

REVIEW

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# A review of the health implications of heavy metals and pesticide residues on khat users

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## Abstract

**Background:** There is an exponential rise in the use of farming chemicals in agricultural practices ostensibly to increase food production. The chewing of fresh khat leaves and shoots has spread across the world from ancient khat producing regions in East Africa and the Arabian Peninsula. Khat is a well-established socialization substance with stimulating characteristics. In this work, we have reviewed the deleterious impacts of several heavy metals such as lead, cadmium, iron in the khat plant and their health impacts. Survey on the health complications of farming chemicals used in khat production is also presented.

**Main body of the abstract:** The toxic effects of heavy metals and farming chemicals in plant matter such as khat leaves are a serious health concern. Heavy metals including cadmium (Cd) and lead (Pb), for instance, bio-accumulate in the body and the food chain as precursors for disease. It has been established that blood that has lead levels of 40–60 ug/dL is a precursor for serious health illnesses such as cardiac arrest and cancer. On the other hand, cadmium is reported to bind itself onto metallothioneins hence forming cadmium–metallothionein complex that is transported to all body organs causing deleterious cell damage. The entry of farming chemical into the food chain especially via the chewing of contaminated khat has been known to contribute to health problems such as cancer, hypertension and liver cirrhosis. khat is branded a ‘substance of abuse’ by the World Health Organization (WHO) because of the adverse health risks it causes to humans. Relevant articles published between 2010 and 2021, and archived in Pub-Med, Google Scholar, Medley, Cochrane, and Web of Science were used in this review.

**Short conclusion:** The health implications of heavy metals and farming chemicals arising from the consumption of contaminated khat shoots are a serious concern to the khat chewing community. Consequently, there is need to develop better farming practices that may minimize the absorption of heavy metals and farming chemicals by the khat plant. Information presented in this review is also important in sensitizing policy makers to advance control measures towards safer khat farming practices.

**Keywords:** Cancer, Contaminated khat, Liver cirrhosis, Pesticides, Hypertension

## Background

Khat is a bushy plant whose leaves are chewed for their stimulating and euphoric effects (Gezon 2012). Generally, the chemical composition of khat and the variety to be grown depends on the geographical region, associated climatic conditions and favorability of the environment (Tadesse and Kebede 2015). Khat varieties differ in terms

leaf color, size and the plant height (Atlabachew et al. 2010a, b). These features collectively make these varieties have different levels of pharmacological adaptation (Hailemariam et al. 2018). In intensely khat producing areas, domestic demand has gone up while international market has widened hence much of the khat shoots and fresh leaves are exported for foreign exchange (Belwal and Teshome 2011; Kandari et al. 2014; Tadesse and Kebede 2015). This has increased its market price and production in order to match the ever-rising demand of khat (Gebrehiwot et al. 2016). Figure 1 gives samples

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**Fig. 1** Samples of fresh khat leaves and shoots— Adapted from Mandi 2019 and Oyugi et al. 2021

of khat leaves and shoots usually chewed. Besides khat being a recreational plant with medicinal effects, it is a foreign exchange earner and of significant economic value. For instance, its cultivation accounts for over 70% of farmer's income in the Ethiopian highlands of Oromia region (Kandari et al. 2014).

Khat chewing is considered a tradition as well as a social habit among the khat consuming communities (Ayano et al. 2019). Generally, khat is widely used for recreational purposes, psychological pleasure, and religious activities, and is known for its medicinal properties (al'Absi et al. 2013). Khat roots and leaves for instance are used to treat coughs, influenza and asthmatic conditions (Yimer and Khan 2015). Furthermore, khat intrusion is used to treat boils and premature ejaculation in men (Mohammed and Engidawork 2011a, b). Fresh leaves and shoots of the khat plant are chewed for their euphoric characteristics especially in Sub-Saharan Africa and parts of the Middle East including Yemen and Saudi Arabia (Al-Motarreb et al. 2002). Its use is particularly prevalent in Yemen, Djibouti, Kenya, Ethiopia, Eritrea, Somalia and Uganda (Al-Motarreb et al. 2002; Thomas and Williams 2013). Nonetheless, khat has also spread to other countries such as Madagascar courtesy of immigrants. For instance, khat arrived in Madagascar with Yemeni dock workers in the early twentieth century and is presently an economic crop grown mainly in Northern Madagascar (Gezon 2017).

Nonetheless, regular khat intake specifically in the form of chewing is reported to have a close association with or increased susceptibility to hypertension (Atlabachew et al. 2011; Nigatu and Libsu 2019), increased pulse rate and liver problems (Getahun et al. 2010; Kassab and Al Moustafa 2017). Chewing of khat leaves and use of khat

products contaminated with pesticides remnants and heavy metals has been confirmed to increase the risk of cardiovascular complications such as oxidative stress and cardiac arrest (Atnafie et al. 2021). Consumption of khat contaminated with Cd over time can lead to bio-accumulation of this metal in the body of a khat chewer. Accordingly, elevated levels of cadmium (Cd) in blood are associated with increased blood pressure although the mechanism by which this occurs is yet to be understood (Swaddiwudhipong et al. 2010; Garner and Levallois 2017). Equally important, the non-biodegradable nature of lead (Pb) makes it potent if it bio-accumulates in the human body for long periods, and may consequently cause nervous breakdown, high blood pressure, cardiovascular diseases and cancer lesions (Flora et al. 2012). Remarkably, blood that has Pb levels of 40–60 ug/dL amounts to severe health problems unless urgent treatment measures are considered (Flora et al. 2012). Accordingly, this review paper is very important in articulating issues of concern such as heavy metals detected in khat resulting from possible use of fertilizers, composite manures and pesticides. Concentrations of heavy metals in khat products show permissible limits as per World Health Organizations and Food Agricultural Organization (WHO/FAO) that may not cause adverse health challenges, but bio-accumulation from khat use can cause risk health effects. Besides, this review gives a detailed description of health diseases such as liver cirrhosis, cancer and hypertension that are life threatening, and can be associated with khat related activities—chewing and smoking of khat. This has created a potential health crisis in the form of human poisoning through consumption of farming chemical and heavy metals bio-accumulated in khat leaves.

On the other hand, since there is no regulation on the limit of pesticide use especially in developing countries (Hassan et al. 2016), farmers use various chemicals which may contain toxic trace elements in order to boost production, and to match the demand of both local and international khat markets. The presence of heavy metals such as lead (Pb), cadmium (Cd), zinc (Zn), copper (Cu), nickel (Ni) and chromium (Cr) in edible parts of khat is well-documented in literature (Atlabachew et al. 2010a, b; Ashenef et al. 2014; Fenta and Kidanemariam 2015; Nigatu and Libsu 2019). Although their detectable concentration limits are low (Ashenef et al. 2014), their continuous bio-accumulation in the biological system is detrimental.

### Methodology

In this review, literature published in the English language was considered. Databases such as the Web of Science, PubMed, Cochrane, Google Scholar, Medley, and published reports were employed in search of relevant terms—khat, insecticides and pesticides, khat chewing, farming chemicals, heavy metals, toxicity, cancer, liver damage and hypertension. Detailed literature search was analyzed online from December 2020 to May 2021 according to the procedures described in previous literature survey protocols (Palmatier et al. 2017). The authors set the online databases to provide notifications of search output that contained information matching the established search standards: PubMed, Science direct, Medley, Cochrane, and Google scholar. The information was saved on personal computers (PCs) and analyzed from a bibliometric perspective.

### Main text

Besides the potential health risks that would be associated with substance abuse arising from excessive consumption of khat, there exists possible adverse problems associated with farming methods and practices involving wrong and or excessive pesticide applications. The chewing of khat is associated with serious health conditions such as cancer, hypertension and liver cirrhosis. This can partly be attributed to excessive consumption of unsafe khat that is potentially contaminated with farming chemicals and heavy metals. The chemical constituents of khat remain largely unknown to government authorities and the khat chewing community. Herein, we examine the health challenges faced by khat consumers as a result of chewing of khat contaminated with toxic trace metals and farming chemicals. The relationship between diseases such as hypertension, liver damage, and cancer cannot, however, be linked to the chemicals found in khat alone. There is sufficient evidence based on this review that the absorption of trace metals and

pesticides by the khat plant can result in serious health consequences among the Khat consuming community. Notably, the use of cheap synthetic pesticides by farmers has gained traction as a quick means to manage pests in farms and increase the supply of food across the world (Daba et al. 2011; Karunamoorthi et al. 2012; Bempah et al. 2012; Krueger and Mutyambai 2020). This has not only increased food production but also precipitated an increase in health problems (Adamu et al. 2020). For instance, most pesticides used such as organochlorines are less expensive, versatile to majority of pests but exhibit persistency in the environment and is responsible for grave ailments including neurological injuries and endocrine disorders (Bempah et al. 2012). It is therefore important to note that the khat plant is susceptible to weeds, pest attack (Atlabachew et al. 2010a, b), and insect causing diseases, thus the applications of fertilizers and pesticides is necessary (Atlabachew et al. 2010a, b; Tadesse and Kebede 2015). Pesticides are believed to protect khat plants from diseases and pest attack (Hassan et al. 2016) whereas the application of fertilizers to increase khat yield is always in the rise (Masoud et al. 2012; Naji et al. 2015; Weyesa 2021). Nonetheless, unregulated application of pesticides can be hazardous because of their toxicity characteristics, environmental persistence and stability (Tiryaki and Temur 2010; Masiá et al. 2015). These chemicals are precursors for serious health problems over long time exposure. They are responsible for the introduction of trace metals into the soil (Woldamanuel 2019). These trace metals eventually enter khat plants and are ultimately absorbed into the biological systems of khat users with possible harm (Matloob 2003). Recent research has shown that use of pesticides and insecticides may result in human poisoning; denaturation of biologically essential enzymes and general environmental pollution (Masoud et al. 2012; Hassan et al. 2016; Regassa and Regassa 2018). The world health organization (WHO) reports an annual pesticide poisoning cases load of about 1–5 million people with fatalities in excess of 20,000 per annum (Karunamoorthi et al. 2012; Weyesa 2021). These statistics correlates with high levels of pesticide toxicity in agricultural products such as khat leaves (Hassan et al. 2016). Several common pesticides used extensively in agriculture, and horticulture in the past contained significant concentrations of metals—for instance in the recent past, about 10% of the chemicals approved for use as insecticides and fungicides in the United Kingdom (UK) were based on compounds which contain Cu, Hg, Mn, Pb, or Zn (Wuana and Okieimen 2011).

The soils where khat is grown can be weakly acidic or basic with pH values estimated in the range of 6.0–8.8 (Fenta and Kidanemariam 2015). Soils naturally contain

both essential and non-essential elements and therefore through active transport, toxic lead (Pb), cobalt (Co) and cadmium (Cd) ions are taken up and may bio-accumulate in different parts the khat plant (Tadesse and Kebede 2015). Heavy metals end up in the soil structure via modern agricultural practices although some of these metals exist naturally in soils (Tadesse and Kebede 2015). The concentration of trace metals in the soil determines the uptake levels by the plant (Tadesse and Kebede 2015). The uptake of toxic heavy metals and other elements in elevated levels enter the food chain hence are responsible for adverse health effects in the life of living organisms especially higher order animals such as man (Tadesse and Kebede 2015).

### Economic importance of khat

Since the benefits of khat are high in terms of income; farmers tend to encroach to natural forests to plant this new cash crop (Dessie and Kinlund 2008). Moreover, as a result of attractive economic benefits, Khat farmers have gone to the extent of using chemical pesticides to boost production which unfortunately contaminates the khat leaves and shoots which are usually sought after for their amphetamine like stimulants (Derso and Dagneu 2019).

Khat cultivation and products greatly contribute to personal income accrued from sales and national economies gross domestic product through export (Patel 2015). They tend to be associated with high demand and increased willingness to pay and hence high returns for farmers, resulting in enhanced household economic flexibility (Gezon 2017; Yahya et al. 2016). Khat farmers and other entities have shown that khat is much better in terms of good returns (Table 1) compared to other well-established crops—coffee and tea (Carrier 2008). Khat production in Kenya, Ethiopia and Yemen is important because it contributes to the economic growth in addition to offering a wide range of employment opportunities to farmers and traders both directly and indirectly (Megerssa et al. 2014; Njiru et al. 2013; Teklie et al. 2017).

The high demand for khat across the world has made farmers use other farming methods to boost production in order to match demand needs (Woldamanuel 2019; Wondemagegn et al. 2017; Yimer and Khan 2015). Besides, high profits accrued from this crop were previously estimated at about 2.7 times more than that of other cereal crops such as maize and beans (Feyisa and Aune 2003). Khat is branded “green gold” in Northern Madagascar and hence its economic viability has enabled households to acquire other items using lots of cash from the sale of Khat (Gezon 2017). In Ethiopia, khat now ranks as one of the country’s most valuable exports earner with an income estimated at US\$80 million in 2005 (Gebissa 2008; Mekuria 2018). Somaliland on the other hand collected approximately US\$5.5 million in khat import taxes in 2005, which means that khat revenues make up around 30 percent of the country’s budget. These figures might have increased over time because of the legal status khat enjoys in these countries. In Mbeere sub county region in Eastern Kenya, farmers receive an income of about US\$ 20,000 per year (Njiru et al. 2013). In Yemen, khat generates about a third of the country’s gross domestic product (Lamina and Lamina 2013). About a decade ago, a bunch of 200 g of khat leaves could easily be purchased in the UK for £3.00 (Pickering 2010), although currently khat can be bought online. From these statics, it can be inferred that khat cultivation is a lucrative business notwithstanding the health challenges associated with it.

There is supposition that Khat growers have better living standards in terms of yearly expenditure on food versus family’s income and furthermore are able to meet other family needs (Feyisa and Aune 2003) although this is debatable. Reports show that in Kenya, other crop farmers are shifting into Khat cultivation because it has extremely high total annual income compared to other crops (Njiru et al. 2013). This involves applying modern farming technologies to maximize production. Khat producers are less affected by seasonal fluctuations in

**Table 1** Some data on the prevalence of khat consumption in different countries where khat is prevalent

Country of study	Type of study	Population segment	Prevalence of khat consumption (%)	References
Ethiopia	Systematic review and meta-analysis	University students	23.22	Gebrie et al. (2018)
Djibouti	Cross-sectional epidemiological survey	Patients (129)	48.1	Bennani and Mohamed (2021)
Eastern region, Kenya	Cross-sectional household survey	Individuals above 10 years	36.8	Ongeri et al. (2019)
Jazan region, Saudi Arabia	Cross-sectional survey	Students (15–25 years)	21.4	Ageely (2009)
Kisenyi, Uganda	Cross-sectional study	Male adults	5.53	Abdinasir (2013)



weather conditions and therefore khat growing can alleviate hunger and poverty (Ruder 2018). High prevalence of Khat use has increased daily consumption rates as a result of high income gains which has motivated farmers to adopt any unconventional methods including the use of banned farm chemicals in order to increase production. Generally, farmers cultivating khat receive higher prices for the sale of khat when compared to other alternative forms of merchandise (Gudata et al. 2019).

### Prevalence of khat consumption

In countries such as Djibouti, men are significantly associated with high consumption of khat hence hinders economic and social status of the society. Consequently, resulting problems on oral hygiene such as dental caries has been reported among regular khat users (Benani and Mohamed 2021). It stands out that an estimated 90% of its population consume khat on a regular basis (Al-Maweri et al. 2018). In Ethiopia, prevalence of khat use is high mostly among university students at 23.22%. This has been the concern as it is being promoted by factors such as family chewing practice, alcohol drinking and peer pressure (Gebrie et al. 2018). Additionally, Jazan region in Saudi Arabia reported a lifetime khat chewing prevalence at 33.2% (Al-Maweri et al. 2018). Moreover, Kenya's khat consumption statistics are quite high since the crop enjoys a good legal status hence its export contributes to the growth in Kenya's economy (Ongeri et al. 2019). Table 1 gives a summary of prevalence of khat among khat users in different countries.

High prevalence to khat could be attributed to factors such as place of residence and gender (Ageely 2009). In places such as Kisenyi, Uganda, it turns out that factors such as family history of khat use and availability of khat plays a role in prevalence to khat use. Notably, the social norms and diversity in culture where khat is consumed plays a critical role in the prevalence khat (Abdinasir 2013). Table 1 demonstrates that khat chewing habit is widely spread in Yemen confirming it as being an integral part of their social life with studies pointing out that women practicing this routine is on the rise (Sadeq-Ali and AlAkhali 2017). In Kenya, it has been reported that khat is consumed regularly as it enables khat users to be active, stimulates their brains and relieves stresses (Njuguna et al. 2013). Also, khat has been chewed for a long time in Harar city and its effects are evident as compared to other parts of Ethiopia because of its long history of khat cultivation and consumption (Gudata et al. 2019). In Ethiopia and other countries in eastern Africa, khat abuse is an ever increasing public health problem—accordingly, the lifetime rate of chewing khat especially among

women in Ethiopia is significant and is related to specific sociodemographic risks (Yitayih and van Os 2021).

### Medicinal and biological uses of khat

Khat can act as an immunosuppressant. The major compound in Khat—cathinone (0.625–1.25 mg/kg) plays a critical role in suppressing undesirable immune response against pathogens that cause disease although is a well-established stimulant (Ketema et al. 2015). A khat chewer is estimated to chew 50–200 g of fresh khat daily (Al-Bayaty et al. 2011; Attafi et al. 2018) which is equivalent to 5 mg amphetamine oral dosage (Ali et al. 2010) leading to a high intake of alkaloid chemicals (Attafi et al. 2018) with possible adverse health consequences such as high blood pressure, stroke, kidney failure and cardiac arrest. Moreover, high dose of khat of more than 500 g/week has the ability to expressively decrease sperm quality, testosterone levels (Mohammed and Engidawork 2011a,b), and in may cause male infertility as demonstrated in a research done on baboons (Gorfu 2006; Nyachieo et al. 2013). It is also important among pregnant women because chewing Khat improves their intimacy and ultimately boosting relationships with their spouses in addition to enabling them cope with stress related to pregnancy challenges (Mekuriaw et al. 2020). Structural resemblance of alkaloid chemicals found in khat especially cathinone with amphetamine has demonstrated immunomodulatory roles in immunosuppressive (infectious) diseases such as tuberculosis (Alvi et al. 2014). Mild khat use (lower doses of khat extract) plays an important role in promoting production of testosterone levels that enhances sexual activities in men (Mohammed and Engidawork 2011a,b). Table 2 shows a summary of confirmed biological properties of khat extracts and their associated benefits to biological tissues.

Treatment with cathinone compound is useful in the management of obesity occasioned by consumption of high-fat dietary considered a major health problem among many people across the world. Furthermore, khat extracts can reduce weight gain as noted in studies using animal models through activation of lipolysis present in adipose tissues (Alshagga et al. 2020). Potent antioxidative activity of khat makes it a potential candidate in medical applications and in food industry with the possibility of serving as a reference standard antioxidant capacity (Dudai et al. 2006). Remarkably, extracts from khat leaves and shoots have shown antidepressant properties that are important in the treatment of asthmatic conditions (Alfaifi et al. 2017).

**Table 2** Some biological uses of khat

Form of Khat used	Study specimen	Confirmation property of Khat under investigation	Perceived body benefits	Reference
Khat ethanolic extract	Animal models (male albino mice)	Antidepressant properties	Cure diseases such as asthma	Alfaifi et al. (2017)
Fresh Khat shoots	Pregnant women	Enhances intimacy	Relieves pregnancy related stresses and boosts intimacy	Mekuriaw et al. (2020)
Fresh Khat leaves	Adult mice	Reduce gain in body weight	Obesity management and reduction in body weight	Alshagga et al. (2020)
Khat extract and cathinone	Swiss albino mice	Immunomodulatory roles	Helps in combating infectious diseases	Ketema et al. (2015)
Khat extract and/or cathinone	Sprague–Dawley rats	Promote production of testosterone levels	Enhance sexual activity	Mohammed and Engidawork (2011a, b)

### Heavy metals in blood samples

Whole blood is the preferred specimen for detecting exposure to toxic heavy metals such as lead (> 95% bound to erythrocytes) that are tightly bound to intracellular proteins (Karri et al. 2016; Keil et al. 2011). Besides, blood is also the preferred sample for detecting a mercury exposure because the most toxic forms of mercury such as dimethylmercury and diethylmercury are not usually eliminated in the urine (Anyanwu et al. 2018; Keil et al. 2011). Heavy metals in the environment are not degradable and can enter into the plant and animal biological system chiefly through air, water and soil and ultimately accumulated in the human body through food chain including khat chewing (Lia et al. 2019). A significant body of knowledge suggests that exposure to multiple diverse heavy metals and metal mixtures can have serious neurotoxic effects (Alrobaian and Arida 2019; Cusick et al. 2018; Karri et al. 2016). Lead exposure, for instance, is known to cause intellectual deficit, neurodevelopmental delay, and increased risk for cognitive disorders including Attention Deficit Hyperactivity Disorder (ADHD) (Canfield et al. 2005; Cusick et al. 2018). Besides, manganese in excess causes direct damage to neuronal cells (Cusick et al. 2018; Yin et al. 2018), while arsenic toxicity in drinking water has been shown to be dose dependent, and inhibit antioxidant activity and increase oxidative stress in the brain (Cusick et al. 2018; Jomova et al. 2011).

Blood transfusions among children especially those of extremely low birth weight are at risk of lead exposure (Bearer et al. 2000; White et al. 2019). A study conducted in Dhaka, Bangladesh, assessed the potential health risks caused by heavy metals on workers working in the plastic industry and showed that lead was found in high concentrations in the blood (Ahmed et al. 2020). It is important to note that the International Agency for Research on Cancer (IARC) has labeled cadmium (Cd) as a group 1

carcinogen to humans, and lead (Pb) is a group 2A possible human carcinogen (Ahmed et al. 2020). Changes in blood cells visible under a microscope or deletion of dense lines in the bones of children as can be observed through X-ray are signs used for detecting lead poisoning (Wani et al. 2015). As of 2012, the Centers for Disease Control and Prevention (USA) set the standard for elevated blood lead level for adults as 10 µg/dL and for children 5 µg/dL of the whole blood (Wani et al. 2015; CDC 2012). Beyond these limits, the system breaks down and the consequences may be fatal (Wani et al. 2015). Lead poisoning in humans damages the kidneys, liver, heart, brain, skeleton and the nervous system which is usually accompanied initial symptoms such as headache, dullness, memory loss and being irritable (Kinuthia et al. 2020; Flora et al. 2012).

In France (Table 3), whole blood samples were taken from 106 subjects—the blood samples were analyzed for a range of heavy metals because of their potential toxicity in humans, and for information regarding clinical concern and public interest, but also for use in industrial hygiene monitoring (Cesbron et al. 2013). In recent years coupled with industrialization, China is a serious case of heavy metal pollution in the world (Lia et al. 2019). As can be noted in Table 3, a high level of lead was noted in blood samples among the inhabitants of the Pearl River delta in China (Lia et al. 2019). Lead toxicity, for instance, is an important environmental disease whose effects on the human body are devastating because there is almost no function in the human body which is not affected by lead toxicity (Wani et al. 2015). Although each metal exhibits unique toxicology, there are common mechanisms of toxicity to include mimicry, oxidative damage, and adduct formation with DNA or protein, for instance; non-essential metals may mimic the essential metals thus causing cellular damage, endocrine disruption, and enzymatic damage (Keil et al. 2011).

**Table 3** Selected heavy metal concentrations in blood from various countries

Country	Target group	Heavy metal in blood	Heavy metal level in blood (%)	References
Uganda	Children	Antimony	99.0	Cusick et al. (2018)
		Lead	97.0	
		Manganese	36.4	
		Cobalt	19.2	
		Cadmium	17.0	
		Copper	12.0	
Country	Target group	Heavy metal in blood	Heavy metal level in blood $\mu\text{g L}^{-1}$	References
Bangladesh	Industrial workers	Lead	$32.78 \pm 9.47$	Ahmed et al. (2020)
		Zinc	$9.08 \pm 1.95$	
		Nickel	$1.42 \pm 1.01$	
		Cadmium	$1.08 \pm 0.47$	
Country	Target group	Heavy metal in blood	Heavy metal level in blood ( $\mu\text{g L}^{-1}$ )	References
India	0 – 30 years	Arsenic	$2.45 \pm 1.72$	Jose and Ray (2018)
		Lead	$31.6 \pm 12.5$	
		Mercury	$1.31 \pm 0.83$	
	31–45 years	Arsenic	$2.05 \pm 1.45$	Jose and Ray (2018)
		Lead	$29.8 \pm 16.3$	
		Mercury	$1.87 \pm 1.42$	
	45 – 60 years	Arsenic	$1.54 \pm 1.00$	Jose and Ray (2018)
		Lead	$41.0 \pm 12.7$	
		Mercury	$1.52 \pm 1.55$	
Country	Target group	Heavy metal in blood	Heavy metal level in blood ( $\mu\text{g L}^{-1}$ )	References
France	Adults	Arsenic	0.02	Cesbron et al. (2013)
		Lead	2.26	
		Mercury	0.05	
		Cadmium	0.06	
		Copper	7.00	
Country	Target group	Heavy metal in blood	Heavy metal level in blood ( $\mu\text{g L}^{-1}$ )	References
China	Inhabitants of Pearl River delta	Zinc	$11.50 \pm 8.03$	Lia et al. (2019)
		Copper	$0.67 \pm 0.09$	
		Chromium	$92.83 \pm 32.63$	
		Lead	$158.84 \pm 160.38$	
		Mercury	$1.19 \pm 1.40$	
		Antimony	$1.92 \pm 1.09$	

In general, heavy metals are defined as those having a specific density of more than 5 g/cm<sup>3</sup> such as lead, mercury, aluminum, arsenic, cadmium and nickel (Alissa and Ferns 2011). With toxic load becoming an increasingly serious clinical problem, accurate evaluation is

very important for not only determining and tracking interventions such as accepted tests for metal toxicity, which often rely on blood and urine, and are known to be mainly useful only for acute exposure but are unreliable for body toxic load (Pizzorno 2015). Heavy metal

toxic load (HMTL) measures the amount of toxic heavy metal present in the biological system that impacts the human health and provides an idea to the regulatory health authority about the extent of damage on the organism (Saha and Paul 2019). Heavy metals become toxic when they are not metabolised by the body system and bio-accumulate in the soft tissues (Alissa and Ferns 2011; Jose and Ray 2018). The general symptoms of heavy metal poisoning include diarrhea, nausea, abdominal pain, tingling in the hands and feet, shortness of breath, confusion, general weakness and pass out (Järup 2003).

### Heavy metal residues in khat products

Generally, heavy metals are non-biodegradable and are therefore precursors for long-term chronic toxicity in animals and humans (Al Bratty et al. 2019). Heavy metals or trace metals in khat products may occur because of regular use of fertilizers, incineration of scrap of metals (Ashenef et al. 2014) and application of pesticides (Atlabachew et al. 2011; Fenta and Kidanemariam 2015). Heavy metals can also be absorbed by the khat plant from contaminated soils (Al Bratty et al. 2019). Ultimately, long term health risks of heavy metal exposure from both occupational and environmental settings involve multi-organ toxicities including disturbances of the nervous system, cognitive faculties, and homeostatic processes, immune system dysregulation, carcinogenesis and possible permanent disabilities (Offor et al. 2021). Previous research reported that chewable and commercially consumable Ethiopian khat products showed the presence of heavy metals such as Zn, Co, Cu, Cr and Fe (Tadesse and Kebede 2015; Yimer and Khan 2015). Moreover, another study in Yemen showed khat contained significant concentrations of Zn, Cu, Pb and Cd metals (Matloob 2003). This is because the khat plant has the ability to accumulate essential minerals for its growth and non-essential minerals (mostly trace metals) which have no role in its growth (Atlabachew et al. 2011). These metals can be

determined and analyzed from various khat samples by the use of various techniques such as inductively coupled plasma-mass spectroscopy technique (ICP-MS), X-ray fluorescence spectroscopy (XRF) (Al Bratty et al. 2019) and flame atomic absorption spectrometry (Yimer and Khan 2015; Woldamanuel 2019).

Farming of food crops including khat and vegetables in contaminated environments are periodically done by small scale farmers using fertilizers and banned farm chemicals to maximize yields this may cause a steady accumulation of heavy metals in the African environment which may exceed the World Health Organization permissible limits (Anyanwu et al. 2018). Toxic heavy metals such as arsenic (As), lead (Pb), and mercury (Hg) are systemic toxicants that are detrimental to human health—these elements are increasing in the environment due to industrialization and chemicalized agricultural activities, accumulation of these metals in human biological system (Jose and Ray 2018). The amount of As, Pb, and Hg in blood samples of the selected individuals was analyzed to show the influence of age on heavy metal accumulation as noted in Table 4.

Table 4 reports that plants including khat can bio-accumulate both essential and non-essential elements from the environment with the later having no direct benefit to the plant (Atlabachew et al. 2011). Soils enriched with fertilizers have a higher content of heavy metals than the natural soils. Proportionate application of pesticides also increases their concentration in soils with the possibility of high uptake by the plant and consequent entry into the food chain (Tadesse and Kebede 2015). Notably, the concentration of heavy metals in plants including Khat influence factors such as concentration in soil, geographical variations, applications of pesticides and fertilizers, prevailing regional climatic conditions (Atlabachew et al. 2011) and their associated atmospheric deposition (Tadesse and Kebede 2015).

Although fresh leaves of khat are customarily chewed to achieve metal stimulation, the long term use of abuse

**Table 4** Adverse health effects associated with toxic levels of selected heavy metals

Health effects	Physiological symptoms associated with the heavy metal	Heavy metals determined in khat	References
Cardiovascular diseases	Heart rate increase, Dry mouth, Blurred vision	Pb, Cd, Cu	Chowdhury et al. (2018)
Gastrointestinal disorders	Diarrhea, Nausea, Vomiting, Abdominal pain	Cu, Mn, Fe, Co, Cd	Pizzaro et al. (1999), Sane et al. (2018), Leyskens et al. (2017), Lia et al. (2019), Tinkov et al. (2018)
Reproductive disorders	Hampered fetal growth, Fertility disorders	Pb	Kumar et al. (2020)
Carcinogenic effects	Tumor growth	Cd	Genchi et al. (2020)
Neurological disorders	Reduced intelligence quotient (IQ) in children, Mental retardation, Behavioral disorders, Suicide attempts	Pb, Cu, Mn, Fe	WHO (2019), Santos et al. (2019), Dobson et al. (2004), Sane et al. (2018)



can be associated with numerous of health problems and conditions that are related to the deposition of its residual compounds and elements in the human blood system. Studies have shown that khat can potentially bio-accumulate heavy metal ions in its soft plant tissues during cultivation system (Jose and Ray 2018). Therefore, long term consumption can predispose perennial khat chewers to a host of some of the adverse health conditions that are related to heavy metal ion accumulation, toxicity and or poisoning. Table 4 gives a summary of selected surveys and clinical diagnostic and studies on the adverse health risks associated with heavy metal toxicities. The health complications such as cardiovascular disease, gut disorders, reproductive disorders, cancers and neurotoxicity are among the common biological effects or health conditions that have been associated with heavy metal accumulation and toxicity. The physiological symptoms related to the biological effects are also enumerated in Table 4. Habitual khat chewers, who consume repeatedly large doses of the leaves perhaps on a daily basis could therefore be more exposed to the negative biological impacts of khat use in the long term.

Table 5 shows the concentration range of heavy metals and/or trace metals from various khat samples and

the provisional tolerable weekly intake (PTWI) in (mg) and recommended daily allowance (RDA) of some heavy metals as provided by WHO and Food Agriculture Organization (FAO) (Tadesse and Kebede 2015; Al Bratty et al. 2019; Woldamanuel 2019). When the concentration of heavy metals does not exceed the recommended PTWI and RDA values, then no adverse health problems is reported, although bio-accumulation in the body tissues may eventually be deleterious (Woldamanuel 2019).

High levels of Fe and Zn can be associated with soils where khat is grown—khat may be grown in soils that are reasonably acidic and to some extent basic with pH values ranging from 5.6 to approximately 7.3 (Atlabachew et al. 2011). Specifically, for Fe, its high concentration is associated with high amounts of organic matter in the soil and anthropogenic activities (Fenta and Kidanemariam 2015). Accordingly, elevated levels of Fe in khat can cause heart and liver damage (Ashenef et al. 2014). Copper concentrations in khat are influenced by its concentration in the soil (Woldamanuel 2019). Previous studies reported emissions of Pb from vehicle exhaust, emission of Cd from incineration practices and application of manure and fertilizers in another major source of Pb and Cd hence their significantly high levels in Khat products

**Table 5** The levels of heavy metals in various khat samples cultivated in selected countries and the WHO/FAO recommended heavy metal permissible limits

Heavy metal	Concentration range of heavy metal in khat samples	Country of study	WHO/FAO recommended values	References
Pb	0.18–0.87 mg/kg	Jazan, Saudi Arabia	1.75 mg PTWI	Al Bratty et al. (2019)
	0.18–0.87 mg/kg	Ethiopia	1.75 mg PTWI	Woldamanuel (2019)
	0.97 ± 0.37 µg/g	Ethiopia	214 µg RDA	Ashenef et al. (2014)
Cd	ND	Ethiopia	2 µg/g PL	Tadesse and Kebede (2015)
	0.00–0.08 mg/kg	Jazan, Saudi Arabia	0.49 mg PTWI	Al Bratty et al. (2019)
	0.15 ± 0.90 µg/g	Ethiopia	0.49 mg PTWI	Woldamanuel (2019)
Mn	0.87 ± 1.44 µg/g	Ethiopia	60 µg RDA	Ashenef et al. (2014)
	ND	Ethiopia	0.02 µg/g PL	Tadesse and Kebede (2015)
	339.63–1284.43 mg/kg	Jazan, Saudi Arabia	6.68 mg PTWI	Al Bratty et al. (2019)
Co	11.64 ± 4.28 µg/g	Ethiopia	2000 µg RDA	Ashenef et al. (2014)
	0.51–1.73 mg/kg	Jazan, Saudi Arabia	1.33 mg PTWI	Al Bratty et al. (2019)
Cu	254.60–1757.37 mg/kg	Jazan, Saudi Arabia	245 mg PTWI	Al Bratty et al. (2019)
	0.10–41.80 µg/g	Ethiopia	245 mg PTWI	Woldamanuel (2019)
Zn	NG	Ethiopia	10 µg/g PL	Tadesse and Kebede, (2015)
	7.17 ± 1.11 µg	Ethiopia	3000 µg RDA	Ashenef et al. (2014)
	351.95–1240.93 mg/kg	Jazan, Saudi Arabia	490 mg PTWI	Al Bratty et al. (2019)
	25.15–73.95 µg/g	Ethiopia	490 mg PTWI	Woldamanuel (2019)
	40.98 ± 20.2 µg	Ethiopia	60,000 µg RDA	Ashenef et al. (2014)
Fe	6.80–8.96 µg/g	Ethiopia	50 µg/g PL	Tadesse and Kebede (2015)
	529.13 ± 350.03 µg	Ethiopia	10,000 µg RDA	Ashenef et al. (2014)
	33.87–59.044 µg/g	Ethiopia	20 µg/g PL	Tadesse and Kebede (2015)

RDA recommended daily allowance by WHO/FAO, PTWI tolerable weekly intake, PT plant limit as per WHO, ND not detectable, NG not given

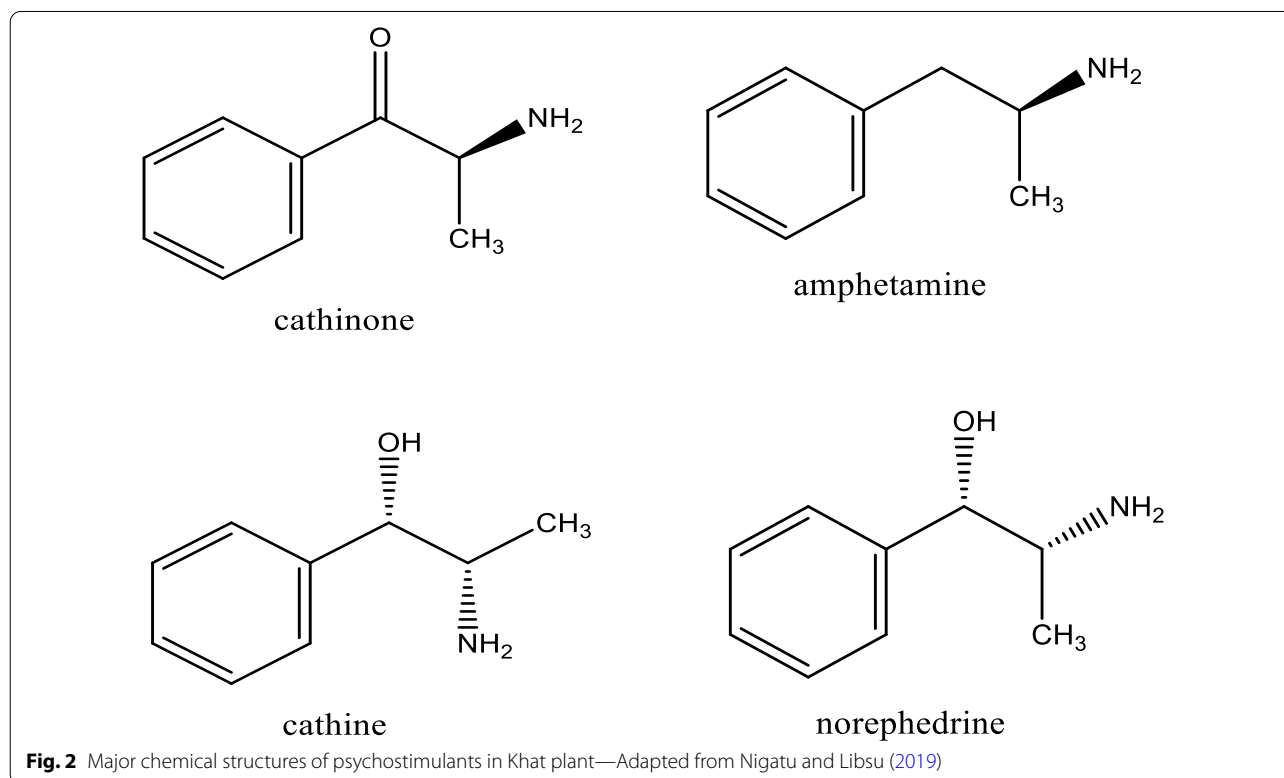
(Ashenef et al. 2014; Woldamanuel 2019). Exposure to Cd leads to liver cirrhosis over time (Kang et al. 2013). The recommended daily allowance (RDA) and PTWI recommendable levels given by WHO/FAO for metals do not pose a health risk when consumption of a maximum amount of preferably 100 g/day of fresh khat is not exceeded, otherwise, if this threshold is exceeded, it may result in adverse health consequences (Tadesse and Kebede 2015; Woldamanuel 2019). Accordingly, chewing of khat is a precursor for heavy metal poisoning (Tadesse and Kebede 2015). A summary of the concentration of various heavy metals detected in khat and their permissible limits is presented in Table 5.

Detection of Pb and Cd heavy metals usually introduced naturally or anthropogenically to enhance the growth of Khat has a potential for severe health consequences (Ashenef et al. 2014). Cadmium metal for instance, is hazardous and is capable of causing chronic toxicity in the body. While in the body, Cd binds itself to metallothioneins to form cadmium- metallothionein complex that is transported to all body organs thus precipitating serious cell injury and damage (Suhartono et al. 2014). Cadmium is largely deposited in the liver, lungs, kidneys and pancreas (Suhartono et al. 2014) and has been proposed to enter the human and animal biological structures through dermal contact, inhalation and ingestion (Wu et al. 2016).

Children should be discouraged from khat use because the detection of Pb in khat has adverse effects in their mental health and growth (Woldamanuel 2019). Agricultural practices such as the use of fertilizers, chemical composition of the soil, climatic conditions and the location where khat is grown determines the heavy metal content in khat products especially the leaves (cf. Table 5) (Tadesse and Kebede 2015). Nonetheless, most of the health problems suffered by the khat chewing community are related to natural alkaloids in khat (cathinone and cathine) which are strongly linked to synthetic pesticides sprayed on khat trees specifically on chewable khat leaves (Nigatu and Libsu 2019). The major alkaloids of khat are presented in Fig. 2, *vide supra*.

#### Pesticides commonly used in khat farms and their health concerns

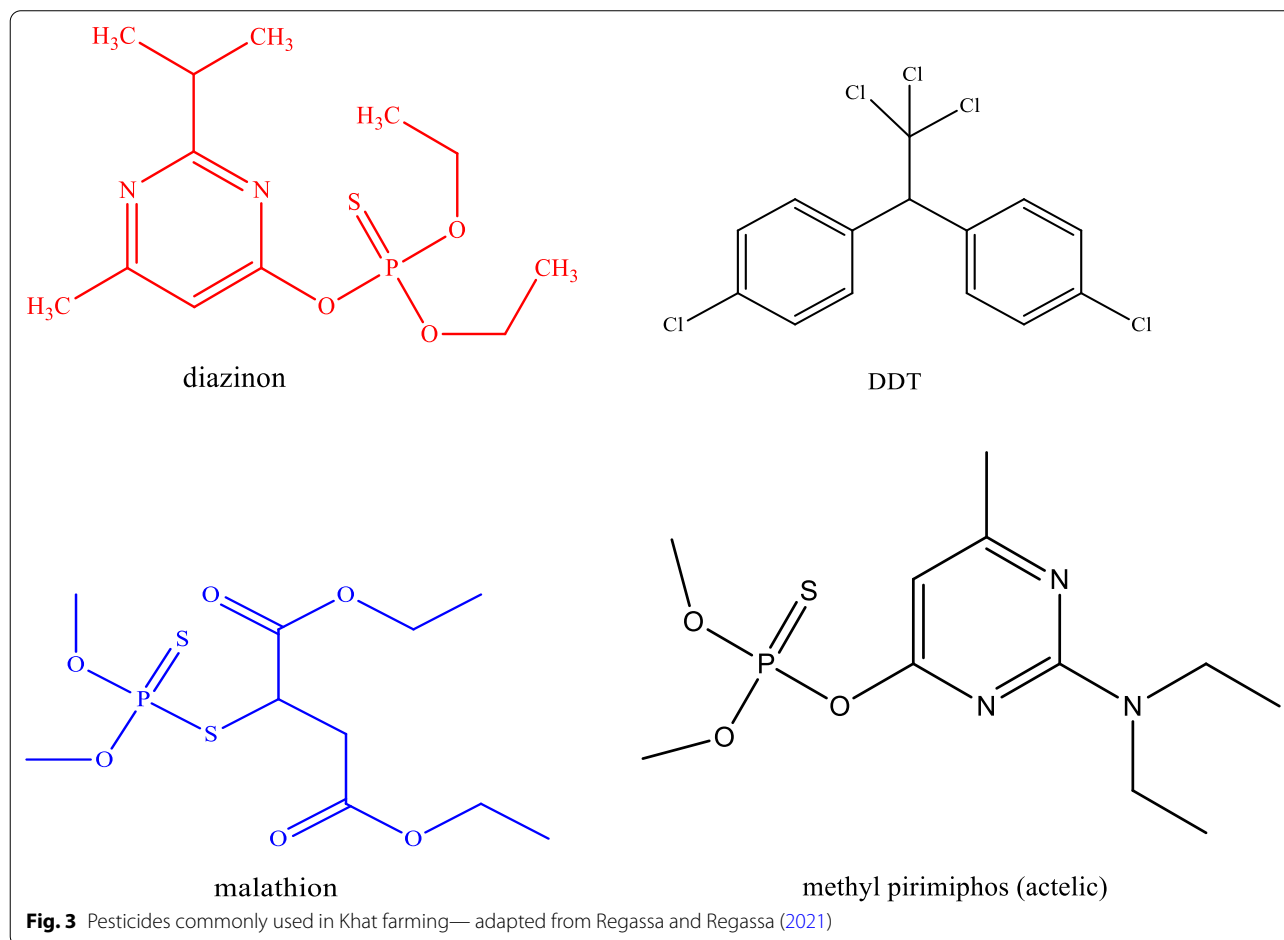
Pesticides are chemicals commonly introduced in farms in order to control disease infestations and target pests (Richardson et al. 2019; Weyesa 2021), in addition to being used as growth regulators (Regassa and Regassa 2018). They can be designed in form of pellets, dusts and liquids (Weyesa 2021). Moreover, they can be classified depending on the target pests including herbicides (weeds), insecticides (insects), rodenticides (rodents) and fungicides (molds and fungi) (Meftaul et al. 2020). Besides, classification is also based on their methods



of application and chemical identity (Richardson et al. 2019). Pesticides act as the backbone of agriculture especially in highly mechanized farms (Richardson et al. 2019). In this regard, they are used to improve the quality, yield and quantity of production hence the reason for their widespread use (Regassa and Regassa 2018). Their use and production is regulated by the regulatory agencies and government authorities globally (Hassan et al. 2016; Meftaul et al. 2020) although their contamination effects are significantly high across the world (Meftaul et al. 2020). Because of their high toxicity levels, they can harm other non-target insects such as honeybees, and birds thus resulting in environmental health pollution challenges (Regassa and Regassa 2018). Vulnerability of khat plant to pest damage and attack is the most important reason why khat cultivators have shifted attention to pesticide use in khat farms with the aim of boosting returns (Regassa and Regassa 2018), and prevent loss of farm produce (Weyesa 2021).

Previous studies have found that khat farmers use chemicals such as dichlorodiphenyltrichloroethane (DDT), wuhagare, sevin, malathion, actelic (Ademe et al.

2020; Regassa and Regassa 2018), diazinon and organophosphate pesticides (Ademe et al. 2020) to deter pests from attacking khat plants. Notably, DDT pesticide is preferred among majority of khat growers since it also increases khat production (Regassa and Regassa 2018; Weyesa 2021). Affordability and effectiveness of a pesticide gives credit to wide spread use despite its illegal status and associated environmental concerns (Regassa and Regassa 2018). Studies conducted in Ethiopia confirmed the presence of diazinon and DDT pesticides in khat and their association with death (Ademe et al. 2020). Malathion, diazinon, DDT and actelic pesticides as shown in Fig. 3 are commonly sprayed on crops to control pest attack (Ademe et al. 2020; Weyesa 2021). Studies on experimental animal models have demonstrated that malathion causes chromosomal abnormalities and micronuclei damage (Daba et al. 2011; Hassan et al. 2016). Voluntary negligence of application procedures of these pesticides can lead to pesticides poisoning and associated fatalities—with khat farmers being the immediate casualties (Regassa and Regassa 2018).



Some of these pesticides are carcinogenic (Weyesa 2021) and upon chronic exposure may lead to genotoxic effects, cases of endocrine disturbances (Swaddiwudhipong et al. 2010; Hassan et al. 2016), and hinder proper functioning of the immune system (Karunamoorthi et al. 2012). Additionally, pesticide application and diseases such as liver diseases, digestive system disorders and respiratory problems are positively correlated (Regassa and Regassa 2018). Besides, there have been immediate cases of headache, eye irritations and increased heart beat during pesticide spray in the absence of protective gear (Weyesa 2021). Moreover, skin irritations, dizziness, depression and breathing difficulties have been reported in literature (Derso and Dagnew 2019). Consumers of khat reported stomach irritations upon chewing khat that has been contaminated with pesticides (Regassa and Regassa 2018).

Table 6 gives a brief overview of the potential health concerns associated with selected organic agrochemical pesticides commonly used in khat farming. Clinical studies have also shown that organic compounds produced

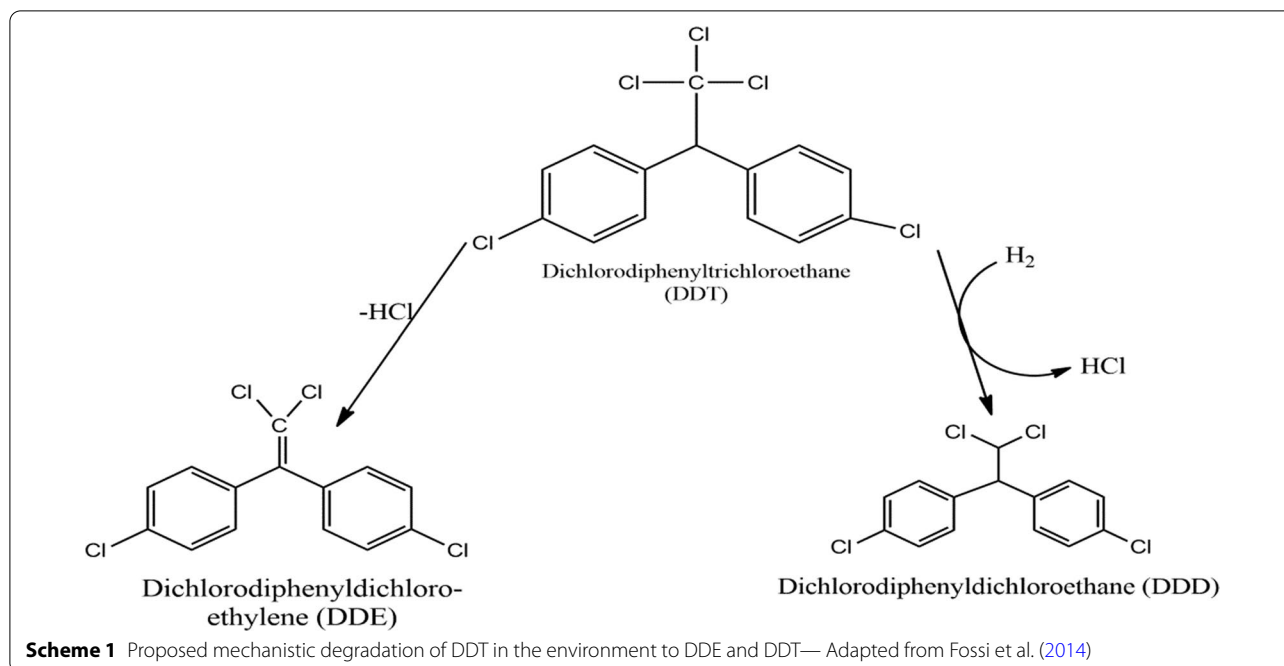
naturally by khat can penetrate the gut system and the human blood plasma after chewing khat leaves (Widler et al. 1994; Halket et al. 1995). Organic pesticides can potentially persist through bio-accumulation mechanisms and become deposited as residues in the human blood system upon prolonged khat consumption. Previous studies have shown detectable levels of organochlorine pesticide residues of benzene hexachloride in human blood (Subramaniam and Solomon 2006).

Benzene hexachloride (BHC) and DDE can therefore be found in human blood as a result of direct and indirect exposure (Subramaniam and Solomon 2006). Other studies have also detected levels of a variety of pesticide residues including aldrin, DDT, BHC, and diazinon in khat leaves from selected Khat-growing farmlands (Adamu et al. 2020). This means that excessive levels of intake of cultivated khat can potentially lead to accumulation of the pesticide residues in the human internal organs and perhaps disrupt the normal biochemistry and metabolic functions of man. This can contribute to negative health

**Table 6** Potential health effects associated with organophosphate and organochlorine pesticides applied in khat farming

Classification of pesticide	Trade name	Molecular formula	Name of the organic active ingredient	Potential health effects and hazards linked to high levels of exposure	References
Organophosphates	Actellic	$C_{11}H_{20}N_3O_3PS$	Primiphos-methyl or O-[2-(Diethylamino)-6-methylpyrimidin-4-yl] O,O-diethyl phosphorothioate	Cholinesterase inhibitor	Syngenta (2013)
	Malathion	$C_{10}H_{19}O_6PS_2$	O,O-dimethyl dithiophosphate of diethyl mercaptosuccinate	Eye and skin irritant Cholinesterase inhibitor Dermal toxicity Reproductive and developmental effects in mammals Endocrine disruption	WHO (2013) Olovi et al. (2013) Cabello et al. (2003) Tchounwou et al. (2015)
	Diazinon	$C_{12}H_{21}N_2O_3PS$	O,O-Diethyl O-[4-methyl-6-(propan-2-yl)pyrimidin-2-yl] phosphorothioate	Endocrine disruption	Nicolopoulou-Stamati P et al. (2016)
Organochlorines	DDT	$C_{14}H_9Cl_5$	Dichlorodiphenyltrichloroethane	Possible carcinogen Endocrine disruption Poor embryonic development	Wallace (2015) Garabrant et al. (1992) Nicolopoulou-Stamati et al. (2016) Tiemann (2008)
	DDE	$C_{14}H_8Cl_4$	Dichlorodiphenyldichloroethylene	Possible carcinogen Neurodevelopment effect in children Endocrine disruption	Breast Cancer Fund Organization (2004) Nicolopoulou-Stamati et al. (2016) Eskenazi et al. (2006)
	Aldrin	$C_{12}H_8Cl_6$	Hexachlorohexahydrodimethano-naphthalene	Endocrine disruption	Lemaire et al. (2006)
	BHC	$C_6H_6Cl_6$	Benzene hexachloride	Endocrine disruption	Nicolopoulou-Stamati et al. (2016)





effects when they are ingested above the threshold limits as documented by WHO (2013).

DDT is a man-made chemical developed in the 1940s specifically for use as an insecticide (Kaoud 2015). Technical-grade DDT may also contain DDE (dichlorodiphenyldichloro-ethylene) and DDD (dichlorodiphenyldichloroethane) (Scheme 1) which are breakdown products of DDT (Fossi et al. 2014). DDT is a long-lasting, toxic chemical which builds up in the tissues of living organisms (Kaoud 2015). Under the Stockholm Convention, it is banned worldwide for use in agriculture, but it is still being used in developing countries for particularly in crop production (Ali et al. 2014). In countries where DDT is still in use, most release is due to its use as an insecticide (Ali et al. 2014). It can enter the atmosphere by evaporation and can contaminate surface water from soil run-off (McKnight et al. 2015). DDT may also escape into the environment as a result of accidental discharges during use or during its manufacture (Fossi et al. 2014). The persistence of DDT and its breakdown products has contributed to their bioaccumulation and bio-magnification (increasing concentration of a chemical in organisms higher up the food chain) in the environment (Vorkamp and Rig t 2014). Besides its breakdown products, DDT is ubiquitous in food and the environment (Kaoud 2015). Exposure to DDT has been linked to breast cancer, reproductive difficulties, liver damage and delays in neurodevelopment during early childhood (Ali et al. 2014). Therefore contamination of khat shoots of leaves by DDT and its by-products can be detrimental to human health.

The non-biodegradability nature DDT makes it a precursor for majority of health diseases because of its massive use in pest control despite having been banned in developed countries (Regassa and Regassa 2018). Organochlorine pesticides such as DDT cause cancers (esophageal and oral) among khat chewers (Daba et al. 2011; Woldetsadik et al. 2021). Notably, DDT pesticide is banned in most developed countries such as US and Europe because of its adverse health effects (Meftaul et al. 2020) such as stillbirth and endocrine disorders (Karunamoorthi et al. 2012). Among other countries that have also banned the use of DDT for agricultural use include Ethiopia and partly Kenya (Adamu et al. 2020). Pesticide residues on chewable khat leaves and young shoots are responsible for pesticide poisoning and eventually death (Ademe et al. 2020). Therefore, proper management practices on pesticide application procedures need be adopted in order to avoid potential pesticide poisoning, possible fatalities and environmental health pollution (Derso and Dagnew 2019). Moreover, allowable limits set by regulatory bodies need be observed and adhered to in order to mitigate the hazardous impacts of these pesticides. For instance, under the European Union (EU), regulation set for both diazinon and DDT pesticides is that the maximum residue level (MRL) is 10 µg/kg particularly for fruits and vegetables (Daba et al. 2011; Adamu et al. 2020).

### The toxicology of khat use

Regular khat use particularly chewing has been associated with human medical problems such as diminishing libido, cancer cases, depression, dental carries, liver damage and hypertension (Tarboush et al. 2019; Belayneh and Mekuriaw 2019; Al Bratty et al. 2019; Tessema and Zeleke 2020). It is believed that psychoactive ingredients in khat—cathine and cathinone are confirmed precursors for cancer (oral and esophageal) among regular khat chewers (Omara 2020; Yadeta et al. 2020). An increase in cathinone concentrations in plasma leads to increase in blood pressure (Geta et al. 2019). It is also important to note that the presence of high levels of toxic metal ions in Khat are hazardous and can potentially damage major body organs such as the liver and kidneys (Al Bratty et al. 2019). Furthermore, consumption of unclean khat leaves containing residual pesticides causes cancer and genotoxicity (Atnafie et al. 2021). The liver is a vital organ responsible for detoxifications functions and metabolic activities (Djurasevic et al. 2019). Due to its central role in the body system, it is highly vulnerable to toxic effects of khat use (Al-Mehdar et al. 2012). Chewing of khat has a close association with severe liver damage, (Kassim et al. 2015; Al-Rajab et al. 2016; Mahamoud et al. 2016; Orlien et al. 2018) and fibrosis (Ademe et al. 2020). Additionally, the presence of tannic acid in khat is responsible for hepatic toxicity (Jayed and Al-Huthi 2016). Fibrosis results in some cases due high Cd accumulation in the liver after exposure to regular low doses (Baba et al. 2013). Unfortunately, the liver may not recover after khat use cessation (Makeen et al. 2021) which may lead to liver transplant (Heidelbaugh and Bruderly 2006; Ademe et al. 2020), in extreme cases. It medically established that liver cirrhosis is a silent disease, with most patients remaining asymptomatic until decompensation occurs (Heidelbaugh and Bruderly 2006).

The liver injuries manifest themselves because of possible metabolization of toxic khat components including heavy metals and pesticides (Heidelbaugh and Bruderly 2006). This may trigger psychological effects such as insomnia and depression (Heidelbaugh and Bruderly 2006). Research conducted on rodents experimented on diet containing khat products showed high liver enzymes and histology necro-inflammatory change, suggesting that khat products cause liver damage (Orlien et al. 2018). Arguably, the liver plays a critical role in the maintenance and balance of Fe and Cu in the body, which mainly enhance lipid peroxidation (Djurasevic et al. 2019). However, absorption of Cu and Fe in excess (Djurasevic et al. 2019) may result in high bio-accumulation levels that are damaging to the liver (Ashenef et al. 2014). Similarly, Cd is an element which is highly toxic with long biological half-life ranging from approximately 6–39 years and

is capable of causing serious health problems including nervous breakdown, liver and kidney failure (Egger et al. 2019). Cadmium is a well-established carcinogen known to lower bone mineral density at relatively high exposure (Egger et al. 2019). Cadmium enters the system of a living organism through gastrointestinal tract and the respiratory airway with exposure period and dosage key to intoxication of the liver (Djurasevic et al. 2019). In humans, epidemiological studies are used to show association of liver dysfunction and exposure to cadmium metal (Kang et al. 2013). It reduces Fe concentration in the liver hence reducing enzymatic activity and causes zero protein regulation (Djurasevic et al. 2019). Moreover, Cd has the potential of damaging the adrenals, causes cell death and is a well-known precursor for kidney impairment (Egger et al. 2019). Unregulated use of illegal pesticides on khat such as 1,1,1-trichloro-2,2-bis [4-chlorophenyl] ethane (DDT), a carcinogenic chemical cause severe liver damages among khat users (Weyesa 2021). Liver cirrhosis is a disease that can lead to death because of its action to impede liver functions (Tsochatzis et al. 2014). Injury to the liver parenchyma attributed to an inflow of acute or chronic inflammatory cells is a precursor for hepatitis—a deadly disease (Adamu et al. 2019).

### Khat as a precursor for cancer

Herein, we discuss two types of cancer—Oral and esophageal cancers that have proved to be fatal mainly in developing countries such as Ethiopia, Somalia, Djibouti and Kenya (Ram et al. 2011; Yang and Chen 2020). Oral cancer is caused by excessive consumption of alcohol and smoking of cigarettes notwithstanding khat use (Warnakulasuriya 2009). It has also been confirmed that khat chewing is associated with esophagitis, periodontitis and oral cancer (Yang and Chen 2020). Oral cancer is among the common cancers globally which affect the lower side of the mouth, tongue, the cheek (Warnakulasuriya 2009; Ram et al. 2011) and buccal mucosa (Ahmed et al. 2011). Most of these are cell carcinomas (Morse et al. 2007). Cancer is significantly associated with dietary deficiencies, viral and dental factors (Ram et al. 2011). Other cancers are significantly associated with parasitic diseases, bacteria and trematode infestations (De Flora and Bonanni 2011). Chewing of khat has been closely associated with oral cancer mainly among khat chewers (Lu et al. 2017; Nigatu and Libsu 2019). The regular chewing side of the mouth of a khat chewer may develop changes such as keratotic white lesions (Schmidt-Westhausen et al. 2014), oral epithelial dysplasia (OED), irritation of the esophagus and white lesions in the mouth that represent a reactive process or the development of cancer (Leon et al. 2017). Oral epithelial dysplasia (OED) is characterized by cellular changes indicative of the

**Table 7** Selected demographic characteristics of khat users, the related physiological symptoms of cancers and the factors actuating consumption of khat

Type of study	Country of study	Age	Descriptive statistics related to cancer cases		Physiological abnormalities associated with cancer development	Factors that actuate the consumption of Khat among the users	References
			Recorded number of participants	Khat consumers in terms of percentages (%) of the respective populations			
Administered interviews	Ethiopia	< 18 years	NP*	NP*	Mouth sores	Peer pressure, Religious beliefs, and Social influences	Sinba (2017)
Cross-sectional hospital study	Yemen	20–65 years	82	75.20%	White lesions on oral mucosa	Social influences	Schmidt-Westhausen et al. (2014)
Population survey	Israel	< 30 years	39	83%	White lesions on skin sections	Global spread of Khat usage, Smoking	Gorsky et al. (2004)
Pilot case–control study	Ethiopia	< 18 years	73 CC*	35.40%	CC*	Traditions, culture and religious beliefs	Leon et al. (2017)
Cross-sectional study	Ethiopia	31.86 years (Mean Age)	NP*	NP*	Lesions	Leisure activities, family history of tobacco use peer pressure	Molla et al. (2017)
Case–control study	Yemen	56.95 years (Mean Age)	NP*	NP*	Lesions, lymph node, mucosal burns	Smoking and experimental Khat chewing	Nasher et al. (2014)
Cross-sectional population based study	Ethiopia	15–69 years	NP*	NP*	NP*	Khat chewing that accompany heavy alcohol consumption	Defar et al. (2017)
Descriptive study	Kenya	Adults	51	75	*NP	Mouth sores, dental carries, alcohol consumption	Njuguna et al. (2013)

\*NP not provided, CC cancer cases

development of malignancy which can later be oral carcinogenesis (Morse et al. 2007).

Table 7 presents some selected case studies conducted in selected khat growing regions which include countries in the horn of Africa and in Arabian regions. These studies have shown a link between the consumption of khat and development of cancer related physiological symptoms. In one pilot case study in Ethiopia, more than a third of the patients reporting various forms of cancer were found to be actually younger khat consumers (Leon et al. 2017). The studies have also revealed and documented some of the factors that actuate and perpetuate the consumption of khat among its consumers. Some of the key factors include peer pressure, social influences, smoking, religion, cultural beliefs and traditions which continue to contribute to the rise in khat consumption

and possible abuse of the recreational psychostimulant herbal drug.

The elevated levels of khat toxins and the precancerous keratotic white lesion development in the cheek where khat boluses are placed during chewing of khat are progenitors for oral cancer (Yarom et al. 2010; Kassab and Al Moustafa 2017). The major organic chemicals; cathine and cathinone induce precancerous chromosomal changes and death of cells through apoptosis (Ahmed et al. 2011). Besides, illegal pesticide remnants on khat leaves and products are the primary cause of cancer for chewers of khat who preferentially consume unclean raw fresh leaves (Karunamoorthi et al. 2012; Weyesa 2021). Excessive use of these pesticides can also cause genotoxicity and ultimately increase the chances for the development of diabetes mellitus (Atnafie et al. 2021). Similarly, application of toxic organochlorine pesticides such as

DDT increases chances of cancer (Al-Akwa et al. 2009; Regassa et al. 2020). DDT has a slow transformation, strong lipophilic and high affinity for animal and human tissues thus causing more harm (Regassa et al. 2020). Oral cancer is responsible for malignancies of the oropharynx and the oral cavity—reports in 2012 estimated nearly 300,000 cases of cancer and 145,000 fatalities globally with survival rate of approximately 60% (Kassab and Al Moustafa 2017). Other cancers such as esophageal cancer may result after chronic irritations of the esophagus associated with khat extract during swallowing (Yadeta et al. 2020).

Regular chewing of khat is associated with the development of white lesions on the oral mucosa as a result of chemical effects (Gorsky et al. 2004; Schmidt-Westhausen et al. 2014). The relationship between khat chewing and oral malignancy is highly suspected despite some studies nullifying this association (Gorsky et al. 2004). Nonetheless, recent studies portray etiological role of this association majorly with esophageal and oral cancers (Leon et al. 2017). Chewing of khat shoots sprayed with DDT and diazinon pesticides have a higher chance to cause cancer cases in human since these pesticides are ranked among the most toxic organics in the environment (Leon et al. 2017). Due to many carcinogenic chemicals in tobacco, it is clear that tobacco smoking causes ailments including cancer (Molla et al. 2017). Remarkably, the percentage of cases observed from khat users is high (Table 7), with studies suggesting the carcinogenicity of khat extract among khat users (Nasher et al. 2014; Defar et al. 2017). It has been reported in literature that over 50% of households in Djibouti, approximately 70% Yemenis, and about 30% of Ethiopians consume khat (Desta and Ataklti 2015; Tadesse and Kebede 2015). With these statistics, it is evident that possible consumption of khat contaminated with farming chemicals and heavy metals is a concern that needs to be investigated further. Already, WHO has reported that in Yemen for instance, 30–50% of female adults use khat regularly (Naji et al. 2015)—a worrying observation.

#### **Hypertension and khat use**

Hypertension is a medical condition that develops when blood flows in the artery walls at a high pressure—diastolic blood pressure equal or greater than 90 mmHg and/or a systolic blood pressure (BP) equal or greater than 140 mmHg (Niriayo et al. 2019; Chuka et al. 2020; Abdissa and Kene 2020). This ultimately results in long term health complications (Haye and Tolera Agama 2020), body disabilities (Huang et al. 2021) and sometimes in premature death (Kassa and Woldeamayay 2019; Badego et al. 2020).

Hypertension is currently a health concern worldwide (Niriayo et al. 2019) mainly affecting population of developing countries such as Ethiopia (Kebede et al. 2020) with cases expected to be higher by the year 2025 (Ibrahim and Damasceno 2012). It is estimated that by the year 2025, three out of four people (75% of total population) will be living with high blood pressure conditions (Huang et al. 2021). Hypertension may also result in heart and damage to the blood vessels (Tessema and Zeleke 2020). Notably, it is a primary cause for cardiovascular diseases (Miller et al. 2010; Niriayo et al. 2019) and kidney diseases including renal failures, myocardial infarctions (Oliver-Williams et al. 2018; Kebede et al. 2020), dementia and maternal death during pregnancy (Badego et al. 2020). Cardiovascular problems are generally initiated by the alkaloid chemicals such as cathinone and cathine (Jayed and Al-Huthi 2016).

During the chewing of khat, the heart rate and blood pressure is reported to increase proportionately as chewing process continues resulting in increase in psychoactive component plasma concentrations (Dagne et al. 2010; Geta et al. 2019). In some studies, it is reported that blood pressure can rise nearly 14 times more than that of non khat chewers (Birhane and Birhane 2014). Table 8 shows a summary of different characteristics and khat chewing processes. The numerous vasoconstrictor activities of the alkaloid cathinone is responsible for the increase in blood pressure (Geta et al. 2019). The psychoactive components in khat also increase the heart rate (Geta et al. 2019). High blood pressure is regarded as a primary cause of worldwide disease burden (Kebede et al. 2020; Haye and Tolera Agama 2020). Globally, about 1 billion people suffer from hypertension with fatalities estimated at 7.1 million annually (Miller et al. 2010). Genetic origin of individual, dietary factors, behavioral aspects (Miller et al. 2010; Geta et al. 2019) and medical disorders contribute to high blood pressure (Ibrahim and Damasceno 2012). Other risk factors of high blood pressure include lack of physical exercise, stress, obesity and regular alcohol use (Geta et al. 2019; Huang et al. 2021). Hypertension is closely associated with possible heart failure and stroke related cases (Oliver-Williams et al. 2018; Geta et al. 2019). Therefore, it is important that early detection, prevention and sensitization on high blood pressure is treated early (Badego et al. 2020). Besides, WHO has adopted worldwide action plan for mitigating measure aimed at reducing the risk of hypertension through awareness programs (Chuka et al. 2020). Contamination of khat leaves and shoots by heavy metals and farming chemicals such as DDT may exacerbate hypertension, liver damage, cancer and kidney related diseases.



**Table 8** Selected studies on the association between hypertension and khat chewing

Type of study	Region/ Country of study	Association with hypertension	Mean age of participants	Prevalence rate of hypertension	References
Comparative study	Butajira, Ethiopia	Yes	NP*	Prevalence of 13.4% for khat chewers while 10.7% for non-khat chewers	Miller et al., (2010)
Facility-based cross-sectional	Addis Ababa, Ethiopia	Yes	41.17 years	Prevalence was 14% for khat chewers who were patients in health centers	
Cross-sectional based	Ethiopia	Yes	NP*	No information on prevalence was provided. Prevalent conditions include lack of enough physical exercise, low salt intake and relatively high weight	Niriayo et al. (2019)
Institution-based cross-sectional based	Sidama zone, Ethiopia	Yes	NP*	Prevalence was 24.5%. Khat chewing, alcohol consumption, old age and obesity are prevalent conditions	Badego et al. (2020)
Hospital-based cross-sectional based	Ethiopia	Yes	42.30 years	Prevalence was 13.2%. Family history of hypertension, overweight, oral contraceptive and diabetes mellitus are prevalent conditions	Gudina et al. (2013)
Community-based	Gurage zone, Ethiopia	Yes	34.36 years	The prevalence was 17.4% for Khat chewers and 8.7% for non-Khat chewers. Age, gender and alcohol intake are prevalent conditions	Geta et al. (2019)

\*NP not provided

### **Suggested improvement in khat farming practices**

Widespread use of synthetic pesticides and chemical fertilizers poses health, environmental, and livelihood risks especially to Khat farmers in the Horn of Africa and the Arabian Peninsula (Krueger and Mutyambai 2020). The consequences can magnify across a wider population since khat leaves are transported and consumed largely in western countries such as the United Kingdom (UK), Netherlands and the USA. It is therefore important to practice khat cultivation methods that are free of synthetic insecticides and chemical fertilizers. Organic farming is therefore an appropriate management system that would improve soil health environment and facilitate quality crop production, an ultimately minimizing the bio-accumulation of non-essential metals (heavy metals) and farm chemical residues in crops which are known to have deleterious impacts on human health. Organic farming is defined as a crop production system that largely avoids the use of synthetic fertilizers, growth regulators, pesticides, and animal feed additives (Yuvaraj et al. 2020). Improved farming practices are very important in mitigating environmental issues arising from conventional farming procedures, and this drive can be taken as a very positive direction in the food system (Drimie and Pereira

2016). Organic farming focuses on agricultural practice of the farm as a whole and aims at enhancing biological diversity within the farming system; to augment soil biological activity, maintain long-term soil fertility, return nutrients to the soil, and to promote the healthy use of soil, water and air as well as minimize all forms of pollution such as bio-accumulation of heavy metals and synthetic chemical fertilizers (Udo de Haes and de Snoo 2010). Because organic agriculture has some important benefits and promising characteristics, for example, its positive influence on local biodiversity, and high productivity in some circumstances; it is suitable not only for the production of various crops but also khat farming. This farming technique exhibits many potential benefits such as higher biodiversity and improved soil and water quality per unit area, improved profitability, and higher nutritional value as well as many potential costs including better consumer prices (Seufert et al. 2017).

### **Conclusions**

On the basis of this review, it can be concluded that regular use of khat is associated with acute and chronic toxicity occasioned by bio-accumulation of toxic trace metals and pesticides in the human biological system.

This can also be augmented by potent psychoactive alkaloids such as cathinone and cathine, and also due to the presence of highly toxic heavy metals—Pb, Cd, Ni and Cr absorbed by khat plant during cultivation. It is noted, for instance that Cd is a chemical element which is highly toxic with long biological half-life and capable of causing serious health problems including nervous breakdown, kidney failure and liver damage. Metal toxicity can lead to numerous disorders and can also initiate oxidative stress induced by free radical formation in the biological system. Heavy metal accumulation to toxicity levels as a result of long term exposure can potentially cause adverse health problems such as liver damage, hypertension and cancer among other health problems. This work has also demonstrated that exposure to malathion can cause chromosomal abnormalities and micronuclei damage in experimental animals and is therefore an health hazard especially when used in khat cultivation. The unregulated use of khat is therefore injurious to the khat consuming community. Accordingly, there is need to advise khat farmers to adopt better agricultural practices that incorporates the use of organic pesticides and organic fertilizers.

#### Abbreviations

BP: Blood pressure; BHC: Benzene hexachloride; CC: Cancer Cases; DDE: Dichlorodiphenyldichloro-ethylene; DDD: Dichlorodiphenyldichloroethane; DDT: Dichlorodiphenyltrichloroethane; FAO: Food Agriculture Organization; ICP-MS: Inductively coupled plasma-mass spectroscopy technique; NG: Not given; ND: Not detectable; NP: Not provided; OED: Oral epithelial dysplasia; PT: Plant limit; PTWI: Provisional tolerable weekly intake; RDA: Recommended daily allowance; UK: United Kingdom; WHO: World Health Organization; XRF: X-ray fluorescence spectroscopy.

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#### Authors' contributions

AMO: Formal analysis and Writing the original draft. JKK: Conceptualization, Methodology, Formal analysis, Writing & Editing, Validation & Supervision. JOA: Data curation, Formal analysis; Supervision, Writing – review & editing. All authors have read and approved the manuscript.

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The authors have no competing interests.

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