



Khat-drug interactions: A systematic review

[Interacciones khat-medicamentos: una revisión sistemática]

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Abstract

Context: Consumption of khat leaves has been disseminated worldwide with the migration of its users from Arabia and Africa. Despite numerous reports regarding the associations of khat chewing with serious health impacts, a significant number of people worldwide uses khat daily, especially in its origin countries. The risk of co-administration of khat and drugs (prescription and over the-counter medications) is high among these individuals, leading to increase probability of adverse khat-drug interactions. The likelihood of khat-drug interactions could be higher than drug-drug interactions because drugs usually contain single chemical entities while almost all herbs (including khat) contain mixtures of pharmacologically active constituents.

Aims: To review the literatures on how khat interacts with some drugs and whether it is favorable or not.

Methods: The study was conducted as a systematic review. The electronic literature searches were made in Google search engine to access publications from databases like PubMed, Google Scholar, and Cochrane using the keywords 'khat', '*Catha edulis*' in combination with the terms 'drug interaction', 'adverse-effects', 'side effects', 'adverse drug reaction', 'safety', and 'toxicity' to identify relevant articles.

Results: A total of 250 articles was identified, and these articles were checked in terms of title, abstract, and content according to inclusion and exclusion criteria. Finally, 18 articles were included in the study. The khat use significantly interact with most drugs and may cause unpredictable pharmacological sequences.

Conclusions: Healthcare providers suggest patients' khat abstinence during medication process. Future studies need to investigate the khat-clinical drugs interactions especially with chronic used drugs.

Keywords: *Catha edulis*; cathinone; drug interactions; drug metabolizing enzymes; khat.

Resumen

Contexto: El consumo de hojas de khat se ha difundido en todo el mundo con la migración de sus usuarios desde Arabia y África. A pesar de los numerosos informes sobre las asociaciones de masticar khat con graves impactos en la salud, un número significativo de personas en todo el mundo usa khat a diario, especialmente en sus países de origen. El riesgo de coadministración de khat y medicamentos (medicamentos recetados y de venta libre) es alto entre estos individuos, lo que aumenta la probabilidad de interacciones adversas entre ellos. La probabilidad de interacciones entre el khat y el fármaco podría ser mayor que la de las interacciones entre fármacos porque los fármacos suelen contener entidades químicas únicas, mientras que casi todas las hierbas (incluido el khat) contienen mezclas de componentes farmacológicamente activos.

Objetivos: Revisar la literatura sobre cómo interactúa el khat con algunas drogas y si es favorable o no.

Métodos: El estudio se realizó como una revisión sistemática. Las búsquedas de literatura electrónica se realizaron en el motor de búsqueda de Google para acceder a publicaciones de bases de datos como PubMed, Google Scholar y Cochrane utilizando las palabras clave 'khat', '*Catha edulis*' en combinación con los términos 'interacción farmacológica', 'efectos adversos', 'efectos secundarios', 'reacción adversa a un fármaco', 'seguridad' y 'toxicidad' para identificar artículos relevantes.

Resultados: Se identificó un total de 250 artículos y se verificaron estos en términos de título, resumen y contenido según los criterios de inclusión y exclusión. Finalmente, 18 artículos fueron incluidos en el estudio. El uso de khat interactúa significativamente con la mayoría de los fármacos y puede provocar secuencias farmacológicas impredecibles.

Conclusiones: Los proveedores de atención médica recomiendan la abstinencia de khat de los pacientes durante el proceso de medicación. Los estudios futuros deben investigar las interacciones entre el khat y los fármacos, especialmente con los fármacos de uso crónico.

Palabras Clave: *Catha edulis*; catinona; enzimas metabolizadoras de fármacos; interacciones con fármacos; khat.

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INTRODUCTION

Consumption of khat leaves has been disseminated worldwide with the migration of its users from Arabia and Africa (Lim et al., 2019). During the past few decades khat chewing has gained global prominence as the result of migration. Khat already has a global market and a recognized economic value comparable to other crops such as tea, coffee, and cacao. The khat trade has a complex distribution network. As a consequence of rapid and relatively inexpensive air transportation, khat has been reported in Great Britain, Netherlands, Canada, Australia, New Zealand, USA and even in Hungary (Abbott et al., 2019). It is estimated that 20 million people worldwide chew khat leaves regularly to enjoy its psychostimulant effects (Balint et al., 2009). In Yemen, khat-chewing is a widespread habit; approximately 80–85% of male and 10–60% of female adults in Northern Yemen chew khat at least once a week (Bogale et al., 2016). Despite numerous reports regarding the associations of khat chewing with serious health impacts, a significant number of people worldwide use khat on daily basis, especially in its origin countries (Lim et al., 2019). The risk of co-administration of khat and clinical drugs (prescription and over-the-counter medications) (Abbott et al., 2019) is high among these individuals, leading to increased probability of adverse khat-drug interactions. The likelihood of khat-drug interactions could be higher than drug-drug interactions because drugs usually contain single chemical entities while almost all herbs (including khat) contain mixtures of pharmacologically active constituents (Wondemagegn et al., 2017). Therefore, herb-drug interactions may pose a potential risk for patients on medication with narrow therapeutic range drugs to cause serious clinical consequences (Bedada et al., 2018). Khat-drug interactions probably alter the drug's pharmacokinetics and/or pharmacodynamics, and hence resulting in adverse drug interactions or decreased treatment efficacy. Clinical drug typically contains single chemical moiety, whereas most of herbal drugs (even single herb drug) contains more than one

chemical moiety having pharmacological activity. Khat is taken by healthy individuals as well as patients with medical conditions including diabetes mellitus, cancer, mental illness and other acute or chronic medical conditions. Khat-drug interaction can occur through either pharmacokinetic or pharmacodynamics mechanisms. Khat can alter the oral bioavailability of the co-administered clinical drugs, which can result in either synergistic/additive (positive) or antagonistic (negative) effect on its action.

Catha edulis (Vahl) Endl. (*Celastraceae*), commonly known as “khat,” is a tree or a large shrub that is endogenously found in Arab peninsula specially in Yemen, and some African countries such as Ethiopia and Kenya, and in western Asia (Hussain, 2011). Its young buds and tender twigs, young shoots or stem tips are chewed to attain a state of euphoria and stimulation. Khat is an ever-green shrub, which is cultivated as a bush or small tree. The leaves have an aromatic odor. The taste is astringent and slightly sweet. The plant is seedless and hardly growing in a variety of climates and soils. Khat can be grown in droughts where other crops have failed and also at high altitudes. Khat is harvested throughout the year and planting is staggered to obtain a continuous supply. The leaves are chewed to release the active constituents slowly to be ingested with saliva. Chewing sessions can last from 3 to 7 h (Cupp, 1999; Al-Juhaishi et al., 2012). Khat contains more than forty alkaloids, glycosides, tannins, amino acids, vitamins, and minerals. The environmental and climate conditions determine the chemical profile of khat leaves. In Yemen, about 44 different types of khat exist originating from different geographic areas of the country (Izzo, 2012; Bedada et al., 2015). The phenylalkylamines and the cathedulins are the major alkaloids (Table 1). The cathedulins are based on a polyhydroxylated sesquiterpene skeleton and are basically polyesters of eunonyminol. Recently, 62 different cathedulins from fresh khat leaves were characterized (Patel, 2000). The khat phenylalkylamines comprise cathinone [S-(–)-cathinone], and the two diastereoisomers

Table 1. Summary of different classes of alkaloids in khat leaves (Nyongesa, 2013).

Alkaloids in khat			
Phenylalkylamines		Cathedulins	
Phenylpropylamines		Phenylpentenylamines	High molecular mass (1000-1170 Da)
Phenylpropanonamine	Phenylpropanolamine	Pseudomerucathine	Medium molecular mass (765-891 Da)
(-) Cathinone	Norephedrine	Merucathinone	Low molecular mass (595-700 Da)
	(+) Cathine	Merucathine	

cathine [1S, 2S-(+)- norpseudoephedrine or (+)-norpseudoephedrine] and norephedrine [1R,2S-(-)-norephedrine]. These compounds are structurally and pharmacologically related to amphetamine and noradrenaline. The plant contains the (-)-enantiomer of cathinone only (Al-Juhaishi et al., 2012). Thus, the naturally occurring S-(-)-cathinone has the same absolute configuration as S-(+)-amphetamine. Cathinone is mainly found in the young leaves and shoots. During maturation, cathinone is metabolized to cathine [(+)-norpseudoephedrine] and (-)-norephedrine. The leaves contain [(+)-norpseudoephedrine] and (-)-norephedrine in a ratio of approximately 4:1 (Al-Juhaishi et al., 2012). Other phenylalkylamine alkaloids found in khat leaves are the phenylpentenylamines merucathinone, pseudomerucathine and merucathine. These compounds seem to contribute less to the stimulant effects of khat (Cupp, 1999; Lim et al., 2019). Almost all khat pharmacological properties are attributed to cathinone, which is an alkaloid that decomposes rapidly *in vivo* by metabolism into nor-pseudoephedrine and norephedrine giving amphetamine-like action (Patel, 2000).

Drug interactions are a specific category of adverse drug reactions, which occur when a food, supplement, herb, clinical drug, or illicit substance affects the therapeutic response of a clinical drug when taken concomitantly (Abbott et al., 2019). When any combinations of these could lead to undesired change in the condition of the patient then that interaction is of potential clinical significance. Drug interactions can be classified as: drug-disease, herb-drug interactions (HDIs), drug-drug,

food-drug, supplement-drug, alcohol-drug, tobacco-drug, and illicit substance-drug interactions (Abbott., 2019). The drug-disease interaction is associated in patient suffering from any disease such as renal or hepatic impairment, aplastic anemia, asthma, cardiac arrhythmia, diabetes mellitus, epilepsy hypothyroidism etc. If the patient uses drug and herb concomitantly then there are chances of drug-herb interaction as both contain pharmacological active compounds (Izzo, 2012). Drug-drug interaction occurs between two clinical drugs like ciprofloxacin taken with antacids (Bedada et al., 2015). There are other examples of interaction of drug with dietary supplements, food, beverages, cigarette etc. For example, vitamin K and anti-coagulants like warfarin, theophylline, and tobacco (Bedada et al., 2015).

When interactions occur between khat and clinical drugs, it can be caused by either pharmacokinetic (PK) or pharmacodynamic mechanisms. While pharmacodynamic interactions could contribute to adverse interactions, pharmacokinetic interactions can occur at any point during absorption, distribution, metabolism, and excretion (ADME). Drug-metabolizing enzymes and drug-transporters play crucial roles in the ADME of xenobiotics, including clinical drugs or illicit substances (Abbott et al., 2019). Khat-drug interactions are based on alteration of the plasma concentrations of a victim drug or its metabolites due to khat causing inhibition and/or induction of the metabolizing enzymes like cytochrome P-450 system and drug transporters or interference and changes the absorption, distribution, metabolism, protein binding, or excretion of a victim drug (Lim et al., 2019).

MATERIAL AND METHODS

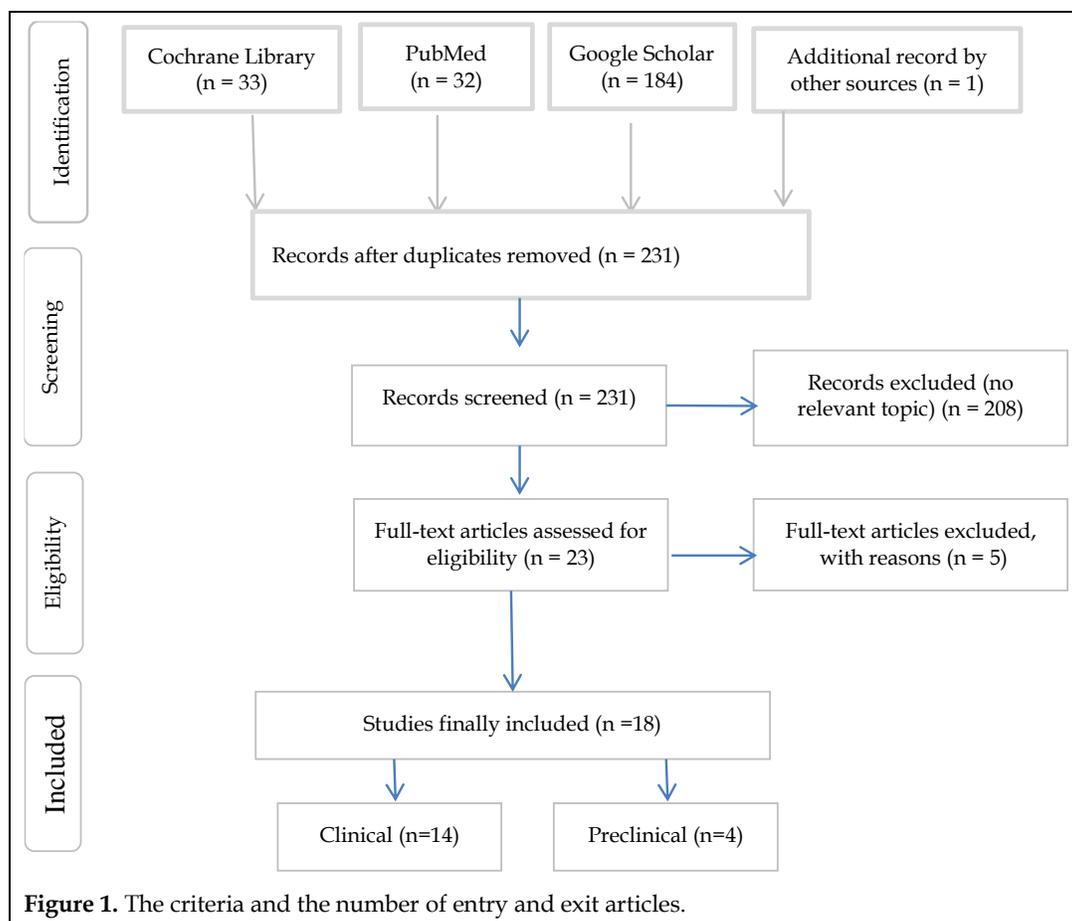
Study design

This study was conducted as a systematic review. Electronic literature searches were made in Google search engine to access publications from databases like PubMed, Google Scholar, and Cochrane using the keywords 'khat', '*Catha edulis*' in combination with the terms 'drug interaction', 'adverse-effects', 'side effects', 'adverse drug reaction', 'safety', and 'toxicity'. The search included journals, reports, books, and related documents published in English language were eligible for inclusion. All preclinical and clinical reports on interactions were read and relevant data were extracted by the first author into predefined tables and validated by the second author. *In vitro* experiments, case reports and case series of possible

interactions between khat and drugs were included. To limit the occurrence of undesirable articles, these keywords and MeSH terms were searched in the "Title/Abstract" category.

Selection criteria

To select the articles, the Rayyan web and mobile app for systematic reviews was used (Ouzzani et al., 2016). 250 articles were identified, and then the identified articles were checked in terms of title, abstract, and content according to inclusion and exclusion criteria. Finally, 18 articles were included in the study. The algorithm for the selection and filtering of articles is represented in Fig. 1. The final selected articles were analyzed in detail to assess the most current and relevant information about possible interactions between khat (*Catha edulis*) and clinical drugs.



RESULTS AND DISCUSSION

The findings of the search on khat and clinical drugs interactions did not identify any review assessing the interaction between khat and clinical drug. Based on the results from studies, it was found that khat interacts with the following medications (Table 2).

Antibacterial drugs

Khat has been shown to reduce the bioavailability of antibiotics such as ampicillin, amoxicillin, cephadrine, ciprofloxacin and tetracyclines (Abbott et al., 2019). Omer et al. (1997) reported a significant decrease in ampicillin bioavailability. However, no effect was noted with amoxicillin. The suggested explanation was that the tannins might have complexed the antibiotics or by interfering with the gut absorption processes. Amphetamine-like compounds affect appetite centrally by acting in the hypothalamus. Apart from its central effect, cathinone enhances sympathomimetic activity leading to a delay in gastric emptying. In another study, the absorption of cephadrine was reduced by 50%, when has been taken concomitantly with khat (Kassem, 2004). Tetracycline-khat interaction has been evaluated both *in vitro* and *in vivo*. *In vitro* studies have indicated a statistically significant interaction between tetracycline and khat. Such interaction may be attributed to possible complexation between tetracycline and certain khat constituents, such as polyvalent cations, calcium, magnesium, iron, cadmium, lead, copper, and zinc or possible complexation and/or adsorption of tetracycline-HCl with and/or onto tannic acid. Other possible complexation may also occur with other khat constituents such as cathinone, cathine and pseudoephedrine. On the other hand, it was consistent with the *in vitro* findings. *In vivo*, khat chewing significantly reduces most pharmacokinetics parameters, which reflect reduction in the rate and extent of tetracycline absorption, which may be attributed to the same causes we mentioned above. The same study reported a significant reduction in a half-life and the elimination rate constant of tetracycline. This reduction occurs due to possible enhancement of renal excretion

rate, perhaps by possibly urinary pH modification by certain khat constituents and/or possible enhancement of tetracycline metabolism via enzyme induction by one or more khat constituents (Farah et al., 2015). A recent study has shown ciprofloxacin-khat interaction that the reduction in pharmacokinetics parameters of ciprofloxacin. The result attributed to the same reasons previously mentioned (Al-Mekhlafi, 2020).

Antimalarial drugs

In Yemen, it was reported that the co-administration of chloroquine (CQ) and khat was found to significantly affects the pharmacokinetics of CQ among both healthy controls and malaria patients and significantly reduces plasma CQ concentrations in malaria patients (Issa et al., 2016). At therapeutic concentration, chloroquine is metabolized into desethylchloroquine primarily by CYP2C8 (60%) followed by CYP3A4 (25%), and CYP2D6 is a high affinity but with significantly low-capacity enzyme to metabolize chloroquine (Projean et al., 2003). Furthermore, a previous study reported no significant inhibition of CYP2D6 by chloroquine in human (Masimirembawa et al., 1996). Thus, khat-chloroquine interaction reported by Issa et al. (2016), may not be at the CYP2D6 level. Nevertheless, concomitant khat use may compromise the antimalarial activity of primaquine. Indeed, a significant association of low-activity CYP2D6 phenotypes with the initial relapse and number of malaria relapses was reported (Bennett et al., 2013). Therefore, khat abstinence while on treatment with CYP2D6 substrate drugs is advisable (Bedada et al., 2018).

Antiplatelet drugs

Noman and Kadi (2012), in their study in healthy volunteers suggested that khat chewing had a worse effect on the bioavailability and pharmacokinetic properties of aspirin. A significant reduction of bleeding time was observed in khat chewers who were taking aspirin (100 mg daily) on a long-term basis compared with non-khat chewers taking the same dose of aspirin. This finding suggested that constituents of khat attenuate the antiplatelet aggregating properties of aspi-

rin, and thereby neutralize the beneficial actions of aspirin (Alkadi et al., 2008). Alhazmi et al., 2020, reported a significant influence of khat on the peak ratio of clopidogrel (CLOP) metabolite, which was found to be significantly decreased in comparison to CLOP alone, suggesting a significant decrease in the conversion of CLOP to its active metabolite due to the inhibition of CYP450 enzymes by khat. Therefore, there might be a need for dose adjustment for regular khat chewers using CLOP.

CNS drugs

Elkady et al. (2020) reported that co-administration of khat with some CNS drugs (clomipramine, vilazodone, aripiprazole, and sertraline) significantly increase their bioavailability in rats, which attributed to the inhibition of their metabolic enzymes CYP450, CYP2D6 and CYP3A4 isoforms by khat.

Anesthetic drugs

Khat has been shown to reduce the effects of a local anesthetic drug, benoxinate (oxybuprocaine) (Abbott et al., 2019). Khat consumption decreases pain threshold and affects patients' comfort during local anesthesia and during surgery in routine cataract surgery (Bamashmus et al., 2010). The effect of khat on general anesthetics was reported by Bamgbade, in Manchester, he noticed the effect of khat consumption on three cases that had general anesthesia and he recommended that optimal perioperative care of khat users requires careful titration of cardiostable anesthetic and comprehensive monitoring (Bamgbade, 2008). However, Mion (2017) observed that the interaction between khat and general anesthesia was not what was commonly believed (the popular perception that patients who chronically ingest amphetamine or amphetamine-like drugs will require high doses of anesthetic drugs to achieve adequate analgesia, sedation, and anesthesia) (Johnston et al., 1972).

Neuroleptics drugs

In addition to psychological adverse effects such as psychosis and exacerbation of pre-existing psychotic disorder, khat interacts with antipsychotic drugs such as haloperidol and risperidone

leading to attenuates all used treatment medications, aggravates the disease symptoms, and deteriorates all biochemical markers of the patients. So that khat chewing in schizophrenic patients is contraindicated (Weli and El-Shaibany, 2011; Kotb El-Sayed and Amin, 2015)

Alteration the metabolizing enzymes activity by khat

The modulation in the activity of CYPs and drug transporters by herbal products may influence the oral bioavailability, which alters the blood levels of affected drug (Brown et al., 2008). Inhibition of drug metabolizing enzymes is considered the most common mechanism underlying PK drug-drug interactions and HDIs (Wienkers and Heath, 2005). *In vitro*, a current study carried by Lim et al. (2019) reported that khat-drug interactions were possible due to administration of clinical drugs metabolized by CYP2C9/CYP2D6/CYP3A4 together with khat chewing and recommended further *in vivo* studies are required to confirm their findings and identify the causative constituents of these inhibitory effects. This recent study investigated inhibitory potencies of khat ethanol extract and its major active constituent cathinone on the major CYP enzymes, CYP2C9, CYP2D6, and CYP3A4 involved in phase I drug metabolism. The CYP450 enzymes are susceptible to inhibition or induction by natural products including herbal medicines that contain mixture of phytochemicals (Delgoda and Westlake, 2004; Wanwinmolruk and Prachayasittikul, 2014; Cho and Yoon, 2015). Chronic use of khat is associated with a variety of mental and personality disorders that require treatment and CYP2D6 metabolizes several psychoactive drugs including psychotropic, anti-depressants and antipsychotics (Bedada et al., 2018). Considerable inhibition of CYP2D6 by khat use may result in unanticipated adverse events and/or treatment failures. CYP2D6 is constitutively expressed in human brain, where it is involved in endogenous metabolism including dopamine and serotonin (Bedada et al., 2018). Cathinone increases the levels of dopamine in the brain, possibly by acting on the catecholaminergic synapses.

Table 2. Some selected khat-drug interactions.

No.	Type of study	Drug Category	Drug	Mechanism of action of the drug	Mechanism of interaction with khat	Outcome	Reference
1	Clinical and basic (8 healthy adult male)	Antibiotic	Ampicillin	Acts as an irreversible inhibitor of the enzyme transpeptidase, which is needed by bacteria to make the cell wall.	Reduce bioavailability	Urine level	Omer et al., 1997
2	Clinical and basic (8 healthy adult male)		Amoxicillin	As above	Reduced the extent of amoxicillin absorption	Urine level	Ghani et al., 1999
3	Clinical and basic (10 healthy adult male)		Tetracycline	Protein synthesis inhibitors.	Formation of non-absorbable complex with polyvalent cations, such as calcium, magnesium, iron, cadmium, lead, copper, and zinc. Delayed in gastric emptying. Prolong resident time in stomach leading to formation of epitetracycline the less antimicrobial activity	Blood level	Farah et al., 2015
4	Clinical and basic (8 healthy adult male)		Cephadrine	Inhibits bacterial cell wall synthesis in a manner similar to that of penicillin	Reduce bioavailability	Urine level	Kassem, 2004
5	Clinical and basic (8 healthy adult male)		Ciprofloxacin	Inhibiting a type II topoisomerase (DNA gyrase) and topoisomerase IV, necessary to separate bacterial DNA, thereby inhibiting cell division	Reduce bioavailability	Plasma level	Al-Mekhlafi, 2020
6	Prospective clinical trial (323 patients undergoing cataract)	Local anesthetic	Benoxinate (oxybuprocaine)	Reversible block, competitive inhibition of Ach, decreased membrane permeability to Na ⁺ influx	Decreases pain threshold	Pain score cart (pain experience during injection, intraoperatively, and postoperatively)	Bamashmus et al., 2010
7	Clinical report (three adult patients)	General anesthetic			Optimal perioperative care of khat users requires	Observational	Bamgbade, 2008
8	Clinical and basic (15 healthy adult male and 103 patients)	Antimalarial drug	Chloroquine	The drug concentrates in the acidic food vacuole of the parasite and interferes with essential processes	Reduce bioavailability	Plasma level, parasite clearance	Issa et al., 2016
9	Clinical and basic (28 healthy adult male)	Antiplatelet	Aspirin	Aspirin is non-selective and irreversibly inhibits COXs	Attenuate the antiplatelet aggregating properties of aspirin	Urine level	Noman and Kadi, 2012

Table 2. Some selected khat-drug interactions (continued...)

No.	Type of study	Drug Category	Drug	Mechanism of action of the drug	Mechanism of interaction with khat	Outcome	Reference
10	Clinical and basic (74 healthy adult male)	Antiplatelet	Aspirin			BT, CT, PT, PTT, PC and BF	Alkadi et al., 2008
11	Pre-clinical (eighteen rats)		Clopidogrel	Inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor	Inhibition of CYP450 enzymes by khat	CYP450 enzymes activity	Alhazmi et al., 2020
12	Clinical trial (170 asthmatic patients)	Anti-asthmatic	Salbutamol	β_2 agonist	Improve the salbutamol effects	Frequent, asthmatic symptoms, FEV ₁ %, PEFR%	Yitna et al., 2018
13	Pre-clinical (twenty-four C57BL/6J WT and twelve DAT-Cnr2 cKO mice)		JWH-133	CB2R agonist	Interact with khat extract-mediated locomotor effects	Locomotor, activity test, immunohistochemistry, reverse transcriptase polymerase chain reaction technique	Geresu et al., 2019
14	Pre-clinical (rats)	CNS drugs	Clomipramine, vilazodone, aripiprazole, sertraline	A tricyclic antidepressant, a serotonin partial agonist-reuptake inhibitor (SPARI), an antipsychotic, a type of antidepressant known as a selective serotonin reuptake inhibitor (SSRI), respectively	Khat significantly increase bioavailability of these drugs, which might be attributed to inhibition of their metabolic enzymes CYP450, CYP2D6 and CYP3A4 isoforms		Elkady et al., 2020
15	Clinical trial (69 patients)	Neuroleptics	Haloperidol, risperidone	A first-generation (typical antipsychotic)	Reduce the effectiveness of drugs and increase the frequency of relapse	Clinical observational study	Weli and El-Shaibany, 2011
16	Clinical trial (37 healthy adult male and 42 paranoid shazo)		Haloperidol, risperidone			DOPAC, homovanillic acid, serotonin 5-hydroxyindoleacetic acid, epinephrine, norepinephrine	Kotb El-Sayed MI and Amin; 2015
17	Preclinical <i>in vitro</i>		Clinical drugs metabolize by CYP2C9, CYP2D6 and CYP3A4		Inhibit CYP2C9, CYP2D6 and CYP3A4	CYP 450 enzymes activity	Lim et al., 2019
18	Clinical and basic (63 healthy adult male)		Drugs metabolize by CYP2D6		Inhibit CYP2D6	CYP 450 enzymes activity	Bedada et al., 2018

JWH-133: A potent selective CB2 receptor agonist; CB2R: Cannabinoid receptor type 2; FEV₁%: Forced expiratory volume in one second; PEFR: Peak expiratory flow rate; BT: Bleeding time; CT: Clotting time; PT: Prothrombin time; PTT: Partial thromboplastin time; PC: Platelets count; BF: Blood film; C57BL/6J WT and DAT-Cnr2 cKO mice: mutant mice.

A previous clinical study suggested that CYP2D6 slow metabolizers might have a higher dopamine tone in the pituitary (Bedada et al., 2018) and the inhibition of CYP2D6 activity in the brain may be another mechanism by which cathinone, the main psychostimulant alkaloid in khat, increases the levels of dopamine in the brain.

Possible khat potential therapeutic interactions

Yitna et al. (2018) have reported that apart from its psycho stimulating prosperities, khat has moderate potential benefit for the improvement of episodes of an asthma attack and reduction of asthmatic symptoms. This study showed that khat chewer asthmatic patients had relatively better peak expiratory flow rate and also relatively lesser recurrent night-time awake due to an asthmatic attack. The possible explanation for this finding could be the effect of khat through its constituents upon activation of α_2 and 5HT₇ receptors and inhibition of ACh thereby modulating airway smooth muscle contraction (Freud-Michel et al., 2008). The results by Geresu et al. (2019) suggested the CB2Rs selectively interact with khat extract-mediated locomotor effects and could be utilized as therapeutic target in central nervous system movement disorders associated with dopamine dysregulation.

Limitations

The present review has several limitations that must be acknowledged with the regard of interpreting the findings. The number of databases searched was more modest and a language constraint was also applied, so that there might be several publications that were ignored. As the selection and assessment criteria were established based on the authors' subjunctives points of views, the quality of the included studies may not be appraised appropriately. In addition, the selected articles included different study types not only clinical trials, but preclinical studies involved *in vitro* and *in vivo*. Another limitation was that the review concentrated on the interaction of khat with clinical drugs and excluded the articles eval-

uated the interactions of khat with alcohol and tobacco and illicit substances.

Future perspectives

Despite the above observations, the literature reviewed is associated with a few shortcomings, suggesting the need for further research and documentation on this area of knowledge. Further clinical studies are recommended to thoroughly investigate the interaction of khat with clinical drugs.

CONCLUSIONS

The study concluded that khat use significantly interact with most clinical drugs and may cause unpredictable pharmacological sequences. Healthcare providers should recommend their patients to stop khat chewing during medication process. The study recommended conducting more studies, which are very important for investigation the khat-clinical drugs interactions especially with chronic used drugs. It is recommended that, in the interim, healthcare providers should be more familiar with the known and suspected adverse khat-drug interactions to optimally serve their patients who chew khat.

CONFLICT OF INTEREST

The authors declare no conflicts of interests.

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AUTHOR CONTRIBUTION:

Contribution	Albaser NA	Mohamad AWH	AL-Kamarany MA
Concepts or ideas	x		x
Design	x	x	x
Definition of intellectual content	x		x
Literature search	x		x
Experimental studies	x		
Data acquisition	x		x
Data analysis	x		
Statistical analysis			
Manuscript preparation	x		x
Manuscript editing	x		x
Manuscript review	x	x	x

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