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Kratom abuse as an emerging issue of addiction, overdose toxicities and deaths: a review

Meray Medhat Shokry Zaghary[1]

[1] Department of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Sohag University, Sohag, Egypt.

Abstract

Introduction: Kratom (Mitragyna speciosa) is a native tree of coffee plant family in Thailand and Southeast Asia. Chewing kratom leaves have long been used as traditional medicine to relieve chronic pain and opioid withdrawal. **Aim:** This review illustrates how kratom abuse is an alarming phenomenon due to related addiction, overdose toxicities and deaths**. Review:** Researched studies demonstrated that kratom have both depressant and stimulant actions according to the dose. In the last few years, kratom has been introduced in Europe and United states, as unregulated safe natural herbal products substitute of opioid products especially by online drug markets in addition to exposure of drug abusers through contaminated products. In Egypt and the middle east, clinical toxicologists must be educated about kratom and its adverse clinical manifestations as a potential problem. **Conclusion:** Research about kratom safety is still lacking.

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Key words Kratom, abuse, toxicity, death

Introduction

Mitragyna speciosa is a native tree of coffee plant family in Thailand and other countries of Southeast Asia. Leaves of this plant are known as kratom (Singh et al., 2017; Adkins et al., 2011). Chewing Kratom leaves have long been used by Asian people as traditional medicine to relieve chronic pain and opioid withdrawal (Ismail et al., 2019; Singh et al., 2016).

Surprisingly, kratom have both depressant and stimulant actions as it has been acting on both opioid receptors giving opioid like effects in large dose and inhibition of monoamine neurotransmitter uptake giving stimulant effect (cocaine-like) in small dose (Smith and Lawson, 2017; Harun et al., 2015).

In recent years, kratom products have been used in the United States as legal herbal substitutes of opioid products and were categorized as atypical opioids. Kratom is chewed by manual workers in low dose to relieve fatigue and in large dose for its analgesic effects (Garcia-Romeu et al., 2020; Oberbarnscheidt and Miller, 2019).

Kratom have been used increasingly among drug abusers with significant adverse effects. Deaths have been reported in United States, and mitragynines have been detected in post-mortem blood samples. Although kratom couldn't be incriminated in those incidences due to poly-drug use, it is reasonably unsafe and the increasing use and wide availability in Europe and United States became an alarming issue (Eggleston et al., 2019).

Development of virtual online drug markets can potentially open the market up to a wider audience of drug abusers. The internet facilitates movement of drugs, new psychoactive substances, precursors, medicines, and information on production techniques across global borders (Aldridge, 2016).

This review illustrates how kratom abuse is an alarming phenomenon due to related addiction, overdose toxicities and deaths.

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What is Kratom?

Mitragyna speciosa is an evergreen psychoactive tropical tree from the Rubiaceae family. (Adkins, et al., 2011; Yusoff, et al., 2016). This native tree of coffee plant is grown in southeast Asia (Muller et al., 2020). The leaves of this plant are known as kratom (Singh et al., 2017). Kratom has been used for decades as medicinal psychoactive herbal products in countries such as Thailand, Malaysia, Myanmar, and others southeast countries. According to the country kratom has alternative street names like "ketum", "biak–biak", "ithang", or "thom". (Sheleg & Collins, 2011; Eastlack, et al., 2020).

It was first known in late 19th century when used traditionally by natives to treat many conditions for examples malaise, increased blood pressure, headache, hyperglycemia, infections, and depression. It was prepared by a variety of ways such as boiling leaves in water then drinking the tincture or inhaling the vapor or chewing the leaves with tea (Alsarraf et al., 2019). Now, kratom is used to enhance mood, concentration, treat withdrawal opioids manifestations and decrease pain (Wong & Mun, 2020).

The scientific interest in kratom is due to two main causes: First, chronic kratom consumption can lead to addiction. Second, its dose related multiple actions as suggested by experimental animal models supporting analgesic, muscle relaxant, anti-inflammatory in addition

to strong anorectic and stimulant effects (Hassan et al., 2013).

Active substances:

The leaves of the mitragyna speciosa tree produce about 40 active substances for example like mitragynine, 7-α-hydroxymitragynine, paynantheine, speciociliatine, speciogynine, mitraphylline, rhynchophylline, mitralactonal, raubasine, and mitragynine that explain why kratom has multiple functions which vary from stimulant to depressant and anxiolytics. The major alkaloid found within the leaves extract, mitragynine which many studies act on this alkaloid to demonstrate that its main active function is opioid-like action (Warner et al., 2016; Stanciu, et al., 2019; Smith, et al., 2021).

Preparations of kratom and routes of administration:

Kratom freshly harvested leaves has been consumed traditionally by the natives of Southeast Asia for centuries to treat fatigue and opium withdrawal. The leaves can be chewed or brewed and drunk as tea. Fresh leaves can be left in the sun to be dried, then the dried leaves rubbed between hands to be powder. The powder form can be filled into capsules or pills and ingested or made into a liquid form which can be injected (Griffin & Webb, 2018; Sharma et al., 2019).

Kratom is sold through world wide web as pills, powder, leaves, topical creams, or tinctures. Consumption of Kratom in the United States is predominantly by liquids, but the use of powders added to food or beverages and consumption of Kratom capsules is growing in popularity. (Stanciu, et al., 2019; Veltri and Grundmann, 2019).

in Malaysia kratom syrup is produced by boiling powdered dried leaves in hot water. The syrup is mixed with finely chopped leaves of palas palm and made into pills known which are smoked in long bamboo pipes (Hassan et al,2013)

In southern Thailand M. speciosa leaves are mixed with caffeine-containing soft drink and codeine- or diphenhydramine-containing cough syrup (Tanguay, 2011)

Hassan, Z., Muzaimi, M., Navaratnam, V., Yusoff, N.H., Suhaimi, F.W., Vadivelu, R.,Vicknasingam, B.K., Amato, D., von Horsten, S., Ismail, N.I., Jayabalan, N.,Hazim, A.I., Mansor, S.M., Muller, C.P., 2013. From Kratom to mitragynine andits derivatives: physiological and behavioural effects related to use, abuse, andaddiction. Neurosci. Biobehav. Rev. 37, 138–151, http://dx.doi.org/ 10. 1016/ j. neubiorev. 2012.11.012.

Pharmacology of Kratom:

The pharmacological effects of kratom are dose dependent. Surprisingly, kratom have both depressant and stimulant actions. Small doses (1-5g of raw leaves) can cause stimulant- or cocaine-like effects due to inhibition of monoamine neurotransmitter uptake. On the other hand, higher doses (5-15g) can produce sedation and opioid-like effects by acting on opioid receptors (Smith and Lawson, 2017; Harun et al., 2015; Oberbarnscheidt and Miller, 2019).

Mitragynine which is the main component has an agonist effect on multiple receptors including the opioid receptors μ, κ, δ, as well as adenosine A_{2A}, postsynaptic alpha-2, dopamine-2s, and various serotonin receptors (Nelsen, et al., 2010). Acting as an agonist at mu receptors and an antagonist at delta receptors, may explain why respiratory depression occurred less frequently with kratom in comparison to pure mu agonists as heroin and oxycodone (Gershman et al, 2019).

Mitragynine is also known as an adjunct to synthetic cannabinoids such as K2/Spice products (Matsumoto et al., 2008). Also, Hassan et al. (2019) experimental study showed that high doses of mitragynine cause memory impairment, which may be due to affection of calcium influx to cells and disruption of hippocampal synaptic transmission.

When kratom is taken orally, 7 -hydroxy mitragynine a mini component has been found to be a more potent opioid agonist than both mitragynine and morphine and it is responsible for the clinical picture. The activity over opioid receptors can explain associated disturbed conscious level. Convulsions reported in some cases can be explained due adenosine activity or serotonergic stimulation similar to tramadol (Nelsen, et al., 2010).

Kratom is highly lipophilic so can easily cross blood brain barrier with rapid and effective central effects mainly through opioid receptors. The effects of kratom on the central nervous system as well as systemic effects can be inhibited or blocked by opioid antagonists (Oberbarnscheidt and Miller, 2019).

Duration of action and method of detection

The onset after chewing the leaves is about 5-10 min and lasts approximately 2-5 hours. The average clearance of mitragynine has been measured as 1.6 L/h, the elimination half-life is reported about 4 hours, and the total clearance is 6.5 L/h /kg. The detection of kratom requires specialized tests: Ultra-high-performance liquid chromatography and high-performance liquid chromatography- tandem mass spectrometry methods have been successfully used in monitoring the major alkaloids and metabolites found in urine following kratom use (Le et al., 2012).

Kratom toxicity:

Kratom is available online which aided its spread to United states, Europe, Japan. Kratom purchased online is more effective than the natural plant as it contains higher concentrations of its psychoactive alkaloids. Due to positive effects like euphoria, relaxation, increased activity, treatment of chronic pain and sensory potentiation kratom is addictive and its abuse became recognized (Anand and Hosanagar, 2021; Wang and Walker, 2018).

In-spite of kratom effect on opioid receptors, toxic effects like respiratory depression, coma, pulmonary oedema, and death mostly not occur (Sabetghadam et al., 2013). However, kratom may make a higher risk for drug toxicity and organ injury

compared to opioids, due to intrinsic properties and adulteration (Shah, et al., 2021).

Kratom is associated with several severe toxic effects including hypertension, nephrotoxicity, psychosis, seizures, and hepatotoxicity. The risks of long-term use of kratom are currently unknown. There are no pharmacological or pharmacokinetic studies on humans published or studies on drug interactions involving kratom (Kapp et. al, 2011).

Animal studies:

Many experimental studies investigated the pharmacologic effects of kratom. For examples Boyer, et al. (2008) revealed that mitragynine is the main alkaloid of kratom which binds mu- and kappa-opioid receptors, it has additional receptors effects this explain its effectiveness as treatment of opioid withdrawal. This was confirmed by Stolt et al. (2014) who demonstrated weak behavioral effects on mice due mu- and kappa-opioid receptors.

Moreover, Japarin, et al. (2021) demonstrated a cross-reinstatement effect between mitragynine and morphine, suggesting a similar interaction in their rewarding motivational properties and a priming exposure to kratom and an opioid may cause relapse for a previously abused drug.Also, Fakurazi, et al. (2013) showed that kratom use with morphine decrease tolerance in chronic morphine abusers. León, et al. (2021) claimed that serotonergic agonism by psychoactive kratom alkaloids may be the cause of the mood-enhancing effects associated with kratom use.

An experimental study by Sabetghadam et al. (2013) revealed that sub-chronic mitragynine use at dose less than 10 mg per kilogram is relatively safe, while dose more than 100 mg per kilogram showed toxicity changes confirmed by liver, kidney, and brain histopathological changes, as well as hematological and biochemical changes.

Mitragynine was also reported to have inhibitory effects on multiple cytochrome P450 enzymes, namely CYP2D6 (noncompetitive), CYP2C9 (noncompetitive), and CYP3A4 (competitive). This effect can potentially produce clinically significant interactions between kratom and other herbs and drugs (Hughes, 2019).

Case reports:

Kratom use was associated with a wide array of adverse effects including renal failure, liver failure, and cardiac toxicity. While some effects have been successfully managed with medical intervention, others left long-term morbidities. Patel et al. (2021) reported a case cerebrovascular accident, transient nonischemic reversible cardiomyopathy rhabdomyolysis, and irreversible renal failure following abusive doses of kratom.

Chronic recreational use of kratom was also associated with intrahepatic cholestasis, autoimmune hepatitis, acute hepatic failure, acute respiratory distress syndrome and intractable vomiting (Kapp, et al., 2011; Pantano, et al., 2016; Jaliawala et al, 2018; Aldyab, et al. 2019; Singh, et al. 2020).

Case reports revealed other side effects with acute or chronic kratom use including decrease thyroid function, hypogonadism, convulsions, disturbed level of consciousness, encephalopathy, and non-cardiogenic pulmonary oedema (Alsarraf et al., 2019).

The mechanism of all these features described with kratom overdose is uncertain and need more research. (Sangani, et al. 2021). Davidson et al., (2021) suggested that the variability of clinical picture may be attributable to differences in the products labelled “kratom,” greater sedative co-exposures, differences in population genetics or use patterns. There is no antidote for kratom. Physicians must be oriented with symptoms as treatment of overdose is largely supportive (Sangani, et al. 2021).

Kratom fatality:

Kratom toxicity and kratom-associated fatalities are being increasingly reported (Corkery, et al., 2019). In the United States between July 2016 and December 2017, Centers for Diseases Control and Prevention (CDC) reported about 100 deaths due to kratom abuse. In about 80% of kratom positive post-mortem cases the decedents had a history of other substances abuse. Fentanyl and its analogues were the most frequently identified co-ingested drugs in about 65% of kratom-positive decedents. Heroin was the second most frequent cause in kratom positive dead cases in about 32% followed by benzodiazepines in 22%, opioids in 20%, and finally cocaine in 18%. The direct cause of deterioration in those cases was attributed to cardiorespiratory arrest. (Aggarwal et al. 2018; Kuehn, B., 2019; Olsen, et al., 2019).

Forty-four cases of mortality related to kratom use have been reported by food and drug administration in 2018, including one death report of concern which involved mitragynine with no evidence of coingestions. Multidrug ingestion was found among most reported fatalities highlighting the difficulty in assessing risks associated with kratom abuse especially with poor understanding of its interactions with other medications, drugs, or herbal supplements. However, it is likely that mitragynine increases the risk of adverse events when ingested with opioids or psychoactive drugs (Gershman et al., 2019; Hughes, 2019).

Eggleston et al. (2019) made a retrospective study including National Poison Data System and a county medical examiner’s office in New York State records and reported more than 2000 cases of kratom exposures, more than 900 cases used kratom only. Kratom use is widespread in United States and poses a public health threat due wide availability as legal herbs.

Medicinal uses:

The use of Kratom in Southeast Asia has been documented back for at least 150 years and described both a stimulant effect for use in hard day labor when fresh leaves are chewed and an analgesic and relaxing effect if brewed into a tea. It also serves as a substitute and mitigation strategy for opium addiction that was widely used in Malaysia and Thailand from the 1830s to the 1920s (Veltri and Grundmann, 2019).

Kratom can be used as self-medication rather than recreational purposes. Reported indications include treatment of opioids dependence, anxiety, managing chronic pain, as weight loss medication in addition to cognitive enhancement for students and

physical enhancement for manual workers. Kratom has anti-inflammatory effect and can be used for gastrointestinal inflammatory diseases (Anand & Hosanagar, 2021; Prevete, et al. 2021). It was recently used to relieve pain of Covid-19 in a case report (Metastasio, et al., 2020).

However, the Food and Drug Administration (FDA) warning that Kratom "should not be used to treat medical conditions, nor should it be used as alternative to prescription opioids," and that the FDA finds no indication that Kratom is safe (Veltri and Grundmann, 2019).

Kratom as addictive substance

The increase in Kratom consumption in the European Union and United States corresponds to an increasing availability of Kratom for sale through the Internet. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) conducted an Internet survey of 27 European online shops in 2008 that identified Kratom as one of the most widely offered "legal highs" along with Salvia divinorum, Hawaiian Baby, Woodrose seeds, Spice, and stimulant-containing capsules (Veltri and Grundmann, 2019)

The rewarding properties of kratom metabolites and its derivatives have been elucidated in animal models. Owing to the agonistic effects of mitragynine on opioid receptors, a possibility that mitragynine may shares a common reward circuit was postulated. Associated sensitization of the dopamine system in mesencephalon was reported as reflected by an enhanced expression of dopamine transporter (DAT) and dopamine receptor-regulating factor (DRRF) mRNA. Serotonergic mechanisms were also identified as potential mechanisms for mitragynine addictive behaviors, however, warrant further investigation. Another cause for kratom liability to be an addicted substance is the antidepressant effect of mitragynine (Idayu, et al. 2011; Hassan et al., 2013; Yusoff et al., 2016).

Kratom psychoactive effects and its rewarding effects due to both stimulant and opioid like effects lead to compulsive use and significant risk of occurring addiction, decline of psychosocial functioning and physical problems that mimic other substances reported in DSM 5 substance use disorders (Oberbarnscheidt and Miller, 2019).

Long-term use of kratom may produce physical and psychological effects that are very similar to its withdrawal syndrome, that is, anxiety, irritability, mood, eating, and sleep disorders, other than physical symptoms resembling opiate withdrawal (Vento, et al., 2021)

A cross-sectional clinical study in Malaysia found that chronic abusers on kratom don't have significant social functioning impairment and kratom is a less harmful substitute to opioids (Singh et al, 2015). Additionally, chronic heavy mitragynine consumption was not associated with altered biochemical levels, although it may propably increase cardiovascular risks (Singh et al., 2020).

The prevalence of lifetime kratom use in the United States as reported by Xu, et al. (2021) was 1.5%. Most of them were white males more than 18 years old. It was also found that kratom use is associated with increased use of stimulants and sedative use disorders.

The Kratom Dependence Scale (KDS) was developed by Saingam and colleagues as a reliable tool to identify Kratom users' potential dependency. The KDS contains 16 items with a 0–3 rating scale, for a potential total score of 0–48. A score of 13–33 indicates moderate dependence whereas a score of 34/35 or higher indicates high dependence (Saingam et al., 2014).

Kratom withdrawal manifestations:

Yusoff, et al (2016) demonstrated that animals on small kratom doses for 14 days showed severe somatic withdrawal signs and anxiety within 24 hours of kratom cessation.

Abstinence of kratom produce both physical and psychological moderate withdrawal symptoms similar to opiate addiction. Reported symptoms include: nausea, vomiting, diarrrhea, rhinorrhea, watery eyes, restlessness, hot flashes, fever, agitation, anxiety, tremors, insomnia, abnormal limb movements, decreased appetite, aggression as well as depression, and craving. The length of withdrawal period can last up to more than one week (Mackay & Abrahams 2018; Oberbarnscheidt and Miller, 2019; Prevete, et al., 2021).

Khazaeli, et al. (2018) and Buresh (2018) reported the response of kratom-related withdrawal manifestation to buprenorphine-naloxone treatment in kratom dependant patients with history of opiate dependence. Similarly, McWhirter and Morris (2010) reported that dihydrocodeine and lofexidine can be used effectively.

Legal status of Kratom:

Until recently, Kratom and its primary psychoactive alkaloids were legal worldwide. However, M. speciosa, mitragynine, and 7-hydroxymitragynine are currently controlled in several European countries, many Southeast Asian countries, and some parts of the United States (Smith and Lawson, 2017).

According to Anand and Hosanagar (2021) kratom is illegal in Thailand, Malaysia, Australia, New Zealand, South Korea, Vietnam, and Myanmar. On the other hand, the legal status of kratom varies in the European Union though having open borders between members and shared currency. kratom is an illegal drug/substance in Denmark, Finland, Ireland, Latvia, Lithuania, Poland, Romania, and Sweden. The legal status of Kratom in the United Kingdom is complex; while kratom or M. speciosa is not listed as a commonly encountered Schedule 1 controlled substance, it most likely falls under the term of "psychoactive substance" of the Psychoactive Substances Act 2016 (Veltri and Grundmann, 2019).

In August 2016, the US Drug Enforcement Administration announced plans to classify kratom and its mitragynine constituents as Schedule 1 controlled substances based on unrecognition of legitimate medical use for kratom. However, there is variability regarding the legal status of kratom from one state to another in the USA. Kratom is legal in all US States except Arkansas, Alabama, Indiana, Rhode Island,

Wisconsin, and Vermont and the District of Colombia (Corkery et al., 2019; Veltri and Grundmann, 2019).

Interestingly, Thailand is reconsidering the legal status of kratom again in an effort to find safer stimulants to fight high rate of methamphetamine addictions (Bergen-Cico and MacClurg, 2016).

Kratom safety:

Unfortunately, no randomized controlled trials on the safety of kratom products are currently unavailable. However, surveys of active abusers suggested many acute and chronic physiological and psychological side effects necessitating medical awareness (Alsarraf et al., 2019).

Reported cases of deaths related to kratom were associated with coadministration of medications or herbs suggesting unsafe drug interactions. Since mortalities associated with kratom use commonly report suspected polysubstance use, the risk of death due to using kratom alone is challenging to determine (McIntyre et al., 2015; Hughes, 2019; Matson & Schenk, 2019).

Particularly in the West, kratom is often used as a recreational drug, where it is perceived as a safe, "legal high". Kratom consumption and associated health effects are debatable. Although adverse health effects are not experienced by most kratom users, physicians should bear in their mind, the side effects, toxicity, addictive potential, and withdrawal symptoms of kratom which are increasingly met in emergency department due to widespread use (Galbis-Reig, 2016).

Henningfield et al. (2019) one of defenders of kratom as safe products, noted that the risk of overdose death is >1000 times greater for opioids than for kratom. Also, Yue and Katz (2018) experimental study demonstrated a limited abuse liability of mitragynine, and its use in reducing opioid abuse. Experimental study of Wilson, et al. (2021) showed that kratom and mitragynine can be of clinical value when used to decrease withdrawal symptoms in morphine dependent animals and produce less physical dependence than other opioids.

Garcia-Romeu et al (2020) suggested that kratom has a relatively benign risk profile compared to typical opioids. Reported adverse effects were mostly mild, short in duration, related to younger age, depression, history of severe pain, and potentially related to co-use with alcohol or other opioids.

But the problem to find clinical value of kratom is explained by Oberbarnscheidt and Miller, (2019) who showed that there many psychoactive materials beside mitragynine are found in kratom like 7-hydroxymitraggynine, paynantheine, speciogynine and more than twenty other substances that are not well understood yet. There are many details to be learned about kratom. Kratom might have some medical properties but unlike FDA approved medications, samples are variable as the concentrations of active ingredients are varying greatly depending on the freshness of the leaf and the potency of the particular plant and its strain.

The labelling of kratom products available to consumers needs to follow appropriate regulatory standards as well as quality good manufacturing practices to ensure that consumers who seek out kratom are not exposed to adulterated or contaminated products and consumers should avoid using other herbs concomitantly to avoid interactions (Veltri and Grundmann, 2019).

Finally, with limited awareness about kratom, cases of toxicity may be under recorded. Diagnosis of kratom toxicity may be confusing being variable from stimulant to depressant effect. In addition, kratom cannot be detected in standard urine drug tests, hence the diagnosis relies on the subjective history and specific questioning by the physician. This makes kratom use increase among bus drivers and manual workers without detection. Increased education among physicians and nurses is needed to provide improved detection and evaluation of kratom toxicity cases.

Medical providers should be aware of emerging substances and concurrent, sequential, or simultaneous use of other drugs which may impact healthcare recommendations and prescribing practices (Striley et al, 2022)

Figure (1): Mitragyna speciosa leaves (Raffa, 2014)

Conclusion

Kratom is an emerging issue of abuse, toxicity, addiction, and mortality worldwide. Current available data are not enough about kratom safety, pharmacology, toxicity, and fatality. Until now the food and drug administration don't recognize any therapeutic uses of kratom. Public awareness and physicians' education about kratom is needed and mitragynine detection in urine by ultra-high-performance liquid chromatography is a must in suspected cases.

Recommendations

Further clinical studies are needed to investigate therapeutic potentials of kratom. Authority of Drug Enforcement in Egypt need to have strict rules about Kratom and make mitragynine concentration test available especially in Forensic Criminal Laboratories.

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تعاطي القرطوم كقضية ناشئة من الإدمان ، وسمية الجرعات الزائدة والوفيات: مراجعة

ميراي مدحت شكري زخاري[١]

الملخص العربى

مقدمة: القرطوم (ميتراجينا سبيشيوزا) هي شجرة محلية لعائلة نبات البن في تايلاند وجنوب شرق آسيا. لطالما استخدمت أوراق مضغ القرطوم كدواء تقليدي لتخفيف الألم المزمن وانسحاب المواد الأفيونية.

الهدف: توضح هذه المراجعة كيف أن تعاطي القرطوم هو ظاهرة مثيرة للقلق بسبب الإدمان المرتبط به، والسميات الزائدة للجرعات والوفيات

المراجعة: أظهرت الدراسات التي تم بحثها أن القرطوم له تأثيرات مثبطة ومنشطة وفقًا للجرعة. في السنوات القليلة الماضية، تم تقديم القرطوم في أوروبا والولايات المتحدة، حيث أن المنتجات العشبية الطبيعية الآمنة غير المنظمة تحل محل المنتجات الأفيونية خاصة من خلال أسواق الأدوية عبر الإنترنت بالإضافة إلى تعرض متعاطي المخدرات من خلال المنتجات الملوثة. يجب توعية علماء السموم الاكلينيكية في مصر والشرق الأوسط حول القرطوم ومظاهره السريرية الضارة كمشكلة محتملة.

الخلاصة: لايزال البحث حول سلامة القرطوم ناقصاً.

١. قسم الطب الشرعي والسموم، كلية الطب، جامعة سوهاج، سوهاج، مصر