

## ELECTRONIC CIGARETTES

# Safety and Effectiveness of Electronic Cigarettes: A Narrative Review

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## ABSTRACT

**Objective:** To current review the literature regarding safety and effectiveness of electronic cigarettes and to find out any contribution from Malaysia, regarding electronic cigarettes research field.

**Design:** To commendably face this new challenge, health care providers need to become more familiar with the existing literature. A narrative review studies conducted from 2004 to August 2014 through multiple electronic databases that available at the author's institution library conducted by using the terms, safety, effectiveness, efficacy, chemical analysis of e-cigs, electronic cigarettes or electronic nicotine delivery system (ENDS). The databases searched only for full text papers published in English from 2004 to august 2014.

**Methods:** 48 original articles identified with help of multiple electronic databanks, that linked to aim title were selected. Nation wise contribution included, USA(16), UK(07), Italy(6), Greece(5), New Zealand(5), Switzerland(4), Canada, Australia, Poland, south Korean, Czech republic each 1. We did not found any article from Malaysia, this indicate us there is a necessity of electronic cigarettes studies on Malaysian population.

**Conclusion:** Due to limited studies with inadequate participants and short time exposure in some developed countries, e-cig cannot accomplish safe and effective in complete terms. In order to conclude firmly, still more research is needed globally in different population to look at its long-term safety and effectiveness particularly on cardiovascular diseases and on smoker's health from different parts of the world.

## KEY WORDS

electronic cigarette, vaping, cessation, safety, effectiveness

## INTRODUCTION

Electronic cigarettes (e-cigs) are gaining popularity and its use rises sharply every year. According to recent report prepared by world health organisation (WHO) stated that, till early 2014 there are 466 brands of e-cigs available in 7764 unique flavours (Zhu *et al.*, 2014) and till the end of 2013 its sales reached to US\$ 3 billion globally and it has been projected, the sales margins can rise up to US\$10 by 2017 (Herzog B *et al.*, 2014). Worldwide there is no data for e-cig users (commonly called vapers). However data from some country suggested that, like North America, the European Union and republic of Korea, the e-cig users doubled among both adults and adolescents from 2008 to 2012 (Grana *et al.*, 2014). The spectacular success of e-cigs is a game-changing event in the field of tobacco control and even the tobacco industry has introduced their own brands.

Electronic cigarettes (e-cigs) are relatively new and the use is becoming a popular type of electronic nicotine delivery system (ENDS). It is a battery-powered device that looks like a cigarette but does not involve smoke and which enables users to inhale vaporized nicotine (WHO, 2009). The e-cigarette was developed with the goal of mimicking the action of smoking, including nicotine delivery, without the toxic effects of tobacco smoke which is responsible for nearly all of tobacco smoking's damaging effect (Cahn and Siegel, 2011; Siegel *et al.*, 2011; Borland 2011; Foulds *et al.*, 2011; and Wagener *et al.*, 2012). Further e-cigs generating vapours which visually look like smoke, that replace most of the bodily, civic and societal elements linked with smoking.

E-cigs transport to the lungs, a chemical mixture primarily consists of nicotine, propylene glycol, glycerine and few flavouring agents. They are often tactically look and feel like cigarettes. They have been promoted as substitutes to cigarettes and for usage in places where smoking is not tolerable since they do not generate smoke. They are also sometimes made to look like daily normal items such as pens, screw driver for people use so that, its appearance deprived of other people observing (WHO, 2009).

Concept of an E-cigarette was first patented in 1965 by Herbert A Gilbert (Gilbert, 1965). But then again the 21<sup>st</sup> century creation of e-cigarettes is recognized to Mr Hon Lik, a Chinese pharmacist (Kcancer, 2010). The device was first introduced to the Chinese domestic market in May 2004 as a support for smoking cessation. Then export began in 2005-2006, before an international patent in 2007.

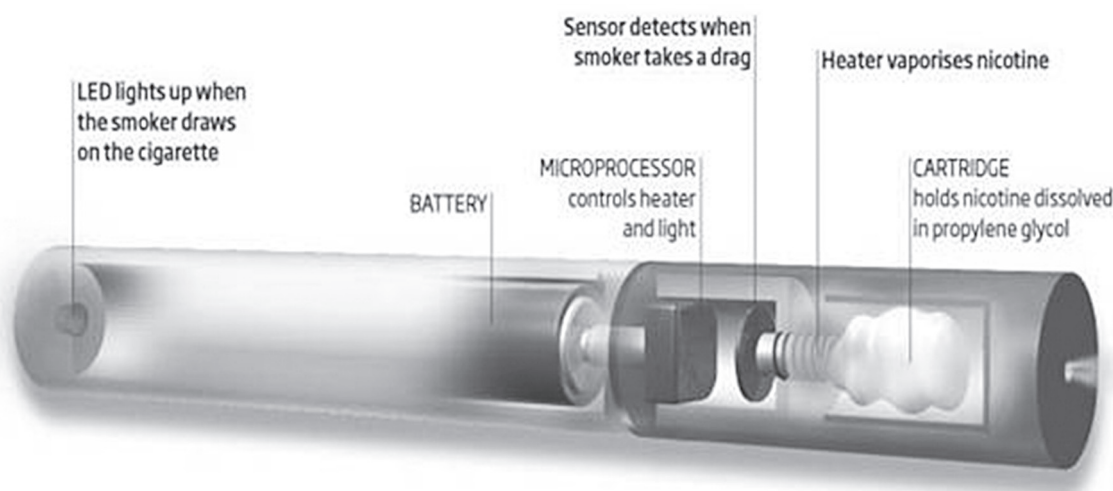
A typical e-cigarette (Figure1) is made up of electronic vaporization system (contains heating coil), rechargeable batteries, electronic circuit and tanks to fill the e-juice to vaporize. The amount of nicotine in the e-juice may differ, the manufacturer's stated that the e juice typically contain between 6 and 24 mg of nicotine (Goniewicz *et al.*, 2012). Currently due to advancement of technology there are three categorizing of E-cigarettes available in the markets. Namely Ist generations (looks like traditional tobacco cigarettes), IInd generations (look like pens and screw drivers also called vape pens) or III<sup>rd</sup> Generations (also called advanced personal vaporizers (APVs or Modes). Each type gets gradually larger as you move up from I<sup>st</sup> Generations to III<sup>rd</sup> Generations. I<sup>st</sup> being the smallest and III<sup>rd</sup> or APVs being the largest.

From I<sup>st</sup> generation to third Generations, there is an improvement in

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**Figure 1. structure of standard entry model Electronic cigarette**

Source: <http://www.e-cigarette-direct.com/pages/How-E-Cigs-Work.html>

features like improvement in battery life, use of different atomisers with various e-liquid filling capacities, advanced features such as variable voltage (VV) and / or variable wattage (VW), all these factors are important for better vapour productions and to increase the number of puffs.

There is rising curiosity as well as worry regarding e-cigs among cigarette smokers, entrepreneurs, health care professionals, policy managers and even tobacco industries. The World Health Organization has urged marketers of e-cigarettes to halt their unproved claims about the therapeutic benefits of using e-cigarettes and has indicated that there is no reliable scientific evidence to confirm the product's safety and efficacy (WHO, 2008). Certain believers of tobacco harm reduction have pointed to these products as feasible alternatives for cigarettes because they produce fewer toxins in the vapour delivered to the use (Cahn and Siegel, 2011; Siegel *et al.*, 2011; Borland, 2011; Foulds *et al.*, 2011; Wagener *et al.*, 2012).

### Cigarette smoking

Smoking is a chief source of adverse health effects in most countries globally. Smoking harms nearly every single organ of the body. Smoking origins many diseases and shrinks the health of smokers in over-all (WHO, 2003). Cigarette smoking is the single biggest avoidable cause of death and disability in developed countries. Smoking is now growing swiftly all over the world and is one of the biggest intimidations to current and future world health (WHO, 2003). For many smokers, leaving smoking is the chief imperative thing they can do to improve their health. Reassuring smoking cessation is one of the absolute cost effective things that physicians and other health professionals can do to improve health and prolong their patients' lives. The adverse health effects of smoking are wide, and have been comprehensively recognized. There is a substantial dose-response link with heavy smoking, duration of smoking, and premature use connected with higher risks of smoking related illness and mortality (Wilson *et al.*, 2000).

### Global Smoking statistics

Tobacco smoking is a global problem, affecting an approximately 1.3 billion people, projected to increase 1.6 billion by 2025 that create significant health problem and economic burden (Mathers & Loncar, 2006). According to the World Health Organization (WHO) tobacco use is presently accountable for the death of one in ten adults' worldwide. Presently 6 million deaths and this number of deaths due to smoking-related diseases are expected to reach 8.3 million by 2030 (WHO, 2008; US Department of Health and Human Services, 1990).

## METHODS

A literature survey was done from March to August 2014 to identify published articles related to safety and effectiveness of electronic cigarettes. In this narrative review, we included studies that are potentially

related to safety and effectiveness of Electronic cigarettes including chemical analysis, because it addresses the safety of device. Each article was revised by all authors and a consent meeting was summoned to ensure worth assurance of the manuscript.

The searched scheme involved nine most widely used electronic databases in health sciences, that included Medline, PubMed, Scopus, ISI Web of knowledge, science direct, Springer link, JSTOR, Proquest and Ebsco Host. The searched structure involved using Boolean operators for combination of the following terms: safety, effectiveness or efficacy, chemical analysis, electronic cigarettes, e-cigarettes, nicotine delivery system. These searches were accompanied by hand search of the reference lists in the reports identified. To ensure reports met the desired criteria, the lists of titles and abstracts from searches were scrutinized and where doubt remained, the whole paper was examined. The searched was limited to full papers articles published in English from 2004 to August 2014.

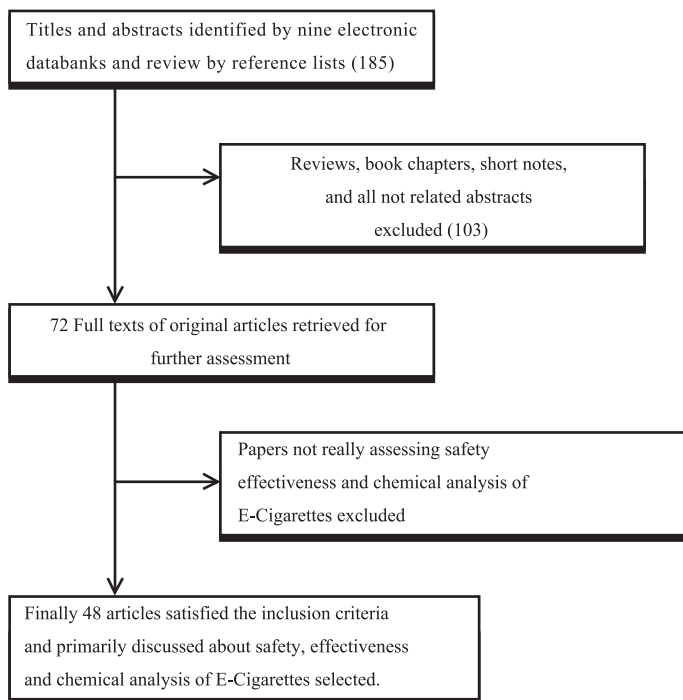
## RESULTS

185 titles and abstracts were identified by all authors from above mention nine databanks and wherever possible by valuation of the reference lists. Among these Articles that includes, Erratum, book chapters, reviews, letter to editors, short communications, editorials notes, opinions, non-original data, not published in English language and duplicated citations were examined and excluded. Of these, 72 original articles that related to our topic were selected. The full text of 72 articles was retrieved and disseminated among all authors for further valuation. Among 72 documents all authors agreed that, 48 were suitable for inclusion in the review. Country wise contribution include, USA(16), UK(07), Italy(6), Greece(5), New Zealand(5), Switzerland(4), Canada, Australia, Poland, south Korean and Czech republic each 1. We did not found any article from Malaysia, this indicate us there is a need of electronic cigarettes studies on Malaysian population. The remaining manuscripts were excluded because their primary focus was not safety, effectiveness and chemical analysis of electronic cigarettes. So in the final review mainly 48 articles were selected. Although some other articles are also cited for background and context. The quorum flow chart for this review is shown in (Figure 2).

### Studies on Effectiveness of E-Cigarette

Evidences strongly suggest that e-cigarettes may be effective in helping smokers to quit and preventing relapse, to our knowledge there have been few published studies to explain why this might be the case. Many health authorities refuse to say that, this product is beneficial for smoking cessation due to limited studies and the risks and benefits are still being calculating. The degree of effectiveness depends on what effect is being measured.

As per the Goniewicz *et al.*, (2013) quitters perceive mainly four benefits these are, desire to smoke (craving), help to cut down cigarettes, help to quit entirely and eradicate the smell of stale smoke.



**Figure 2. Quorum flow chart of the review process**

Some online surveys on e-cigarette users suggested that, e-cigarette helped them to quit or reduce smoking and vapers believe that it is less harmful than smoking (Etter, 2010; Etter & Bullen, 2011; Siegel *et al.*, 2011; Foulds *et al.*, 2011).

The trial by Bullen *et al.*, 2010 on 40 naïve smokers measured the short-term effects of e-cigarettes on desire to smoke, withdrawal symptoms, acceptability, pharmacokinetic properties and adverse effects in a cross-over trial design. The results demonstrated that electronic cigarettes deliver nicotine effectively, more rapidly than a nicotine inhaler, and the electronic cigarette use significantly reduced craving but less than with a regular cigarette (Bullen *et al.*, 2010).

The Siegel *et al.*, (2011) on 216 respondents, more than 70% male between 18 to 65 ages smoking for last 5-30 years, reported after 6 months of vaping, 31% of participants were no longer using tobacco cigarettes.

The clinical trial done by Caponnetto, P *et al.*, (2013a) on 300 smokers in a randomized clinical trial (RCT) with no intention to quit, performed the efficiency and safety of an electronic cigarette (ELCAT), have found out smoking reduction was documented in 22.3% and 10.3% at week-12 and week-52 respectively. Complete abstinence from tobacco smoking was documented in 10.7% and 8.7% at week-12 and week-52 respectively. Declines in cig/day use and expired carbon monoxide (eCO) levels were observed and a substantial decrease was found in the adverse events as well. In another study by same author on 14 chronic schizophrenic smokers reported similar reductions in cigarette consumption and abstinence after a yearlong trail by using e-cigs (Caponnetto *et al.*, 2013b).

The clinical trial done by Polosa, R *et al.*, (2011) in a 6 month pilot study on 40 regular smokers with no desire to quit, reported a six-month prevalence smoking cessation rate of 22.5%. An additional 32.5% of smokers reduced their cigarette consumption by at least 50% by using e-cigarettes. The Polosa *et al* continued the trial in a naturalistic settings have been found out a 50 % reduction in the number of cig/day after 24 months was shown in 27.5 % participants with a median of 24 cig/day use at baseline decreasing significantly to 4 cig/day ( $p = 0.003$ ). Smoking abstinence was reported in 12.5 % participants while combined 50% reduction and smoking abstinence was observed in 40% participants in two years (Polosa, R *et al.*, 2013).

The trial by Dawkins *et al.*, 2012 in 86 smokers, examined whether the e-cigarette can reduce desire to smoke and abstinence-related withdrawal symptoms among three groups during 0, 5, 20 minutes period after vaping ad libitum for 5 minutes. It was found that the electronic cigarette can reduce desire to smoke and nicotine withdrawal symptoms 20 min after its use. In another study by same author, on 1347 partici-

pants from 33 countries (> 70% European) online survey reported that, e-cig are mostly used for smoking cessation, but need a longer duration than nicotine replacement therapies (Dawkins *et al.*, 2013).

The survey conducted by Goniewicz *et al.*, (2013) on 179 respondents reported that 72% of users believed that e-cigs were beneficial in reducing cravings and withdrawal symptoms while 92% declared that the devices had reduced the number of conventional cigarettes they smoked. Indeed, in the same survey, 96% of former smokers claimed that e-cigarettes had helped them quit, and 79% reported a fear that if they stopped using them they would start smoking again.

In study done by Barbeau *et al.*, (2013) on 11 participants ages between 18-64 in a focus group discussion posing open ended questions, revealed that, vaping was more successful in maintaining cigarette abstinence than FDA approved NRT therapies due to retention of behavioural and social element of smoking dependence .

Farsalinos *et al.*, (2013) recruited 111 participants more than 84% male smoked before at least 20 30 cigs/day, who had completely substituted conventional cigarette with e-cig for last one month shown, e-cig with high nicotine content were more successful in the smoking abstinence process.

Kralikova *et al.*, (2013) taken interview of 2012 participants on the street of 17 cities of Czech republic, identified that about 20% of smokers who tried e-cigs go on to become regular e-cig users (Kralikova *et al.*, 2013).

Pokhrel *et al.*, (2013) in a cross sectional study survey on Hawaiian islands on 1567 participants shown, smokers who tried e-cigs appear to be more serious about smoking cessation and treat e-cig as valid alternative to FDA approved nicotine replacement therapies.

A randomized controlled trial on large number of participant done by Bullen *et al.*, (2013) to verify safety and effectiveness of e-cigs among 657 people shows that e-cigs, with or without nicotine, were modestly effective at helping smokers to quit, with similar abstinence rate achieved with nicotine patches. However, the study was underpowered to conclude superiority of nicotine over nicotine patches (Bullen *et al.*, 2013).

A recently worldwide survey of more than 19,000 consumers by farsalinos *et al.*, (2014) on characteristics, perceived side effects and benefits of electronic cigarette use reported, E-cigs were mostly used to avoid the harm associated with smoking and it is effective in highly-dependent smokers and are used as long-term substitutes for smoking. The study also stated 57.9% participants faced at least one symptoms and the most common side effect were dry mouth and sore throat (38.9%) .

A new recent cross sectional population study on 5863 adults to quit smoking with smoking aids such as E-cig, nicotine replacement therapy (NRT) and deprived of smoking aid for smoking cessation, were selected in a real world settings without professional support. Among smokers, who more likely to report for quit smoking were E-cig users compare to NRT and no aid cessation users respectively (Brown *et al.*, 2014).

An outline of the studies involving effectiveness of e-cigs, summarized in the Table 1

### Studies on E-Cigarettes Safety

A draft review by the WHO's Tobacco Regulatory Group in 2009 notes that the extent of nicotine uptake and the safety of e-cigarettes have yet to be fully established. Most of the safety concerns regarding electronic cigarettes relate to the absence of appropriate product regulation and inconsistencies in quality control (WHO 2009).

The study done by Eissenberg (2010) on 16 smokers, naive to e-cigarettes were cycled through the four device groups revealed that, smoking but not vaping, notably increase nicotine and heart rate (Eissenberg, T. 2010).

The trails done by vansickel *et al.*, (2010) in above correlated situation, reported similar results. The key findings were, nicotine, expired carbon monoxide and heart rate all increased after smoking, but not vaping, but later in 2013 Vansickel and Eissenberg study on 8 experienced E-cig users reported that, both smoking and vaping induced similar concomitant increases in heart rate and blood levels of nicotine (vansickel *et al.*, 2010 ;2013).

The results reported by Etter and Bullen (2011) on 31 respondents of e-cigarettes users from different countries after vaping ad libitum but abstained from cigarettes and NRTs for 48hrs. The study shown vaping and smoking induce similar increases in salivary cotinine levels than conventional cigarettes

Czogala *et al.*, (2012) have done comparison study on hemodynamic parameters (Systolic and diastolic pressure, pulse and heart rate) in smokers and vapers on 42 subjects. The study shown that vaping e-ciga-

**Table 1. Summary of studies involved in effectiveness of Electronic Cigarettes.**

Authors	Study design	Patient sample size	Clinical outcomes and key findings
Bullen <i>et al.</i> , (2010) Australia.	RCT, four groups comparison effect E-cig with or without nicotine, tob cigarette & Nicorette nicotine inhaler	40 adult naïve dependent smokers Average age (mean $\pm$ SD): 47.6 $\pm$ 12.4	Tobacco cigarette effectively remove craving and withdrawal symptoms'-E-cig with nicotine and nicotine inhaler have similar effect greater than e-cig without nicotine.
Etter (2010).	Online French survey	81 participants, between 19-65, 63% former smokers 23% daily smokers 13% occasional smokers from different country	e-cigarette helped to quit smoking
Etter and Bullen, (2011)	Internet survey	3587 respondents, between 31-52, 70% former smokers, 19% daily smokers 11% occasional smokers	Respondent reported E-cigs helped them to quit or decreased smoking and vaping less toxic than smoking.
Foulds <i>et al.</i> , (2011). (interview)	Survey at e-cig enthusiast convention	104 respondents mean between 34 $\pm$ 9, 78% former smokers, 19% daily smokers	E-cig helped them to quit or decreased cigarette consumption and vaping less harmful than smoking
Siegel <i>et al.</i> , (2011).	Online survey	216 participants ages 18-65 $\pm$ years , smokers for 5-30 + years	After 6 months of E-cig 31% of participants were no longer using tobacco cigarettes.
Dawkins <i>et al.</i> , (2012).	RCT; single-blind	86 e-cigarette naïve smokers (43 female, 43 male; age range: 18-52 [mean: 28.8	E-cig helped to decreased desire to smoke and abstinence related withdrawal symptoms over a 20 minutes period.
Bullen <i>et al.</i> , (2013)	Randomized controlled trail on 657respondents.	e-cig group(n = 289) age 44 $\pm$ 13 years, nicotine patch group(n = 295) age 40 $\pm$ 13 years e-cig placebo group (n = 73), age 43 $\pm$ 12 years	E-cig with or without nicotine were effective at helping smokers to quit smoking as nicotine patches
Barbeau <i>et al.</i> , (2013).	Focus group discussions facing open ended questions	Nine men and two women, between 18-64 years	Participants reported E-cig is more helpful than FDA approved nicotine replacement therapies due to retention of behavioral and social components of smoking addiction
Caponnetto <i>et al.</i> , (2013a).	RCT: prospective 12-month randomized, controlled trial.	300 smokers no intention to quit, mean age 44 $\pm$ 13 years, 63% male and smoke at least 15-25 cigarettes/day	The use of e-cig with or without nicotine , decreased cigarette consumption and elicited tobacco abstinence
Caponnetto <i>et al.</i> , (2013b).	Chronic schizophrenic patients observed for 12 months	14 Chronic schizophrenic patients mean age 45 $\pm$ 13 years and consumed 20-35 cigarette /day	e-cig use decreased cigarette consumption without causing any significant side effects in schizophrenic patients
Dawkins <i>et al.</i> , (2013).	Online survey	1347 participants, mean age 43 years Respondents from 33 countries.	E-cig mainly used to quit smoking .study also reported there is very little evidence that E-cig is not the gateway for nonsmokers.
Farsalinos <i>et al.</i> , (2013).	Smokers substituted with e-cig for at least 1 month	111 participants, average 37 $\pm$ 6 years, smoked 20-30 cig/day from Greece.	E-cig with higher nicotine useful in quit smoking compare to less or no nicotine.
Goniewicz <i>et al.</i> , (2013a).	Internet survey	179 respondents from Poland	E-cig mainly used to quit smoking with less harm effects.
Polosa <i>et al.</i> , (2013).	A 24 month observational study	40 regular smokers, 26 males, 14 females; mean $\pm$ SD age of 42.9 $\pm$ 8.8 years Regular smokers (mean $\pm$ SD): 34.9 $\pm$ 14.7 pack/years.	After Long term e-cig use decreased in > 50% consumption of traditional cigarette along with 12.5% of abstinence rate as verified eCO(exhaled carbon monoxide).
Polosa <i>et al.</i> , (2011).	A prospective 6 month pilot study	40 regular smokers, 26 males, 14 females; mean $\pm$ SD age of 42.9 $\pm$ 8.8 years Regular smokers (mean $\pm$ SD): 34.9 $\pm$ 14.7 pack/years	After 6 month , E-cig decreased 50 to 80% consumption of traditional cigarette as verified by exhaled carbon monoxide
Kralikova <i>et al.</i> , (2013).	Interview of people on the street	2012 respondents, age 34 year mean, 17 cities across the Czech republic	About 20% of smokers who try e-cigs go on to become regular e-cig users.
Pokhrel <i>et al.</i> , (2013) .	Cross sectional survey of Hawaii i slanders recruited from 2010 to 2012	1567 repondents divided in two groups .ever e-cig users(n = 202) mean age 42 $\pm$ 1 years , never e-cig users (n = 1365), mean age 46 $\pm$ 0.4 years	Smokers who tried E-cigs is more confident to quit smoking .

Farsalinos et al., (2014).	Worldwide Internet survey over 19414	Participants were age > 18. respondents divided into two groups , current and former smokers	E-cigs effective in highly-dependent smokers and used as long-term substitutes for smoking. The study also reported 57.9% participants reported at least one symptoms and the most common side effect were dry mouth and sore throat (38.9%).
Brown J et al., 2014	A Large cross sectional	5863 smokers observed for quit smoking in three groups E-cig, NRTand cold turkey without any professional support	Smokers who more likely to report for abstinent are E-cig users compare to NRT and going cold turkey.

rette failed to induce changes in hemodynamic parameters that usually associated with traditional smoking (Czogala *et al.*, 2012).

The study by Goniewicz *et al.*, (2013) after switching from tobacco to electronic cigarettes nicotine exposure were unchanged while exposure to selected toxicants was substantially reduced Goniewicz *et al.*, (2013).

Flouris *et al.*, (2013) carried out study on 15 cigarette smokers and 15 never smokers who used the same brand of E-cigarette. The study reported that, acute smoking, but not acute vaping induced increased in white blood cell lymphocyte which reflects sign of inflammation and significant decrease in forced expiratory volume in one second (FEV<sub>1</sub>) whereas vaping lacking these effects.

Farsalinos and Romagna (2013) mention in a case report that, smoking cessation and use of e-cigarette reversed the symptoms of chronic idiopathic neutrophilia in a 28 year old male patient.

A study on 18 heavy smokers with mild to moderate asthma symptoms using a regular dose of inhaled corticoids and long acting beta agonists gone through pulmonary function tests before and after 6 and 12 months of E-cig use. Smokers with asthma who switched to E-cigs, found no adverse effects, rather e-cigs users shown significant improvement in FEV<sub>1</sub>. Further author stated that out of 18 smokers 10 quit smoking completely and reaming 8 become dual users, decreased their consumption of cigarettes from average of 22.4 at baseline to 3.9 day after 12months (polosa R *et al.*, 2014).

A recent study compared the acute effects of smoking and E-cigs on myocardial function on 36 healthy smokers and 40 vapers respectively. The study stated that, e-cigs has no immediate effect on myocardial function as compare to smoking, which causes delay in myocardial relaxation. But further author suggested that, to conclude firmly for long term beneficial effects, intense study should be performed on smoker's health (Farsalinos *et al.*, 2014).

In comparison with above analysis, the below studies shown undesirable impact of e-cigarette and vaping on health.

Bahl *et al.*, (2012) mention mixed response of e-cigarette on Human embryonic stem cells and pulmonary fibroblasts carried out on In vitro cultures. The study shown that, nicotine in e-cigarette refill fluid had no cytotoxic effect on the Human embryonic stem cells where as the number and concentration of chemicals other than nicotine used to flavour e-cigarette refill fluids increased cytotoxicity.

McCauly *et al.*, (2012) mention in a case report that, stopping of e-cigarette use cleared the exogenous lipoid pneumonia in a 42 year old woman, but the case study does not publicized that patient is a current or ex-smoker (McCauly *et al.*, 2012).

A case of atrial fibrillation in an elderly person after E-cig use has been reported. But report further explains, this could be the effect of nicotine on autonomic nervous system (Monroy. A.E *et al.*, 2012).

A study done by Vardavas *et al.*, (2012) on 10 healthy smokers to find out the effect of E-cigs on pulmonary functions shown, after acute ad libitum puffing from e-cig (Nobacco, 11 mg/ml of nicotine) for five minutes, found no effect on spirometry but shown 18% dynamic airway resistance and 16% decreased expired nitric oxide. The limitation of this study is small sample size. Even though this study suggest that e-cigs constricts peripheral airways which could be particular concern to COPD, Asthma, emphysema and bronchitis people and some authors conclude this effect, is a sign of pulmonary inflammation (Schober *et al.*, 2013).

A case report by thota, and latham, (2014) mention, electronic cigarettes possibly associated with acute eosinophilic pneumonitis (AEP) in a previously healthy 20 year old active-duty sailor. The data suggested that, there could be a link between use of e-cig and AEP. But author further stated that studies are needed to establish a correlation between these two (Thota, and Latham.,2014).

An outline of the studies involving safety of e-cig summarized in the Table 2

## Studies on Chemical Analysis of E-Cigarette

The review on chemical analysis, address the safety of the e-cigs. It has been found that, nicotine content of the e-liquids in the cartridges from some brands, failed to claim labelled and actual nicotine content. (Goniewicz *et al.*, 2013;Cameron *et al.*, 2014) and also many questions are raised for the contents of E-cigs, even though there is more comprehensive knowledge of the chemical constituents of e-cigarette than tobacco ones (Cahn and Siegel, 2010).

Cigarette smoke from burn tobacco products contains thousands of compounds, many of which have been exposed to promote carcinogenesis such as trace elements (i.e., cadmium, arsenic, chromium, nickel and lead), the tobacco specific N-nitrosamines (TSNA), the polycyclic aromatic hydrocarbons (PAH), and volatile organic compounds (VOCs) (Rodgman and Perfetti.2009; Talhout R *et al.*, 2011).

As mention above the main basic ingredients of E-cigs liquids are propylene glycol and glycerine. Propylene glycol is considered generally recognized as safe (GRAS) by the U.S. Food and Drug Administration (USFDA). But the literature survey revealed that it can cause eye and respiratory irritation, long and repetitive inhalation may affect central nervous system(MDSS,Sciencelab.com).when propylene glycol heated or vaporised can form propylene oxide and as per international agency for research on cancer it is a class 2B carcinogen (Iaino *et al.*,2012).whereas glycerol on heating may forms acrolien, which can causes upper respiratory tract irritation(US EPA).some physical injuries and illness also reported by e-cig use, due to explosions and fires (Chen IL, 2012; CBS News 16,2012).

Apart from above debated questions, the below studies also reported toxicants and impurities found in E-cigs liquids, cartridges and mists.

The study done by FDA found, some small amounts of diethylene glycol (DEG) approximately 1% and, tobacco specific nitrosamines (TSNAs). DEG is known carcinogen and ingredient use as anti-freeze, detected in one out of 18 cartridges analysed by FDA. The cause of the DEG contamination is not apparent but could reveal the use of non-pharmaceutical grade propylene glycol (Laugesen M., 2008).

The study done by Westenerberger BJ (2009), FDA division of pharmaceutical analysis department and Cobb NK and Abrams DB (2011) revealed that, the ingredients chiefly found in e-cigarette are Nicotine, propylene glycol, glycerine and tobacco flavouring agents. The study further mention that, propylene glycol, a FDA approved solvent for foods and vehicle for some injections as the major constituent found in e-cig fluids, make up about 90% of the solution (Westenerberger BJ.,2009).

In another study held by Laugesen M (2008) approved by Health New Zealand ltd (HNZ) found levels of arsenic, cadmium, chromium, nickel and lead to be undetectable in e-cig cartridge liquid along with trace amount of TSNAs .

Cahn and seigel (2010) determine the levels of TSNAs in various cigarettes and nicotinic delivery products including e-cig .The study shown that, TSNAs in e-cigs were very low compare to various cigarettes brands but slight high against Nicorette gum and Nicoderm CQ patch. (Table 4)

A few other studies also inveterate some low levels of TSNAs, undetectable levels of particulate matter, trace elements, VOCs, and PAHs in cartridges and refill solution of e-cigarettes (McAuley *et al.*, 2012; Goniewicz ML *et al.*, 2013; Schripp T *et al.*, 2013; Kim HJ and Shin HS.2013; Pellegrino *et al.*, 2012).

FDA issued warning to several e-cigs companies for selling e-cartridges and refill solutions containing active pharmaceutical substances (Woodcock J, 2013). Analysis of some e-cigarettes cartridges and solutions revealed the presence of some active pharmaceutical ingredients such as rimonabant (Zimulti) and aminotadalafil, although the amount of these substances that is able to transfer from liquid to vapour phase is low (Hadwiger ME *et al.*, 2010; Moorea TW *et al.*, 2011).

**Table 2. summary of studies described safety of Electronic cigarettes.**

Authors	E-cig brands	Parameters tested	Study Design	Key findings
Eissenberg (2010).	Njoy Crown Seven	Plasma nicotine and heart rate measured before and after 10 puffs of each device on four different groups.	16 smokers, naïve to e-cigarettes were cycled through the four different groups	Smoking, but not vaping, raised plasma nicotine and heart rate.
Vansickel <i>et al.</i> , (2010)	Njoy Crown Seven	Plasma nicotine ,carbon monoxide and heart rate taken before and after 10 puffs on different groups	16 smokers, naïve to e-cigarettes were cycled through the four different groups.	Nicotine, expired carbon monoxide and heart rate all raised after smoking, a but not vaping
Etter and Bullen., (2011).	Own brand e-cig	Salivary cotinine and heart rate	E-cig users vaped ad libitum but abstained from cigarette and NRT for 48 hrs.	Vaping and smoking induced similar increased in salivary cotinine and heart rate.
Czogala <i>et al.</i> , (2012).	Not mention	Systolic pressure Diastolic pressure Pulse, Heart rate	Hemodynamic parameters are measured in smokers after smoking cigarette or vaping	Vaping e-cigarettes fail to induce the typical hemodynamic parameters linked with traditional smoking.
Vansickel <i>et al.</i> , (2012).	Vapour King	Plasma nicotine concentration, heart rate, urge to smoke cigarette, and nicotine withdrawal symptoms tested in four smokers	Twenty smokers ,not currently using e-cig were cycled through four experimental sessions	e-cig substantially deliver nicotine, increase heart rate, reduced withdrawal symptoms and urge to smoke
Dawkins and corcoron., (2013)	First generation e-cig (18 mg/ml)	Plasma nicotine Tobacco withdrawal symptoms Urge to smoke	14 E-cig users abstinent from smoking and vaping for 12 hr before test period.	Vaping helped in reducing tobacco related withdrawal symptoms and urge to smoke.
Farsalinos and Romagana.,(2013).	Case report	A 28 year old male with chronic idiopathic neutrophilia		Smoking abstinence and use of e-cig reversed symptoms of chronic idiopathic neutrophilia.
Flouris <i>et al.</i> ,(2013).	Giant,Nobacco GP Greece (11mg/ml)	Repeated measures controlled study	30 smokers gone through a control session, active smoking and active vaping session	e-cig use induced smaller changes in pulmonary function but similar nicotinic impact compared to smoking
Vansickel and Eissenberg.,(2013).	Own brand	Plasma nicotine Heart rate	Blood samples were collected at baseline and after 1 hr ad libitum	Vaping and smoking induced similar increased in plasma nicotine and heart rate
Thota and latham (2014).	Case report	Acute eosinophilic pneumonitis(AEP).	E-cig possibly associated with eosinophilic pneumonitis in a previously healthy active-duty sailor.	The data suggested that, there could be link between use of e-cig and AEP. Further studies are needed to establish a correlation.
Monroy. A.E <i>et al.</i> , (2012).	Case report	Atrial fibrillation	Elderly person	E-cig reported to induced atrial fibrillation.
Farsalinos <i>et al.</i> , (2014).	eGO-T battery (nobacco ,Athens , greece	36 healthy smokers average age 36 ± 5, 40 E-cig users average age 35 ± 5	Ecocardiographic examination and myocardial performance index before and after use of tobacco cig and E-cigs	E-cigs does not show any immediate effect on myocardial function whereas tobacco cig causes delay in myocardial relaxation.

The analysis done by (Cheah *et al.*, 2012; Cameron *et al.*, 2013) on various brands of e-cigs cartridges and solution to determine the nicotine and its impurities reported that, Variable nicotine content in cartridges of same brands, inconsistency with product labelling and misleading information on labels raised e-cig safety (Cheah *et al.*, 2012; Cameron *et al.*, 2013).

Similar to above study, another investigation done by Kim and shin (2013), reported related results. The analysis done on 105 refill fluids from 11 companies in Korea, founds a three order amount variation in TSNA concentrations, ranging from 330-8600 mcg/ml.

In contrast to above study, the analysis done by Etter *et al.*, (2013) on numerous brands of e-cig refill solutions, revealed nicotine content to be precise and reliable to what was printed on the label (Etter *et al.*, 2013).

The chemical analysis done by Goniewicz *et al.*, (2014), to determined toxic and carcinogenic compounds on twelve brands of E-cigs

aerosols, tobacco cigarette and nicotine inhaler revealed that, the levels of toxicants in the e-cigs aerosol were 1 to 2 orders of lower magnitude than tobacco cigarette but higher than nicotine inhaler. (Table 5)

The studies involving chemical analysis of e-cigs summarized in the Table 3.

## DISCUSSION

Electronic cigarettes use or vaping gaining attractiveness worldwide. Their usage is greatly debatable as scientific outlook. Despite rapid market penetration of e-cigs still many question are unclear about their safety, efficacy for harm reduction and total impact on public health. Now e-cig becomes a global debate, with authorities wanting to ban it or legalize it. Given the debated nature to e-cigs, the medical

**Table 3. Summary involved Studies of Chemical Analysis of Electronic Cigarettes.**

Authors	E-cig brands	Substance tested	Analysis	Key findings
Laugesen (2008).	Ruyan	TSNA, MAO-A and B inhibitors, PAH, Heavy metals, CO	LC-MS, Fluorometric assay GS-MS, ICP-MS, CO analyser	TSNAs found but much lower than tobacco cigarette not carcinogenic level, PAH, heavy metals undetectable. Exhaled eCO does not increase after e-cigarette use.
Westenberger (2009). FDA Study.	Njoy, Smoking every Where	TSNA, DEG, Tobacco specific impurities	LC-MS, GC-MS, GC-MS	TSNA,DEG present, Tobacco specific impurities present Measured Nicotine in several e-cig solutions is irregular to be in safe.
Hadwiger <i>et al.</i> , (2010), FDA Study	Not mention	Amino Tadalafil Rimonabant	HPLC-DAD-MMI-MS	Amino tadalafil and Rimonabant present Presence of nicotine in products labelled as containing no nicotine
Trehy <i>et al.</i> , (2011). FDA Study	Njoy, Smoking every Where CIXI, Jhonson creek	Nicotine related impurities	HPLC-DAD	Nicotine related impurities present.
Cheah <i>et al.</i> , (2012)	20 different brands of e-cigs	Nicotine contents in cartridges and e-cig quality.	GC-MS and Visual inspection of produc	Variable nicotine content in cartridges of same brands, inconsistency with product labelling and misleading information on labels raised e-cig safety.
Goniewicz <i>et al.</i> , (2012).	eleven polish brands and one English brands	Carbonyls, VOC TSNA, Heavy metals.	HPLC-DAD,GC-MS, UPLC-MS, ICP-MS	TSNA,VOC, and carbonyl compounds were found to be 9 to 450 times lower in e-cigs mist compare to conventional cigarette smoke.
McAuley <i>et al.</i> , (2012).	Not mention	TSNA, PAH, DEG, VOC Carbonyls	GC/MS,GC/MS,GC/MS, HS-GC/MS HPLC-UV	TSNA, PAH, diethylene glycol, VOC, and carbonyls in e-cigarette mist were all negligible compared to cigarette smoke.
Pellegrino <i>et al.</i> , (2012).	Italian brands of e-cigarettes	Particulate matter	Particle counter and smoking Machine	Particulate matter found in E'cig mist but lesser than cigarette smoke.
Schripp <i>et al.</i> , (2012).	Three unidentified brands	VOC, Particulate Matter	GC-MS, Particle counter and smoking machine.	VOC in e-cig cartridges, solution and mist but lower than tobacco cigarette, PM is low in e-cig mist compared to cigarette smoke.
Cameron <i>et al.</i> , (2013).	Vapour liquid Smart smoke, BE112 No brand liquid	Nicotine content in solutions and cartridges	LC-MS	Nicotine levels in e-cig solutions were too irregular to be reflected unsafe.
Kim and Shin (2013).	105 liquids brands from 11 korean e-cig companies	TSNA	LC-MS	TSNA are present at low levels in e-cigarette replacement fluids
Etter <i>et al.</i> , (2013).	10 brands of refill liquids	Nicotine contents, nicotine degradation and its impurities	GC and LC	Measured Nicotine content in refill liquids are similar as indicated on the label. Impurities found but below dangerous level.
Williams <i>et al.</i> , (2013).	Not mention	Heavy metals Silicate particles	ICP-MS, Particle counter and smoking machine, light and electron microscope, cytotoxicity testing, x-ray, Microanalysis.	Heavy metals and silicate particles found in e-cig mist

Abbreviations: TSNA= tobacco specific nitrosoamines;PM=particulate matter; LC-MS, = liquid chromatography-mass spectrometry; MAO-A and B = monoamineoxidase A and B; PAH = polycyclic aromatic hydrocarbons; GS-MS = gas chromatography - mass spectrometry; ICP-MS = inductively coupled plasma mass spectrometry; CO= carbon monoxide, VOC = volatile organic compounds; UPLC-MS = ultra-performance liquid chromatography-mass spectrometry; HPLC-DAD-MMI-MS = high performance liquid chromatography-diode array detector-multi-mode ionization-mass spectrometry.

community are in quandary to advice this as a smoking cessation aid to their patients. Most of the studies reported mix response regarding e-cig effectiveness and safety. Maximum of the studies done on internet, that is consumer based surveys regarding personal view on vaping, some observational studies (Caponnetto, Polosa, Russo, Leotta, & Campagna, 2011; Farsalinos & Romagna, 2013; Schneiderhan, 2012), few randomized trials (Bullen *et al.*, 2013; Caponnetto, Campagna, *et al.*, 2013), one large scale cross sectional study (Brown *et al.*, 2014) Suggest that e-cigs help smokers quit or reduce smoking. Outside these clinical studies, few longitudinal studies of vapers have been published (Adkison *et*

*al.*, 2013; Vickerman, Carpenter, Altman, Nash, & Zbikowski, 2013) and it is still unclear how the behaviour of vapers evolves over time.

The evaluation from above limited studies on inadequate participants with short time periods from some countries on electronic cigarettes without sufficient data worldwide about its safety, effectiveness and health impact cannot accomplish e-cigarettes is harmless in complete terms. In order to conclude firmly, still more research is needed globally in different population to look at its long-term safety and effectiveness particularly on cardiovascular diseases and on smoker's health from different parts of the world. Our literature survey shown USA,

**Table 4. Maximum Tobacco Specific Nitrosamine (TSNAs) Levels in Various Cigarettes and Nicotine-Delivery Products (Cahn and Siegel, 2010)**

Product	NNN	NNK	NAT	NAB	Total
Nicorette gum (4 mg)	2.00	ND	ND	ND	2.00
NicoDerm CQ patch (4 mg)	ND	8.00	ND	ND	8.00
Electronic cigarettes	3.87	1.46	2.16	0.69	8.18
Swedish snus	980	180	790	60	2010
Winston (full)	2200	580	560	25	3365
Newport (full)	1100	830	1900	55	3885
Marlboro (ultra-light)	2900	750	1100	58	4808
Camel (full)	2500	900	1700	91	5191
Marlboro (full)	2900	960	2300	100	6260
Skoal (long cut straight)	4500	470	4100	220	9290

Abbreviations: NNN = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNK = N'-nitrosanornicotine; NAT = N'-nitrosoanatabine; NAB = N'-nitrosoanabasine. ND = Not detected.

UK, Italy, Greece, new Zealand, Switzerland have higher E-cigs research output compare to other countries of the world, this indicate us there is necessity of E-cigs research globally including Malaysia to a make generalised statement about its safety and effectiveness.

Although our literature survey from 2004 onwards but we found first article as per our objective topic in 2008. E-cigs research emerging more from 2009 to present date, indicating that research in progress. Despite its availability in most the countries except some countries they ban sale of electronic cigarettes with nicotine (Australia, Brazil, Canada, Mexico, Panama, Singapore and Switzerland) the data is lacking country wise including Malaysia.

In our review literature survey many authors concluded that many questions about E-cigs use are unanswered, primarily effectiveness of this device as a smoking cessation aid, long term users and device safety and it use might promote nicotine addiction in non-smokers especially youth generation and has potentiality to renormalize smoking act. Presently very little research has been carried on human health in some nations. Existing available few studies largely conducted on healthy peoples with short time exposure revealed that, minor side effects like mouth irritation, dry cough, nausea, vomiting and with little or no effects on pulmonary and cardiovascular functions without any serious side effects and withdrawal symptoms have been reported with e-cig use. But lot of questions upraised about the safety of its basic contents like propylene glycol that cause respiratory irritation, bronchial constriction and about engineering of the device. The study conducted by FDA found TSNAs and DEG, PAH, VOC and some trace elements in lower quantities, detected in electronic cigarettes cartridges, solutions and mists, open lot of questions regarding its quality, regulations and health issues.

Our study is not without limitations, as per the topic and searching key words and narrative nature of this manuscript only original articles that reported mainly safety, effectiveness and chemical analysis of electronic cigarettes in above mention databases were included. Despite some articles cited with other topics or key words might be missed and might give some important information regarding safety and effectiveness of E-cigs. Additionally articles published other than these data-banks and published in other languages such as German and French were not selected, might give some important information regarding safety and effectiveness was missed.

## CONCLUSION

Due to limited studies with inadequate participants and short time exposure in some developed countries, e-cig cannot accomplish safe and effective. In order to conclude decisively, still more research is required globally in different population to look at its long-term safety and effectiveness particularly on cardiovascular diseases and on smoker's health

**Table 5. levels of toxicants in E-cigs Aerosol compared with nicotine inhaler and tobacco smoke (Goniewicz *et al.*, 2014)**

Level of toxicants	Content in Aerosol from 12 E-cig samples/15 puffs	Content in tobacco cigarette mcg in mainstream smoke from 1 cigarette	Content in Nicotine inhaler mist Per 15 puffs
Formaldehyde,mcg	0.2-5.61	1.6-52	0.2
Acetaldehyde,mcg	0.11-1.36	52-140	0.11
Acrolein, mcg	0.07-4.19	2.4-62	ND
o-Methylbenzaldehyde, mcg	0.13-0.71	...	0.07
Toluene,mcg	ND-0.63	8.3-70	ND
p,m-xylene,mcg	ND-0.2	...	ND
NNN, ng	ND-0.00043	0.0005-0.19	ND
NNK, ng	ND-0.00283	0.012-0.11	ND
Cadmium, ng	ND-0.022	...	0.003
Nickel, ng	0.011-0.029	...	0.019
Lead, ng	0.003-0.057	...	0.004

from different parts of the world including Malaysia. Hence, the current literature review does not warrant a conclusion that electronic cigarettes are safe and effective smoking aid in absolute terms. In view of this, it is important to investigate and establish the long term safety and effectiveness of these devices in order to ensure that, the decisions of regulators, healthcare providers and consumers are based on science.

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