IJOEM
International Journal of Occupational and Environmental Medicine

Systematic Review

To review this article online, scan this QR code with your Smartphone

Qat Chewing and Risk of Potentially Malignant and Malignant Oral Disorders: A Systematic Review

S El-Zaemey, J Schüz, ME Leon

Abstract

Background: *Qat* (also known as *Khat, Kat* and *Miraa*) is a green-leaved plant (*Catha edulis*). It is a shrub indigenous to Yemen and certain parts of eastern Africa. Chewing the leaves, which have sympathomimetic and euphoric effects, has been documented in many countries and increased with worldwide migration. The effect of long-term chewing *Qat* on the oral cavity is unknown.

Objective: A systematic review was performed to identify any associations between *Qat* chewing and the occurrence of potentially malignant and malignant oral disorders.

Methods: Medline and the Web of Science were searched for articles published before May 2014 without limits with regard to publication date and language.

Results: From a total of 890 papers identified, 17 English papers reported potentially malignant or malignant oral disorders and *Qat* chewing. One additional paper in Arabic language was identified from reviewing the list of references of eligible papers. It was found that exposure to *Qat* may be associated with potentially malignant and malignant oral disorders, but methodological issues, such as inadequate study design, sample size, selection of study subjects, clinical evaluations of outcome and limited adjustment for confounders, limit the strength of the evidence base in this area.

Conclusion: The association between *Qat* chewing and potentially malignant and malignant oral disorders remains debatable and requires further investigations.

Keywords: *Catha edulis*; Oral disorders; Yemen; Euphoria; Neoplasms; Oral health

Section of Environment and Radiation International Agency for Research on Cancer, Lyon, France

Introduction

Qat (also known as *Khat, Kat* and *Miraa*) is a green-leaved plant (*Catha edulis*) and belongs to the Celastraceae family. It is a dicotyledonous evergreen flowering tree that grows in the equatorial climates mainly in the Arabian Peninsula and the regions around the horn of Africa (Fig 1).[1] Ethiopia, Yemen, Kenya, Madagascar and Somalia are the five main *Qat* growing countries.[2] The plant also grows to a lesser extent in Uganda, Tanzania, Rwanda, Zimbabwe, Zaire, Angola, Malawi, Mozambique, Zambia, Swaziland and South Africa.[3,4] *Qat* is known by various names in different regions; it is called *Miraa* in Kenya, *Qat* in Somalia and Yemen, and *Chat* in Ethiopia (Fig 2). The environment and climatic conditions in which it is grown determine the chemical profile of *Qat* leaves and, to some extent,

Correspondence to Sonia El-Zaemey, PhD. Section of Environment and Radiation, International Agency for Research on Cancer, 150, cours Albert Thomas, 69372 Lyon Cedex 08, France
Tel: +618-9346-8573
E-mail: ElzaemeyS@fellows.iarc.fr
Received: Nov 3, 2014
Accepted: Mar 16, 2015

Cite this article as: El-Zaemey S, Schüz J, Leon ME. Qat chewing and risk of potentially malignant and malignant oral disorders: A systematic review. *Int J Occup Environ Med* 2015;**6**:129-143.

Figure 1: Fresh *Qat* leaves

its taste. For example, in Yemen, there are 44 types of *Qat* cultivated in different geographic areas of the country.[1,5] Normally, *Qat* leaves have an astringent taste and an aromatic smell but the young leaves are slightly sweet.[1,5] *Qat* chewing has been traditionally a habit of men in Yemen however, recently it has been reported that women start to chew *Qat* as integral part of their social life.[6]

Figure 2: Blue area shows areas where *Qat* has been reported grown and/or consumed.

Qat contains a number of chemicals including cathine and cathinone.[7,8] These chemicals are similar in structure to but less potent than amphetamine. However, they cause similar psychomotor stimulant effects.[7] Cathinone is considered the main active ingredient in the fresh leaves of *Qat* and has sympathomimetic effects that have been shown to increase heart rate and blood pressure.[1] In 1980, the World Health Organization (WHO) classified *Qat* as a drug of abuse that can produce mild to moderate degrees of psychological dependence, but to a lesser extent than tobacco and alcohol.[8] Furthermore, *Qat* has been reviewed several times by a WHO Expert Committee on Drug Dependence, and it was concluded that the level of abuse and threat to public health is not significant enough to warrant international control.[8,9] Nevertheless, some countries including Finland, Germany, New Zealand, Sweden, France, Norway, Denmark, Canada, USA,[10] UK,[11] and Saudi Arabia,[12] have prohibited *Qat* consumption. Even though *Qat* import into these countries is illegal, certain quantities are believed to be smuggled into them.

Qat leaves are chewed for different purposes: relieve fatigue, enhance work capacity, stay alert, reduce hunger, induce euphoria, and enhance self-esteem.[13,14] *Qat* has been appreciated for medical purposes too.[15] However, it is mainly chewed for recreational purposes. For example, it is usually chewed during informal gatherings (*Qat* sessions) in which the participants are engaged in discussions and preserve social contact. During *Qat* sessions, the leaves and the tender younger stalks of the plant are chewed in the mouth over sever-

al hours and the residues are stored in the cheeks. As new leaves are taken, a bulging cheek pouch is created.[16] Given that the process of *Qat* chewing has a drying effect on the oral mucosa, its users tend to consume a great quantity of non-alcoholic fluids such as water, coffee and soft drinks. Some of *Qat* users also supplement their chewing practice with tobacco smoking.[17]

Based on the Family Health Survey carried in 2003 in Yemen, it was estimated that 58% of males and 29% of females aged 10 years and older chewed *Qat* during their life time.[18] More recently, a national household survey conducted in 2006 showed that 78% of males and 53% of females contacted in Sana'a reported current *Qat* use.[19] Among a random sample of 1200 adults of a rural community in Ethiopia, Belew, *et al*,[20] reported that 18% of women and 40% of men currently chew *Qat*. In the UK, among the Somali communities, approximately one-third chewed *Qat* on regular basis,[21] with *Qat* chewing reported also an emerging problem in Australia[22] and among Somali immigrants in Norway[23].

Qat Use and Effects on Health

The half-life of the active compound of *Qat* is about four hours, depending on the amount of chewed *Qat*.[24] Once the acute effects disappear, chewers experience feelings of anxiety, irritability, emotionlessness, depression, lack of energy, and mental fatigue.[25] Chronic use of *Qat* has been shown to be associated with cardiovascular effects (*eg*, acute coronary vasospasm and myocardial infarction), gastrointestinal tract problems (*eg*, chronic constipation), cytotoxic effects on liver and kidney,[26] reproductive effects (*eg*, low fetal birth weight, infant mortality),[16] and mental illness (*eg*, psychosis)[27]. Several effects of *Qat* chewing on the oral cavity have been reported. They are included periodontal pocket formation, gingival recession,[28,29] discoloration of teeth, xerostomia,[29] and pain in the temporo-mandibular joint[30].

It has been estimated that about 90% of the alkaloid content of *Qat* is extracted into saliva during chewing and most of it is absorbed through the oral mucosa.[24] Therefore, oral tissues might be exposed to high doses of *Qat* constituents during *Qat* chewing rendering them susceptible to its potential toxic effects. In addition, chewing *Qat* causes mechanical and/or chemical irritation, leading to thickening and keratinization of the mucosa that might cause oral lesions associated with *Qat* chewing.

In experimental studies, a higher rate of genetic damage in buccal mucosa cells has been observed among *Qat* chewers compared to non-chewers. *Qat* consumption lead to an 8-fold increase in the formation of micronuclei in human oral cells in one study, suggesting genotoxic effects of *Qat* consumption.[31] An organic *Qat* extract was shown to induce tumor suppressor proteins and G1 cell cycle arrest in normal oral fibroblast and keratinocytes *in vitro*.[32] Furthermore, the study showed that *Qat* induced premature differentiation and keratinization in oral keratinocytes grown in co-cultures with normal fibroblasts, possibly through signaling of p38 MAP kinase.[32] When exposed to a higher concentration of *Qat* the oral fibroblasts and keratinocytes underwent programmed cell death in a process involving reactive oxygen species.[33] Moreover, the study also found that oxidative stress can occur in oral cells exposed to *Qat*. If this occurs *in vivo*, it could lead to a host of cellular and tissue responses such as increased or decreased proliferation, increased keratotic differentiation and damage to macromolecules like DNA.

Qat-mediated cell death in normal oral fibroblast and keratinocytes was lately described to involve an early effect on mitochondrial integrity and function.[34] A study showed that *Qat* induced alterations such

For more information on *Qat* consumption among Yemeni women see http://www.theijoem.com/ijoem/index.php/em/article/view/402

as premature differentiation, senescence and abnormal keratinization, which was accompanied by increased levels of p38.[35] Other studies have also found *Qat* to be associated with free radical production.[36] *Qat* was also shown to induce cell death through mechanisms involving activation of a family of cysteine proteases named caspases (caspase-1, -3 and -8).[37,38] Therefore, the cytotoxic effects associated with *Qat* raise concerns about *Qat* chewing and the possible development of potentially malignant and malignant lesions in the oral cavity. Potentially malignant oral disorders are epithelial lesions with an increased propensity towards oral cancer. The WHO working group on oral cancer classifies leukoplakia, erythroplakia, dysplastic leukoplakia, actinic keratosis, dysplastic lichenoid lesion, oral submucous fibrosis, and lichen planus as potentially malignant oral disorders.[39]

Considering that the oral cavity is the first place directly exposed to *Qat* in those who chew it and that there are few studies on whether chewing *Qat* causes potentially malignant and malignant oral disorders,[40,41] we conducted this systematic review to summarize the available scientific literature on the association between chewing *Qat* and developing potentially malignant and malignant oral disorders.

Materials and Methods

Medline and Web of Science were searched for articles published before May 2014 without any limits for the publication date or language. We carried out a title/abstract search in the PubMed, abstract search in Medline and topic search in Web of Science, using the following terms: *khat* OR *qat* OR *miraa* OR *Catha edulis*. We did not limit the search to a particular health outcome to make sure not to miss any relevant papers. In addition, to the electronic database search, we reviewed the list of references of all eligible studies included in this systemic review. All search results were combined in a bibliographic management tool, EndNote®, with duplicate record removed.

Studies on potentially malignant oral disorders, based on the WHO definition,[39] or oral cancer were included in our review, if they met the following criteria: 1) published in English or Arabic, and 2) reported as case-series, case report, and cross-sectional, cohort and case-control studies. Because *Qat* is most frequently used in Yemen, some studies were expected to be published in Arabic. Therefore, we included Arabic articles in our review too. To identify eligible studies we reviewed abstracts of all papers identified by the above-mentioned search strategy. When it was unclear from the abstract of the article if it is matched our criteria, the full text of the paper was reviewed.

TAKE-HOME MESSAGE

- *Qat* chewing is common in the Horn of Africa and in Yemen.
- Chewing *Qat* has health hazards.
- Chewing *Qat* may be associated with potentially malignant oral disorders at the site of the chewing.

Results

The search generated 2083 citations. After removing duplicates, 890 abstracts were reviewed for eligibility based on the above-mentioned criteria. Full text articles were reviewed for 45 studies published in English, with 18 reporting on potentially malignant or malignant oral disorders and *Qat* chewing, of which two papers reported the same study results. One additional paper was identified from reviewing the list of references of the 18 eligible papers, which was in Arabic. Therefore, in total, 18 dis-

tinct studies were identified for inclusion in this review. There were one retrospective cohort, two case-control, and seven cross-sectional studies, and six case-series and two case-reports (Table 1).

Retrospective Cohort Studies

A retrospective cohort study was carried out to investigate the practicability of using exfoliative cytology to detect the presence and severity of oral epithelial atypia in 300 males (150 chewers and 150 non-chewers) in Yemen. The study found that among *Qat* chewers, 4% had atypical cytological changes and 16% had hyperkeratosis in the buccal mucosa; none of these outcomes were seen among non-chewers, resulting in odds ratios (OR) of 1.6 (95% CI 0.8 to 7.2) and 3.0 (95% CI 1.1 to 21.9), respectively. The study indicated that *Qat* chewing might be considered a risk factor for the occurrence of cytological atypia and hyperkeratosis in the buccal mucosa, which are frequently seen in premalignant and malignant oral lesions.[41]

Case-Control Studies

In overall 200 voluntary Yemeni *Shamma* users (smokeless chewing tobacco), the association between oral lesions with *Shamma* chewing was examined, based on 58 non-diseased controls and 142 cases with oral lesions. Scheifele, *et al*,[42] reported that 31% of the examined persons presented with mucosal burns, 27% with oral leukoplakia, and 13% with other potentially malignant oral disorders (frictional keratosis, oral lichenoid reaction, pseudomembraneous candidiasis, oral squamous cell carcinoma, *morsicatio buccarum*, oral lichen planus, and white sponge nevus). Of the 200 *Shamma* chewers, 184 chewed *Qat*. *Shamma* chewers who chewed *Qat* for more than six hours a day were at increased risk of oral leukoplakia (OR 4.2; 95% CI 1.4 to 12.4) and mucosal burns (OR 3.0; 95% CI 1.1 to 8.4) compared with *Shamma* chewers who chewed *Qat* for less than three hours a day.

A case-control study of 85 cases and 141 controls was conducted in Kenya to determine the role of tobacco, alcohol and *Qat* chewing in the development of oral leukoplakia.[43] The study did not find a significant association between *Qat* chewing and developing oral leukoplakia (OR 1.8; 95% CI 0.7 to 5.0). However, the study was not able to disentangle the influence of *Qat* from that of tobacco smoking (OR 8.4; 95% CI 4.1 to 17.4). Furthermore, the study had a very low frequency of chewers (10 cases and 10 controls) possibly due to the banning of cultivation, sale and chewing of *Qat* by the local administration in the study area. Therefore, it was likely that some persons did not dare to report this habit.

Cross-Sectional Studies

In a cross-sectional study in Yemen, 162 female participants, of whom 67% were *Qat* chewers, were studied. Leukoplakia appeared in 75% of participants at the chewing site.[44] The lesion was found on the opposite side in only 5.5% of subjects. The study also reported a positive correlation between cigarette or water pipe smoking and presence of oral leukoplakia. However, the duration of smoking was not significantly correlated with the presence of the lesion.

In another cross-sectional study 490 (75.4%) of 515 males and 135 females from Yemen were *Qat* chewers. White patches on buccal or gingival mucosa were observed in 94.7% of *Qat* chewers at the chewing sites and in 8% of non-chewers ($p<0.001$); red patches on the buccal and gingival mucosa were observed in 3.8% of *Qat* chewers and none of the non-chewers.[45] Sixty percent of the chewers also smoked either cigarette or water pipe. The authors reported that when the study was stratified by tobacco use, the risk remained among *Qat* chewers

Table 1: Characteristics of the studies reviewed

Author name, years, study area, study period	Study design	Study population definition	Age range	Exposed population	Comparison group	Characteristics of chewers	% tobacco *Qat* chewers:% tobacco Non *Qat* chewers if available	Health outcomes if applicable and/or assessment
Ahmed, 2011, Yemen, Not reported[41]	Retrospective cohort	From 600 randomly selected volunteers living in the city of Hajja without bad oral hygiene, non-tobacco users, and non-alcohol consumers	13-80	*Qat* chewers ≥3 years with a frequency of more than 2 times per day (n=150)	Non *Qat* chewers (n=150)	100% chewed *Qat* for at least 3 years with a frequency of >2 times per day	None of the participants smoked any kind of tobacco	Atypical cytological changes and hyperkeratosis in the buccal mucosa; exfoliative cytology
Scheifele, 2007, Yemen, April-October 2004[42]	Case-control	Yemeni *Shamma* users in 48 different Yemeni villages and cities	11-74	Cases: Individuals with mucosal burns, oral leukoplakia and other potentially malignant oral disorders (n=142)	Controls: Individuals without any oral precancerous lesions or oral cancer (n=58) not matched to the cases	100 individuals chewed *Qat* for >6 h/day, 37 individuals for >3 h/day, and 46 individuals for <3 h/day	61% (n=122) were cigarettes smokers regardless of their *Qat* chewing status	Clinically confirmed by health professional
Macigo, 1995, Kenya, Not reported[43]	Case-control	Any household member who were age 15 years or older and living in Githongo sublocation in Meru District and residence for at least 5 years in the study area	21-75	Cases: Individuals with oral leukoplakia (n=85)	Controls: Individuals free of disease (n=141) matched with the controls in terms of gender and age (±3 years), neighbourhood	Not reported	Regardless of *Qat* chewing status 42% (n=96) were cigarettes and/or *Kiraiku* smokers	Clinically confirmed by health professional
Schmidt-Westhausen, 2013, Yemen, 2006-2008[44]	Cross-sectional	Female patients who presented to dental clinics of Al-thawara health institution in Sana'a city for dental treatment	20-65	*Qat* chewers >5 year, chewed on one side of their mouths only, non-*Shamma* user (n=109)	Non *Qat* chewers (n=53)	31%, 48%, and 21% started chewing at 10-20, 20-30, and 30-40 years of age, respectively. 15%, 29%, 9% and 62% chewed *Qat* for 1-2, 3-5, 6-7 days/week, respectively. Average period of chewing *Qat* was >6 h/day.	19% (n=21) cigarette smokers and *Qat* chewers; 17% (n=9) cigarette smokers and non *Qat* chewers 39% (n=43) water pipe smokers and *Qat* chewers; 17% (n=9) water pipe smokers and non *Qat* chewers	White patches on buccal mucosa and gingival mucosa, red patches on buccal mucosa and gingival mucosa; clinical examination and surface palpation
Al-Sharabi, 2011, Yemen, Not reported[45]	Cross-sectional	Subjects randomly selected from patients attending dental clinics in two hospitals in Sana'a, Yemen	18-60	Qat chewers for >3 years and chewed on one side of their mouths (n=490)	Non *Qat* chewers (n=25)	73%, 20%, 7% chewed Qat every day, 1-2 and 3-5 days per week, respectively. 77%, 15%, 8% chewed Qat for 3-5, >6, 1-2 hours per session, respectively. All the participants chewed *Qat* for >10 years	43% (n=210) cigarette smokers and *Qat* chewers; 4% (n=6) cigarette smokers and non *Qat* chewers 26% (n=125) water pipe *Qat* chewers; 1% (n=2) water pipe and non *Qat* chewers	Hyperorthokeratosis, hyperparakeratosis and epithelial dysplasia; clinical examination and surface palpation

Continued

Table 1: Characteristics of the studies reviewed

Author name, years, study area, study period	Study design	Study population definition	Age range	Exposed population	Comparison group	Characteristics of chewers	% tobacco *Qat* chewers:% tobacco Non *Qat* chewers if available	Health outcomes if applicable and/or assessment
Yarom, 2010, Israeli, Not reported[46]	Cross-sectional	Population survey of 1500 male Yemenite Israelis Jews of 1 city in Israel with large population of Yemenite Jews	30-84	Chewed *Qat* ≥2 times a weeks for >3 years (n=47)	Never chewed *Qat* (n=55)	Mean years of *Qat* chewing is 24 years Mean days per week of *Qat* chewing is 3.4 days Mean hours of chewing in each session is 4 hours	68% (n=32) cigarette smokers and *Qat* chewers; 46% (n=25) cigarette smokers and non *Qat* chewers	Leukoplakia; clinical examination
Ali, 2007, Yemen, Not reported[47]	Cross-sectional	Yemeni volunteers free from any systemic disease	22-58	Chewed *Qat* for >10 years on one side of the mouth. Biopsies from the non-chewing side (n=33)	Same individuals of the exposure group but the biopsies are from the non-chewing sides (n=33)	100% chewed *Qat* for more than 10 years	33% (n=11) cigarette smokers and *Qat* chewers; 33% (n=11) water pipe smokers and *Qat* chewers	Leukoplakia; histopathologically
Ali, 2004, Yemen, February 2001-August 2002[48]	Cross-sectional	Yemenis patients registered at the faculty of dentistry, Sana'a University. Patients with systemic diseases were excluded	Mean age 27 years	*Qat* chewers (n=1538)	Non *Qat* chewers (n=342)	3%, 45%, 27%, 24% chewed *Qat* for 1, 2-5, 6-10, >10 years, respectively 46% chewed every day, 47% chewed 1-2 days/weeks and 7% chewed 5 days/week.	Regardless of *Qat* chewing status, 26% (n=659) were cigarette smokers, 5% (n=115) *Mada* users, and 2% (n=47) *Shamma* users	Oral keratotic white lesions; clinical examination
Ali, 2003, Yemen, 2001[49]	Cross-sectional	Yemeni patients randomly selected at the faculty of dentistry Sana'a University	5-85	*Qat* chewers (n=605)	Non *Qat* chewers (n=395)	Not reported	Regardless of their *Qat* chewing status, 26% (n=260) were cigarette smokers, 11% (n=110) water pipe smokers, and 2% (n=20) used smokeless tobacco	Keratotic white lesions; clinical examination
Hill, 1987, Yemen, Not reported[50]	Cross-sectional	Yemeni men and have a minimum of four pairable teeth in each quadrant registered at the Jibla Baptist Hospital	Mean age 35 years	*Qat* chewers (n=121)	Same individuals of the exposure group but the clinical examination are from the non-chewing side (n=121)	Average of *Qat* chewing 20 years and at least 5 days a week.	Not collected	Keratosis; clinical examination

showing that white lesions on the oral mucosa might be exclusively caused by *Qat* chewing. Furthermore, if the lesions were attributed to any types of smoking, they would have been present anywhere in the oral cavity and not just at the site of *Qat* chewing.

In another cross-sectional study aimed at assessing the association between habitual *Qat* chewing and development of oral leukoplakia among Yemeni Jewish men,[29,46] 47 *Qat* chewers who chewed *Qat* at least twice a week for over three years and 55 controls who did not chew *Qat* were compared. Leukoplakia was found in 39 (83%) *Qat* chewers and 9 (16%) non-chewers. A significantly higher rate of occurrence of leukoplakia was observed on the chewing side (n=37 [95%]) compared to the non-chewing side (n=3 [8%]). Although it was expected that more lesions would occur among those who were also smokers, the prevalence of leukoplakia in *Qat* chewers who also smoked (84%) was not significantly different with that in those who did not smoke (80%); this also supports a possible direct association between development of leukoplakia and *Qat* chewing.

A study on 33 Yemeni volunteers who had chewed *Qat* for more than 10 years, revealed hyperorthokeratosis in 12%, hyperparakeratosis in 67%, and epithelial dysplasia in 30% of the participants' chewing side. None of these abnormalities, however, were reported in the non-chewing side. On the other hand, when the 22 smokers (cigarette or water pipe) were compared with 11 non-smokers, the lesions appeared respectively in 9%, 73%, and 41% of the chewing side of the smokers, and in 27%, 55%, and 9% of the chewing side of the non-smokers; none of these lesions were observed in the non-chewing side of either smokers or non-smokers.[47] Therefore, it seems that most of the changes observed in the oral mucosa could be attributed to *Qat* chewing. Regardless of the amount of *Qat* consumed, the histopathological changes between those who chewed large or small to moderate amounts of *Qat* were not different.[47]

In a cross-sectional study of 1818 male and 682 female Yemeni citizens,[48] 1538 (61.5%) were *Qat* chewers.[48] Of the *Qat* chewers 342 (22.2%) had oral keratotic white lesions at the chewing side; only 6 (0.6%) of non-chewers had similar lesions. While most of the *Qat* chewers smoked tobacco, the lesions appeared at the chewing side and did not extend to other parts of the oral cavity. Of those with keratotic white lesions, 26% were only *Qat* chewers, an observation supporting the possibility of association between *Qat* chewing and development of the lesion.[48] The study showed that these lesions were increased in number and severity as the duration and frequency of *Qat* chewing increased. For example, 2.6% of chewers who chewed *Qat* one day per week and 37% of daily chewers had oral white lesions; similarly, 11% of those who had chewed *Qat* for less than five years and 48% of persons who had chewed *Qat* for more than 10 years had oral white lesions. Moreover, most of the grade III white lesions occurred in those who had chewed *Qat* daily for at least 10 years.

In another cross-sectional study of 1000 Yemeni citizens (722 males and 278 females), 605 (60.5%) were *Qat* chewers.[49] Keratotic white lesions appeared on the oral mucosa in 142 (23.5%) *Qat* chewers of whom 14.9% had grade I, 6.3% grade II, and 2.3% had grade III disease. Only 3 (0.8%) of non-chewers presented with keratotic white lesions (all grade III). From the non-smoker *Qat* chewers 41% presented with keratotic white lesions.[49]

Of 115 Yemeni male *Qat* chewers, 48% had degrees of keratosis in the chewing side;[50] none of the lesions were suggestive of malignancy or dysplasia.[50]

Case Series

To investigate the effects of *Qat* and *Shamma* on oral mucosa, a study was conducted in Saudi Arabia University Hospital between 1981 and 1983.[51] In a 2-year period, 64 cancer patients (56 men and 8 women with a median age of 46 years) were reported to the hospital. From the 64 cancer patients, 38 had oral cancer of whom 16 had used *Shamma* alone; 22 had used both *Qat* and *Shamma*. The other 14 of 64 cases developed pharyngeal and laryngeal cancers, none of whom reported *Qat* chewing. The median duration of use for *Shamma* was 15 and for *Qat* was 12 years. Alcohol was not consumed by studied patients. Only 14% of the patients were cigarette smokers.

In a 2-year review of cancer patients registered at the Asir Central Hospital, Saudi Arabia, Soufi, *et al*,[40] reported head and neck cancers among 28 patients who lived in border areas of Yemen and Saudi Arabia. Ten of these cancer patients presented with a history of *Qat* chewing. Of 28 cancer patients, eight had oral cancer all of whom reported habitual *Qat* chewing; some of them reported keeping a *Qat* bolus on the same side as the lesion. The other two cases had parotid tumor with metastases to cervical lymph nodes. All were non-smoking and had chewed *Qat* for 25 years or more.

Another study identified 36 Yemeni patients with cancer (23 males and 13 females, median age of 50 years) diagnosed between 1997 and 1998 at the Ear, Nose and Throat Clinic and Dermatology Clinic of the Saudi Hospital, Hajjaj, Yemen, of whom 30 patients were habitual *Qat* chewers.[52] Seventeen patients had oral cancer and all were *Qat* chewers; 10 were also *Shamma* users and five were tobacco smokers. However, the authors suggested that the findings were inconclusive.

An examination of all primary solid tumors recorded in the surgical pathology files at Al-Thawara Hospital in Sana'a in 2004[53] revealed that oral cancer was the most frequent (18% of 649) malignancies in both males (17.2% of 348) and females (19.6% of 301). Among those with chewing and smoking information (92 of 119), 76% were tobacco chewers, 59.8% were *Qat* chewers, and 23.9% were cigarette smokers; 26% of men and 13% of women chewed both tobacco and *Qat*.

In 2002–2003, Ali, *et al*,[54] studied the histopathological changes in 50 Yemeni patients (43 males and seven females, mean age of 38 years), of whom 40 were *Qat* chewers (17 cigarette smokers) registered in the Department of Oral Pathology and Medicine in Yemen. Biopsy was taken from the chewing side of the 40 *Qat* chewers, from the non-chewing side of 20 *Qat* chewers (11 cigarette smokers), and from the oral cavity of 10 participants who neither chewed *Qat* nor smoked cigarette. Mild orthokeratosis, parakeratosis, and epithelial dysplasia of the oral mucosa were found on the chewing side in 39, 10, and 10 individuals, respectively. The frequencies of the histopathological changes were lower on the non-chewing side with 10, 2, and none of the individuals presented with orthokeratosis, parakeratosis, and epithelial dysplasia, respectively. All biopsies taken from the oral mucosa of non-chewing individuals were normal. No differences were demonstrated in the histopathological changes between the biopsies of *Qat* chewers, whether they smoked or not.

In a study sample of 79 Yemeni males, whitening with mild corrugation, frictional keratosis or keratosis with mild or sever corrugation were present in 100% (n=54) of the *Qat* chewers on the chewing side and in 4% (n=1) of non-chewers.[55] The types of the clinical findings on the chewing sides varied according to the duration of *Qat* chewing habit with more lesions

among those with longer duration of chewing *Qat*. There was no statistical difference when comparing the clinical findings between the right and left side of the non-chewers, smokers and non-smokers, while the difference was statistically significant between chewing and non-chewing sides of the *Qat* chewers. Furthermore, the authors reported there was statistical difference when comparing chewing sides of *Qat* chewers with both sides of non-chewers, smokers and non-smokers. On the other hand, no statistical difference was found between non-chewing sides of *Qat* chewers and both sides of non-chewers whatever the smoking habit was. The authors concluded that *Qat* chewing causes oral white lesions on the chewing side and that smoking, clinically, does not exacerbate such lesions.

Case Reports

A case report of a 42-year-old female originally from Kenya living in the UK presented with squamous cell carcinoma of the floor of the mouth reported *Qat* chewing.[56] She had also smoked more than 30 cigarettes a day and drunk alcohol. Two case reports of histologically confirmed oral verrucous carcinoma were presented at the University of Nairobi in Kenya. Both of them had history of *Qat* chewing; one also had a history of tobacco chewing and snuff consumption.[57]

Discussion

Based on the retrospective cohort study, the two case-control studies, the seven cross-sectional studies, the six case series and the two case reports studied, it is suggested that potentially malignant or malignant oral disorders would occur more likely in the mucosal tissue of the buccal side where *Qat* is chewed and stored. However, in the majority of these studies, tobacco use (smokeless and smoking) was also reported among *Qat* users. Smoking and smokeless tobacco are known to be associated with pre-malignant oral lesions[58,59] and thus, proper adjustment for tobacco use is essential for the examination of *Qat* use and the occurrence of potentially malignant lesions in the oral cavity. The harmful effect of *Qat* use could be due to the mechanical friction during chewing over many years of inducing irritation and inflammation as well as cytotoxic effects of *Qat* on oral mucosal cells.

It is noteworthy to acknowledge that the results of the above reviewed literature of *Qat* chewing should be interpreted cautiously. Important limitations were identified that limit the conclusions that can be drawn from these studies: a) limitations in the study design, such as poorly implemented retrospective studies that do not fully comply with a typical case-control study design or historical cohort study design, definitions with scant descriptions of periods of observations, temporal sequence between health outcome and exposure detection being questionable, and sample selection of study participants potentially having an impact on estimates derived from the studies; b) lack of controlling for known risk factors of pre-malignant oral cancerous lesions that are highly correlated with *Qat* use, such as tobacco use (smokeless and non- smokeless) or alcohol consumption, which are established causes of pre-cancerous oral lesions and oral cancer; c) not clear for most of the case series whether they included consecutive patients or a selection of patients; d) some studies were from Saudi Arabia where *Qat* use is prohibited so reporting of *Qat* chewing might not have been accurate; e) in several studies, the diagnosis was solely based on clinical evaluations and the histopathological examination was not performed or not reported. In addition, most of the studies were conducted in Yemen and there is a lack of data from oth-

er countries where *Qat* is chewed. Chewing behavior could be different in those countries as well as the *Qat* variety chewed.

In summary, despite of being very popular in some parts of the world, there are relatively few sound epidemiological studies on *Qat* use and its association with potentially malignant or malignant oral disorders. Considering the limitations identified in the few studies conducted so far, it is not possible to draw firm conclusions.

Qat Chewing and Tobacco Smoking

Tobacco smoking is common among those who chew *Qat* in various populations.[60-62] In a study of 204 male *Qat* chewers identified from *Qat* outlets in the UK, 21% used tobacco only when chewing *Qat*, and 44% were daily cigarette smokers.[63] While between 12% and 30% *Qat* chewers reported initiations of tobacco smoking with *Qat* chewing, apparently *Qat* is also a "getaway" from tobacco smoking.[60,62] In a cross-sectional study among Jewish Yemeni, smoking *Qat* chewers smoked more than non-chewers smokers and the mean number of cigarettes was 29.5 compared to 22.3 per day.[46] In line with these findings, Belew, *et al, a*lso reported that both daily and over two years of *Qat* chewing increased the risk of heavy smoking.[20] The co-occurrence of *Qat* chewing and tobacco smoking is increasing and is reported mainly amongst *Qat* chewers in the diasporas.[61,63]

Women and men may use different tobacco products during *Qat* sessions, as there are different forms of tobacco (cigarettes smoking, water pipe smoking, and smokeless tobacco *Shamma*) available in the countries where *Qat* is used. For example, Nakajima, *et al,* reported that the number of cigarettes smoked during a *Qat* session was higher among men than among women, whereas the frequency of water pipe use during the session was higher among women than men.[64]

To the best of our knowledge, no reliable research has studied the acute and chronic effects of cathinone-nicotine combination with potentially malignant oral disorders and oral cancer. Therefore, future studies are needed to study if *Qat* is associated with excess risk of cancer in the oral cavity, if this effect is independent of tobacco smoking and whether there is a synergistic effect on the cancer risk when both products are concomitantly used.

Qat Chewing and Alcohol Drinking

Due to the acute stimulating effects of *Qat* and its effects on mood and sleep, *Qat* users may also use alcohol as a method to calm down. One study in Kenya reported that among 100 randomly selected outpatients at the Meru District Hospital, 29 were *Qat* chewers including 20 who were also heavy alcohol consumers.[65] Similarly, a study in Ethiopia showed that 43.3% of 427 *Qat* chewing students also drank alcohol.[62] However, alcohol drinking is not common among the Yemeni population as most of them are Muslim where their religion prohibits drinking and hence reporting alcohol use. Nevertheless, it should be investigated if alcohol exacerbates the effects of *Qat* chewing on the oral mucosa.

Qat Chewing and Pesticides

Future studies need to take into account the role of pesticides on the risk of potentially malignant oral disorders and oral cancer. Several cancers have been identified to be associated with pesticide exposure, including oral cancer.[66] *Qat* trees are frequently sprayed with pesticides, including banned products, and at higher doses in *Qat*-producing countries to improve its quality.[67] Therefore, chewing the leaves without any cleansing (such as washing, soaking in hot water, or thermal treatments), which is the traditional way of using the product, may lead to higher exposure to pesticides. A

study conducted in 1997-1998 to evaluate the acute toxic effects of pesticides used on *Qat*, estimated that 70% of all pesticides used in Yemen were used on this plant.[68] The study indicated that some of the globally banned pesticides, such as DDT, were still used in Yemen in 1997-1998.[69] A study by Al-Gohry[70] in 1997-1998 indicated that DDT, aldrin and lindane pesticides were still commonly used by farmers in Taiz governorate. In 2007, a survey among 319 *Qat* farmers in Yemen, reported that few farmers used DDT and lindane.[67] A survey among 70 *Qat* farmers in Ethiopia showed that 86% of them used DDT and other pesticides in *Qat* farming.[71]

Furthermore, it has been reported that *Qat* farmers do not follow the safety instructions. For example, a substantial proportion of *Qat* farmers in Yemen ignored the required period to harvest after the last spraying. Al-Haja, *et al*,[72] reported that 50% of farmers interviewed stated that a period of 7–10 days was required between harvesting *Qat* and the last spraying, and that half of the farmers said that the period should be 10–20 days. A field study among six *Qat* farmers in Addwan village in Yemen found that farmers harvested *Qat* between 3 and 52 days from the last spraying, with an average of 30 days.[70] A field study by Al-Mola found that 39% of *Qat* farmers harvested *Qat* after 3–6 days, 41% after 7–10 days, and 5% did so after 11–15 days from the last spraying.[73] A study by Abdulaziz in Ethiopia indicated that some *Qat* farmers harvested a recently sprayed *Qat* for sale and self-consumption,[71] potentially putting themselves and their consumers at higher risk of oral exposure to and ingestion of pesticides.

Some *Qat* farmers prefer to use higher doses of pesticides than that recommended on the label. For example, Al-Haja, *et al*,[72] reported that 40% of the farmers restricted their use to concentrations of pesticides on the label, but 60% did not follow the instructions. *Qat* harvesting during the waiting period after pesticide application and the use of high pesticide concentrations for spraying will increase the amount of pesticide residues on *Qat*.[72]

Another study conducted in 2009 investigated the presence and level of pesticide residues in *Qat* samples collected from various parts of Ethiopia.[74] The *Qat* samples had *pp'*-DDT concentrations ranging from 141.2 to 973.0 µg/kg. Maximum concentrations were found between 240 and 1200 times the European Union maximum recommended levels for DDT in food (vegetables 10 µg/kg, and cereals 50 µg/kg). The high levels of DDT in the *Qat* samples instead of DDE suggested that DDT is currently in use as a pest control agent in the study region. In another study in Ethiopia, 60 of 70 *Qat* farmers surveyed mentioned the use of DDT and other pesticides for *Qat* cultivation.[75] It is therefore of utmost importance that information on the source of *Qat* and if it is cultivated, is collected in any future study on *Qat* use and health effects.

Conclusions

From the literature reviewed in this publication, dominated by studies from a single country, namely Yemen, it is still not clear whether *Qat* use is a risk factor in the development of potentially malignant or malignant oral disorders. This is due to the limitations of studies conducted so far, which are small in number anyway. Additionally, evidence in the reviewed literature is conflicting about whether *Qat* may play a tobacco-independent direct role in the development of potentially malignant oral disorders and oral cancer in populations. However, from the literature there is some suggestive finding that *Qat* chewing can provoke pre-cancerous lesions at the site of the chewing.

Conflicts of Interest: None declared.

References

1. Al-Motarreb A, Baker K, Broadley KJ. Khat: pharmacological and medical aspects and its social use in Yemen. *Phytother Res* 2002;**16**:403-13.
2. Carrier N, Gezon L. Khat in the Western Indian Ocean. *Études Océan Indien* 2009;**42-43**:271-97. Available from *http://oceanindien.revues.org/851* (Accessed October 20, 2014).
3. Al-Hebshi NN, Skaug N. Khat (Catha edulis)-an updated review. *Addict Biol* 2005;**10**:229-307.
4. USDA, ARS, National Genetic Resources Program. Germplasm Resources Information Network - (GRIN). National Germplasm Resources Laboratory, Beltsville, Maryland: National Germplasm Resources Laboratory, 2011. Available from *www.ars-grin.gov.4/cgi-bin/npgs/html/index.pl* (Accessed October 15, 2014).
5. Geisshüsler S, Brenneisen R. The content of psychoactive phenylpropyl and phenylpentenyl khatamines in Catha edulis Forsk of different origin. *J Ethnopharmacol* 1987;**19**:269-77.
6. AL-abed AA, Sutan R, Radman Al-Dubai SA, Aljunid SM. Biomed Res Int. 2014; 2014: 505474. Available from *www.ncbi.nlm.nih.gov/pmc/articles/PMC4055061/?report=classic* (Accessed October 25, 2014).
7. Manghi RA, Broers B, Khan R*, et al.* Khat use: lifestyle or addiction? *J Psychoactive Drugs* 2009;**41**:1-10.
8. World Health Organization (WHO). Assessment of khat (Catha edulis Forsk). Proceedings of the 34th Meeting, Expert Committee on Drug Dependence, **2006**.
9. Nutt D, King LA, Saulsbury W, Blakemore C. Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet* 2007;**369**:1047-53.
10. Anderson D, Carrier N. *Khat Social harm and legislation a literature review.* In: University of Oxford, ed. London, UK: Home Office, **2011**.
11. UK Home office. Khat fact sheet for England and Wales: UK Home office, **2014**.
12. Alsanosy RM, Mahfouz MS, Gaffar AM. Khat chewing among students of higher education in Jazan region, Saudi Arabia: prevalence, pattern, and related factors. *Biomed Res Int* 2013:487232.
13. Kalix P. Catha edulis, a plant that has amphetamine effects. *Pharm World Sci* 1996;**18**:69-73.
14. Brenneisen R, Fisch HU, Koelbing U*, et al.* Amphetamine-like effects in humans of the khat alkaloid cathinone. *Br J Clin Pharmacol* 1990;**30**:825-8.
15. Carrier N. Is miraa a drug?: categorizing Kenyan khat. *Subst Use Misuse* 2008;**43**:803-18.
16. Al-Habori M. The potential adverse effects of habitual use of Catha edulis (khat). *Expert Opin Drug Saf* 2005;**4**:1145-45.
17. Giannini AJ, Miller NS, Turner CE. Treatment of khat addiction. *J Subst Abuse Treat* 1992;**9**:379-82.
18. Ministry of Health and Population. Family Health Survey 2011 . Available from: *www.mophp-ye.org/arabic/docs/Familyhealth_english.pdf* (Accessed March 3, 2014).
19. World Bank. Yemen towards qat demand reduction. Country Development III. Sustainable Development Department, Middle East and North Africa Region, **2007**.
20. Belew M, Kebede D, Kassaye M, Enquoselassie F. The magnitude of khat use and its association with health, nutrition and socio-economic status. *Ethiop Med J* 2000;**38**:11-26.
21. Patel SL, Wright S, Gammampila A. Khat use among Somalis in four english cities. *Home Office Report 47/05* **2005**.
22. Stefan J, Mathew B. Khat chewing: an emerging drug concern in Australia? *Aust NZJ Psychiatry* 2005;**39**:842-3.
23. Al-Samarraie M, Khiabani HZ, Opdal MS. Khat--a new drug of abuse in Norway. *Tidsskr Nor Laegeforen* 2007;**127**:574-6.
24. Toennes SW, Harder S, Schramm M*, et al.* Pharmacokinetics of cathinone, cathine and norephedrine after the chewing of khat leaves. *Br J Clin Pharmacol* 2003;**56**:125-30.
25. Colzato LS, Ruiz MJ, van den Wildenberg WP*, et al.* Long-term effects of chronic khat use: impaired inhibitory control. *Front Psychol* 2010;**1**:219.
26. Al-Habori M, Al-Aghbari A, Al-Mamary M, Baker M. Toxicological evaluation of Catha edulis leaves: a long term feeding experiment in animals. *J Ethnopharmacol* 2002;**83**:209-17.
27. Odenwald M, Neuner F, Schauer M*, et al.* Khat use as risk factor for psychotic disorders: a cross-sectional and case-control study in Somalia. *BMC Med*

2005;**12**:10.1186/741-7015-3-5.

28. Al-Kholani AI. Influence of Khat Chewing on Periodontal Tissues and Oral Hygiene Status among Yemenis. *Dent Res J (Isfahan)* 2010;**7**:1-6.
29. Yarom N, Epstein J, Levi H*, et al.* Oral manifestations of habitual khat chewing: a case-control study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;**109**:60-6.
30. Shariff M, Al-Moaleem MM, Al-Ahmari NM. A multidisciplinary approach in the treatment of tempromandibular joint pain associated with qat chewing. *Case Rep Dent* 2013;139419.
31. Kassie F, Darroudi F, Kundi M*, et al.* Khat (Catha edulis) consumption causes genotoxic effects in humans. *Int J Cancer* 2001;**92**:329-32.
32. Lukandu OM, Costea DE, Dimba EA*, et al.* Khat induces G1-phase arrest and increased expression of stress-sensitive p53 and p16 proteins in normal human oral keratinocytes and fibroblasts. *Eur J Oral Sci* 2008;**116**:23-30.
33. Lukandu OM, Costea DE, Neppelberg E*, et al.* Khat (Catha edulis) Induces Reactive Oxygen Species and Apoptosis in Normal Human Oral Keratinocytes and Fibroblasts. *Toxicol Sci* 2008;**103**:311-24.
34. Lukandu OM, Bredholt T, Neppelberg E*, et al.* Early loss of mitochondrial inner transmembrane potential in khat-induced cell death of primary normal human oral cells. *Toxicology* 2009;**263**.
35. Lukandu OM, Neppelberg E, Vintermyr OK*, et al.* Khat alters the phenotype of in vitro-reconstructed human oral mucosa. *J Dent Res* 2010;**89**:270-50.
36. Al-Akwa AA, Shaher M, Al-Akwa S, Aleryani SL. Free radicals are present in human serum of Catha edulis Forsk (Khat) abusers. *J Ethnopharmacol* 2009;**125**:471-3.
37. Dimba EA, Gjertsen BT, Bredholt T*, et al.* Khat (Catha edulis)-induced apoptosis is inhibited by antagonists of caspase-1 and -8 in human leukaemia cells. *Br J Cancer* 2004;**91**:1726-34.
38. Dimba E, Gjertsen BT, Francis GW*, et al.* Catha edulis (Khat) induces cell death by apoptosis in leukemia cell lines. *Ann N Y Acad Sci* 2003:384-8.
39. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med* 2007;**36**:575-80.
40. Soufi HE, Kameswaran M, Malatani T. Khat and oral cancer. *J Laryngol Otol* 1991;**105**:643-5.
41. Ahmed HG, Omer AS, Abd Algaffar S. Cytological study of exfoliative buccal mucosal cells of Qat chewers in Yemen. *Diagn Cytopathol* 2011;**39**:796-800.
42. Scheifele C, Nassar A, Reichart PA. Prevalence of oral cancer and potentially malignant lesions among shammah users in Yemen. *Oral Oncol* 2007;**43**:42-50.
43. Macigo FG, Mwaniki DL, Guthua SW. The association between oral leukoplakia and use of tobacco, alcohol and khat based on relative risks assessment in Kenya. *Eur J Oral Sci* 1995;**103**:268-73.
44. Schmidt-Westhausen A, Al Sanabani J, Al-Sharabi A. Prevalence of oral white lesions due to qat chewing among women in Yemen. *Oral Dis* 2014;**20**:675-81.
45. Al-sharabi AK. Condition of oral mucosa due to takhzeen al qat. *Yemeni Journal for Medical Sciences* 2011;**5**:1-6.
46. Gorsky M, Epstein JB, Levi H, Yarom N. Oral white lesions associated with chewing khat. *Tob Induc Dis* 2004;**2**:145-50.
47. Ali AA. Histopathologic changes in oral mucosa of Yemenis addicted to water-pipe and cigarette smoking in addition to takhzeen al-qat. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;**103**:55-9.
48. Ali AA, Al-Sharabi AK, Aguirre JM, Nahas R. A study of 342 oral keratotic white lesions induced by qat chewing among 2500 Yemeni. *J Oral Pathol Med* 2004;**33**:368-72.
49. Ali A. [Oral disease related to qat chewing in Yemen.] *Damascus University Journal For Health Science* 2003;19:143-59. [in Arabic]
50. Hill CM, Gibson A. The oral and dental effects of q'at chewing. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1987;**63**:433-6.
51. Ibrahim EM, Satti MB, Al Idrissi HY*, et al.* Oral cancer in Saudi Arabia: the role of alqat and alshammah. *Cancer Detect Prev* 1986;**9**:215-8.
52. Nasr AH, Khatri ML. Head and neck squamous cell carcinoma in Hajjah, Yemen. *Saudi Med J* 2000;**21**:565-8.
53. Sawair FA, Al-Mutwakel A, Al-Eryani K*, et al.* High relative frequency of oral squamous cell carcinoma in Yemen: Qat and tobacco chewing as its aetiological background. *Int J Environ Health Res* 2007;**17**:185-95.
54. Ali AA, Al-Sharabi AK, Aguirre JM. Histopathological changes in oral mucosa due to takhzeen al-qat: a study of 70 biopsies. *J Oral Pathol Med* 2006;**35**:8-

15.

55. Halboub E, Dhaifullah E, Abdulhuq M. Khat chewing and smoking effect on oral mucosa: a clinical study. *Acta Medica (Hradec Kralove)* 2009;**52**:155-8.
56. Fasanmade A, Kwok E, Newman L. Oral squamous cell carcinoma associated with khat chewing. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;**104**:53-5.
57. Awange DO, Onyango JF. Oral verrucous carcinoma: report of two cases and review of literature. *East Afr Med J* 1993;**70**:316-8.
58. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Smokeless tobacco and some tobacco-specific N-nitrosamines. *IARC Monogr Eval Carcinog Risks Hum* 2007;**89**:1-592.
59. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco Smoke and Involuntary Smoking. *IARC Monogr Eval Carcinog Risks Hum* 2004;**83**:1-1452.
60. Kassim S, Croucher R. Khat chewing amongst UK resident male Yemeni adults: an exploratory study. *Int Dent J* 2006;**56**:97-101.
61. Kassim S, Islam S, Croucher RE. Correlates of nicotine dependence in U.K. resident Yemeni khat chewers: a cross-sectional study. *Nicotine Tob Res* 2011;**13**:1240-9.
62. Reda AA, Moges A, Biadgilign S, Wondmagegn BY. Prevalence and determinants of khat (Catha edulis) chewing among high school students in eastern Ethiopia: a cross-sectional study. *PLoS One* 2012;**7**:e33946.
63. Kassim S, Rogers N, Leach K. The likelihood of khat chewing serving as a neglected and reverse 'gateway' to tobacco use among UK male khat chewers: a cross sectional study. *BMC Public Health* 2014;**14**:448.
64. Nakajima M, al'Absi M, Dokam A*, et al.* Gender differences in patterns and correlates of khat and tobacco use. *Nicotine Tob Res* 2013;**15**:1130-5.
65. Omolo OE, Dhadphale M. Alcohol use among khat (Catha) chewers in Kenya. *Br J Addict* 1987;**82**:97-9.
66. Rusiecki JA, Hou L, Lee WJ*, et al.* Cancer incidence among pesticide applicators exposed to metolachlor in the Agricultural Health Study. *Int J Cancer* 2006;**118**:3118-23.
67. Food and Agriculture Organization (FAO), Ministry of Agriculture & Irrigation (MAI). [Production of qat in Yemen, water use and the competitive alternatives available to policy change]. Cario, Egypt FAO, **2008**. [in Arabic]
68. Al-Hadrani AMT, A.R. Acute adverse health effects of pesticides sprayed on khat trees. *J Pest Cont Environ Sci* 2000;**8**:97-106.
69. World Health Organization (WHO). The WHO recommended classification of pesticides by hazard and guideline to classification 2004. Geneva, Switzerland: WHO, **2006**.
70. Al-Ghory A. Sociogeographical Situation Analysis of Resource Management for Al-Mawasit district/Yemen: Freie Universitaet Berlin, **2004**.
71. Mohammed A. An assessment of possible health risks of using DDT and Farmers' Perception towards toxicity of pesticides used on Khat (Catha edulis): In Haromaya Woreda, Ethiopia: Addis Ababa University, **2010**.
72. Al-Haj MA, Awadh NA, Ali AA. Survey of pesticides used in Qat cultivation in Dhale' and Yafe' and their adverse effects. *J Nat Appl Sci* 2005;**9**:103-10.
73. Al-Mola IEA. Survey on identification of pesticides used on qat grown around Sana'a. Republic of Yemen, Ministry of Agriculture and Water Resources. General Department of Plant Protection. Yemen-German Plant Protection Project, **1993**.
74. Daba D, Hymete A, Bekhit AA*, et al.* Multi residue analysis of pesticides in wheat and khat collected from different regions of Ethiopia. *Bull Environ Contam Toxicol* 2011;**86**:336-41.
75. Abdulahi AM. An assessemt of possible health risk of using and Farmers's perception towards toxicity of pesticides used on Khat (Catha edulis): In Haromaya Woreda, Ethiopia: Addis Ababa University, **2010**.