid including duplicate entries and formatting errors from the use of multiple data sources. However, we have conducted a parallel analysis on Web Of Science and, where relevant, added to the narrative review of research clusters the documents that are not available on Scopus. Moreover, the current study only used the search term "Captagon", while some documents using some synonyms such as Fitton or Biocaptagon might have been inadvertently neglected. Moreover, some important clinical studies and results may have been overlooked because they did not mention or investigate the possibility of Captagon use among participants. For example, many studies that detected amphetamines in blood samples did not specifically test for traces of Captagon.

Table 4
Summary table for documents regarding the "Captagon-Related Toxicities".

Reference	Summary
Adebahr et al. (1979)	This study focuses on the toxicological aspects of Captagon intoxication.
Al-Ghadyan et al. (2009)	This study reports three cases of hemorrhagic central retinal vein occlusion linked to continuous use of fenethylline hydrochloride.
Al-Imam and Michalak (2024)	This letter to the editor emphasizes the urgent need for research on the rising issue of suicidal ideation among users of Iraqi crystal methamphetamine.
Alabdalla (2005)	This study analyzed 124 seized batches of Captagon using gas chromatography-mass spectrometry (GC–MS) and found that the samples contained amphetamine, caffeine, and other substances but lacked fenethylline itself.
Dakil and Hasan (2024)	This study investigated the effects of amphetamine and Captagon abuse on liver and kidney functions.
DEA (2003)	This report provides an overview of Captagon's origins, its effects, and the challenges associated with its illicit use, including its growing availability and associated health risks.
Elasfar et al. (2014)	This study evaluated the clinical characteristics and outcomes of acute heart failure in captagon users.
EMCDDA (2023)	This technical report examines Captagon trafficking and its implications for Europe. It discusses the growing production and distribution of Captagon, particularly from the Middle East, and highlights the increasing demand and risk factors associated with its use in Europe.
Gokdemir and Giden (2019)	This study presents a case of a 23-year-old patient who developed acute myocardial infarction (AMI) as a result of Captagon use.
Gresnigt et al. (2023)	This study systematically reviewed cases of acute coronary syndrome associated with the use of amphetamines and cathinones.
Gul et al. (2023)	This study reports two cases of Brugada phenocopies as a result of Captagon abuse.
Katselou et al. (2016)	This study provides a comprehensive review of Captagon, detailing its chemistry, synthesis, pharmacology, and toxicology.
Kristen et al. (1986)	This paper evaluates fenetylline's medical therapeutic applications alongside its potential for misuse and addiction.
Nevešćanin et al. (2008)	This study utilized gas chromatography/mass spectrometry to analyze 32 batches of amphetamine samples from three separate cases in Serbia, focusing on the identification of active components and additives.
Nichols and Kravitz (2015)	This study provides an overview of Captagon trafficking during the Syrian war and its implications for the US foreign policy.
Pergolizzi et al. (2024)	This study examined the history, production, and patterns of abuse of Captagon, detailing its rise as a prominent drug in the Eastern Mediterranean Region.
Preve et al. (2017)	Through a systematic literature review and a case report, this report reviews the clinical evidence of Captagon as a drug of abuse.
Shalaby et al. (2023)	This study investigated the link between Captagon use and delusions of infidelity among 101 male patients diagnosed with amphetamine-induced psychosis in Jeddah, Saudi Arabia.
Shalaby et al. (2022)	This study examined the relationship between sleep deprivation and amphetamine (Captagon)-induced psychosis.
Shufman and Dickman (1999)	This paper presents two cases of fenethylline-induced psychosis.
Twark and Suzuki (2017)	This paper presents a case report of fenethylline-induced psychosis in the United States.
Uluçay et al. (2012)	This report details a case of a patient who experienced an acute anterior myocardial infarction following the consumption of a Captagon tablet.
U.N.O. (2012)	This report provides an overview of global drug trends, highlighting the evolving patterns of drug use, production, and trafficking.
Wazaify et al. (2022)	This study explored the experiences of 27 individuals using Captagon and their therapists in Jordan. Through semi-structured interviews, the authors analyze addiction severity, withdrawal symptoms, and the drug's impact on quality of life.
Wu et al. (2019)	This study investigated the mechanisms underlying Captagon addiction.

Table 5
Summary table for documents regarding the "Role of customs in detecting different types of Captagon".

Reference	Summary
Alabdalla (2005)	This study analyzed 124 seized batches of Captagon using gas chromatography-mass spectrometry (GC–MS) and found that the samples contained amphetamine, caffeine, and other substances but lacked fenethylline itself.
Alharthy et al. (2022)	This study evaluated various chromatographic methods for analyzing methamphetamine in combination with other commonly abused drugs in Saudi Arabia, focusing on their environmental impact.
Aljohar et al. (2019)	This study applied gas chromatography/mass spectrometry to profile 55 seized samples of Captagon from the Saudi market.
De La Torre et al. (1996)	This study assessed the efficacy of immunological methods, specifically fluorescence polarization immunoassays, for detecting stimulants in sports drug testing.
EMCDDA (2023)	This technical report examines Captagon trafficking and its implications for Europe. It discusses the growing production and distribution of Captagon, particularly from the Middle East, and highlights the increasing demand and risk factors associated with its use in Europe.
Fiorentin et al. (2020)	This study developed and validated a new portable gas chromatography-mass spectrometry method to identify drugs of abuse and their adulterants in seized materials.
Goenechea and Brzezinka (1984)	This study focuses on fenethylline metabolization.
Iffland (1982)	This study focuses on the urine levels of fenethylline and amphetamine after administration of Captagon.
Kikura and Nakahara (1997)	This study investigated the incorporation of fenethylline and its metabolite amphetamine into rat hair and evaluated the effectiveness of hair analysis for distinguishing between fenethylline and amphetamine use.
Mohamed (2017)	This study investigated a method to analyze 11 amphetamine-like drugs in oral fluid samples.
Rücker et al. (1988)	This study investigated the biotransformation of Captagon after oral administration.
Shimamine et al. (1992)	This study focuses on the identification of psychotropic substances, including fenethylline.
Slechtova and Chundela (1972)	This study investigated isolating and identifying amphetamine as a metabolic product of the drugs Aponeuron, Captagon, and Prenylamin.

6. Conclusion

The current work reveals that Captagon literature predominantly focuses on its use and impact in conflict zones, often examining its intersection with other substances used by civilians and militias. Combining amphetamine and theophylline, Captagon is a potent stimulant that increases alertness, energy, helps users stay awake and alert for extended periods, reduces fear, and increases aggression, making it a preferred drug among fighters despite its addictive properties, high liver and renal impairment, and other side effects.

In line with the findings of Pergolizzi et al. (2024), there still remains a significant gap in understanding the health effects and fatality risks of Captagon, as well as management protocols for discontinuing its use. Additionally, the inconsistent composition of Captagon, as highlighted by Alabdalla (2005), further complicates understanding its health effects. This therefore emphasizes the urgent need for updated analyses to better predict its risks and develop effective management protocols. Moreover, information on Captagon metabolism and toxicology is still scarce. Detailed toxicological profiles are missing, which are essential to understanding the long-term health impacts of Captagon use. Limited data is also provided on the specific long-term impact on various organs, particularly the brain, liver, and kidneys. Although Captagon is a highly addictive substance, no evidence was found on the management of withdrawal symptoms as well as related mental health conditions such as depression, anxiety, and psychosis, and, ultimately, mortality risk. Despite the growing scientific interest, there is a clear lack of

standardized protocols and treatment programs for Captagon addiction and very few studies are focusing on how Captagon affects different demographic groups, including adolescents, women, and individuals with pre-existing health conditions. Furthermore, the socioeconomic factors underlying its consumption have been marginally explored in the literature and we lack data on the behavioral patterns and lifestyles of Captagon users. Encouragingly, the results of our bibliometric analysis indicate a growing trend in Captagon research, with Saudi Arabia, Jordan, and Iraq emerging as leading contributors to the literature. Conversely, the results from the present work's bibliometric analysis on single-country publications and multiple-country publications showed that few studies have been conducted in other parts of the world (e.g., the United States of America), despite Captagon's expansion and the association with extremism, which represents a major global threat. Addressing these gaps will be crucial for developing effective interventions and policies to mitigate the adverse effects of Captagon abuse on individuals and public health systems worldwide.

Authors contribution

Conceptualization: SF, AC, GE, OC; Methodology: SF, AC; Formal Analysis: SF, AC; Investigation: SF, AC; Writing–original draft preparation: SF, AC; Writing–review and editing: SF, AC, AR, EP, GE, OC; Supervision: GE, OC. All authors have read and agreed to the published version of the manuscript.

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.

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