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E-cigarettes: A Novel Phenomenon

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ABSTRACT

Electronic cigarettes (e-cig), since it developed, have very big market all over the world, and which increases day by day. Nowadays e-cigarette represents a new "tobacco" industry that could reduce the incidence of tobacco smoking. Electronic cigarettes are electronic delivery system are devices designed to deliver aerosolized nicotine with at least one vehicle. The main purpose of electronic cigarettes is to give the user the feeling of smoking without using tobacco. E-cigarette suppliers are marketed e-cigs as a way to reduce or completely quit smoking, and many users, especially young, prefer e-cigarettes because they thought it was safer than tobacco cigarettes in general. Many e-cigarette brands are currently sold in the markets and a new one is added every day. In addition to this there are various e-liquids with distinctive aromas which contain many different types of sweetening agents for e-cigarettes. Main ingredients of these e-liquids are nicotine, propylene glycol and vegetable glycerin. Due to various e-liquid ingredients, e-cigarette's effect on human health after inhalation is still undetermined. In this review is focused on general information about the e-cigarette history, its working mechanism, development and marketing, parts and feature of it, ingredients, nicotine and nicotine's pharmacokinetics, regulation of the countries.
Keywords: Electronic cigarettes; cigarette; nicotine.

E-sigaralar: Yeni Bir Fenomen

ÖZ

Elektronik sigaralar, geliştirildiğinden beri, tüm dünyada her geçen gün artan bir pazara sahiptir. Günümüzde e-sigara, tütün kullanımı insidansını azaltabilecek yeni bir "tütün" endüstrisini temsil etmektedir. Elektronik nikotin verme sistemi olarak da bilinen elektronik sigaralar minimal bir araçla aerosol haline getirilmiş nikotini vermek üzere tasarlanan cihazlardır. Elektronik sigaraların asıl amacı kullanıcıya sigara içiyor hissini tütün kullanmadan vermektir. E-sigara üreticileri elektronik sigaraları, sigarayı azaltmanın ya da tamamıyla bırakmanın bir yolu olarak pazarlamakla birlikte pek çok kullanıcı, özellikle gençler, e-sigarayı tütün sigarasından daha güvenli olduklarını düşündükleri için tercih etmektedirler. Birçok e-sigara markası marketlerde satılmakta ve bunlara her gün yeni bir tanesi eklenmektedir. Ek olarak, e-sigaralar için birçok farklı tatlandırıcı madde içeren ve birbirinden farklı aromalara sahip çeşitli e-likitler vardır. Bu e-likitlerin ana içerikleri; nikotin, propilen glikol ve bitkisel gliserindir. Çeşitli e-likit içerikleri nedeniyle, e-sigaranın inhalasyondan sonra insan sağlığı üzerindeki etkisi hala belirsizdir. Bu derlemede, e-sigaranın tarihi, çalışma mekanizması, gelişimi ve pazarlaması, bölümleri ve özellikleri, içerdiği maddeler, nikotin ve nikotinin farmakokinetiği, ülkelerin getirdiği düzenlemeler hakkında genel bilgiler ele alınmıştır.
Anahtar Kelimeler: Elektronik sigaralar; sigara; nikotin.

INTRODUCTION

Electronic cigarettes or e-cigarettes (e-cigs) also known as electronic delivery system are devices designed to deliver aerosolized nicotine with at least one vehicle. The main purpose of electronic cigarettes is to give the user the feeling of smoking without using tobacco. E-cigarette suppliers are marketed e-cigs as a way to reduce or completely quit smoking. The companies of e-cigarette use the perception that e-cigarettes are healthier than tobacco cigarettes as a way

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to reduce or completely quit smoking. The companies of e-cigarette use the perception that e-cigarettes are healthier than tobacco cigarettes as a marketing strategy. The reason for this is the idea that e-cig products will not be exposed to the same chemicals as normal tobacco use due to not combusting tobacco. As a result of this idea, the companies plan to make much more profit by emphasizing that it will not cause lung diseases frequently associated with inhalation of chronic tobacco smoke such as lung cancer and chronic obstructive pulmonary disease (COPD).

E-cigarette represents the fastest growing market in tobacco products all over the world and Turkey although 10-year of history in it (1). E-cigarette has a system that transmits nicotine to the user by producing aerosol as a result of heating, and it does this by not combusting tobacco. Due to this reason, the number of nicotine users identified as e-cig users instead of normal smokers is increasing rapidly. "Vaping", namely "e-cigarette use", is very common especially among non-adult youth.

The forms of electronic cigarettes may look differ from each other; these are traditional tobacco cigarettes, cigars, tobacco pipes, or produced look alike daily items such as a pen or USB memory stick. Electronic cigarettes with a refillable tank may look different from other e-cigarettes. Regardless of their design and appearance, these devices generally work in a similar way and are made from similar components. More than 460 different e-cigarette brands are currently sold in the markets in the US (1). Although the amount and components of nicotine contained in each of these varies, many electronic cigarettes also offer different artificial flavor options to the user. However, despite such widespread use, there are important debates regarding the disease risks and toxicity of e-cigarette today. E-cig advocate's state that they are reliable because they are used Food and Drug Administration (FDA) approved ingredients, which are included in the GRAS (generally recognized safe substances) list in e-cigarettes. However, the vast majority of GRAS components have been tested only orally and their effect on the lung is unknown.

In addition, no safety information is available in humans or animals, since e-cigarettes are not currently under the patronage of healthcare organizations such as the FDA, typical toxicological assessments have not been conducted.

1. E-cigarettes

Electronic cigarettes (e-cigarettes) are one of the most widely used products in the product which category called electronic nicotine delivery system. E-cigarettes are the newest products that give the user the feeling of smoking by heating a solution containing various sweeteners, propylene glycol and vegetable glycerin. Cigars, pipes or hookahs are one of the other nicotine delivery devices that can be considered.

1.1. History of E-cigarette

The first electronic cigarette (e-cig) patent was obtained in 1965 by Herbert A. Gilbert (2). Today's electronic cigarette was invented and patented by a Chinese pharmacist Hon Lik in 2003 (3), and entered the US market in 2007.

In 2007, when commercial consumption became widespread, electronic cigarettes has developed from the first generation cigarettes, also called disposable "cigarette-like", to second generation cigarettes which is reusable e-cigarettes containing e-liquid in a closed or refillable tank or cartridge (cartomiser). Finally e-cigarettes has been transformed into the latest 'modular' e-cigarettes which called as third new generation, consisting of a separate battery, reservoir and atomizer components. These latest generation modular e-cigarettes usually contain user interfaces that can measure the number of puffs, battery level, resistance (ohms), control temperature, power (watts) and voltage (Figure 1).

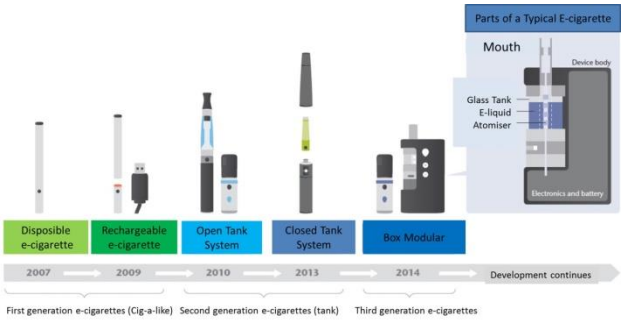

Figure 1. Change of e-cigarette design over time; each e-cigarette on the figure shows that e-cigarettes change over time from single-use to reusable cigarette-like e-cigarettes, from second generation electronic cigarettes to open and closed tank/cartridge systems, and finally to third generation modular e-cigarette devices (1).

Robust scientific methods are needed to evaluate e-cigarettes more widely. A study conducted in the UK reveals that those who try to quit smoking and therefore use e-cigarettes feel more nicotine withdrawal than those who use non-prescription nicotine replacement therapy drugs (4). Recent research results in the US (5) and France (6) also support this research.

Any effective product to be used in place of smoking to imitate real smoking well requires that provide the user with nicotine in an amount close to that of real cigarette. Dr. Michael Russell (7) has researched on the development of new tobacco products that maintain nicotine yield and to reduce the amount of harmful components in cigarettes.

It has been stated that the use of nicotine with e-cigarettes is one of the positive features of e-cigarettes in the promotion of smoking cessation or preventing re-smoking by doctors in UK. As a matter of fact, literature studies have revealed that e-cigarettes play an important role in quitting smoking (8). However, the lack of quality and reliable studies examining the effect of e-cigarettes on smoking cessation has reduced confidence in this outcome, and other meta-analyzes have questioned the effectiveness of e-cigarettes (9).

1.2. Smoking Terms

Tobacco cigarette, which contains tobacco products, must be burned for inhalation of tobacco leaf. Traditional cigarettes, cigars, fine and short cigars, hookahs and pipes can be included in this group. Electronic cigarette aerosol; although it is often referred to as "steam", it generally refers to the spread of an e-cigarette smoke as a gas suspension. Second-hand aerosol exposure; is the name given to non-smokers for their exposure to only

aerosole due to they are in a smoking environment. Third-hand aerosol exposure; is the name given to exposure to nicotine and other toxic substances on the surfaces in e-cigarette or smoking environment (1). In the literature, e-cigarettes are often referred to as "electronic nicotine delivery systems" due to they contain nicotine from tobacco plants.

1.3. Parts of E-cigarette

An e-cigarette has four general parts, which are the battery, the heating element (atomizer), the chamber where the steam is held, and the cartridge containing the solution (Figure 2).

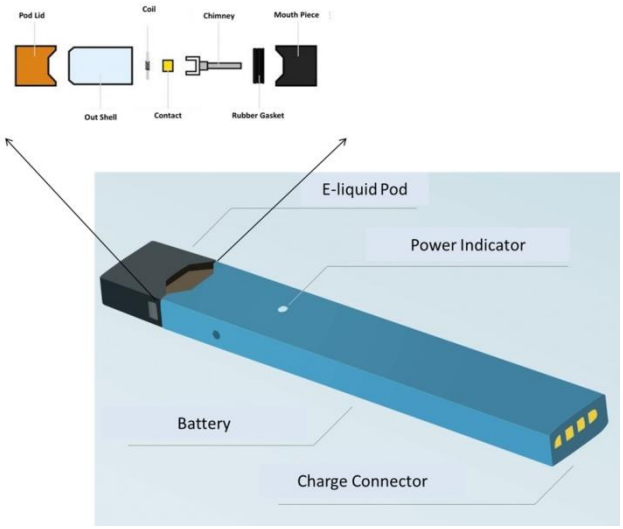

Figure 2. The general structure of a new generation e-cigarette (1)

The battery is the power source that allows the heating element to reach high temperatures enough to aerosolize the e-liquid solution by means of electric current. Batteries found in e-cigarettes are generally cylindrical shaped, lithium-ion and rechargeable batteries. The size and shape of the battery varies with the overall size and ease of use of the e-cigarette. As a matter of fact, smaller devices provide easier portability while they need to be charged more frequently than large devices. Lithium ion batteries provide higher voltage (> 3 volts) than the voltage required producing the desired amounts of aerosols compared to conventional batteries (1.5 volts).

The heating element is also called atomizer. It includes a voltmeter that allows many e-cigarette users to select the amount of aerosol produced and the amount of nicotine inhaled.

The cartridge part contains a reservoir which keeps the e-liquid solution containing nicotine and different sweeteners until it gets aerosol process takes place. The content of this e-liquid generally includes propylene glycol, vegetable glycerin, artificial sweeteners and different doses of nicotine. This content can be replaced by users which e-cigarettes with cartridges that can be reused, replaced or pre-refillable. While the number of options in e-cigarette solutions increases day by day, the content written on the label of the product and the actual contents and concentrations contains varies considerably (10). For example, the ratio of propylene glycol (PG) to vegetable glycerine (VG) in e-cigarette liquid may vary from brand to brand and this ratio can be 0: 100-100: 0 or between these two values. As a matter of fact, in some e-cigarette brands, the ratio of these two main components to each other is 60:30, in some it can be 55:45 or 50:50.

1.4. Working Mechanism of E-cigarette

E-cigarettes are battery-powered electronic devices that turn a solution called e-liquid with or without nicotine into an aerosol (volatile substance). The aerosol is produced by manually activating an electric heating system in an electronic cigarette or by the user taking vapor from the device. This process causes the e-liquid to evaporate and this vapor concentrates to form the aerosol. Due to inhalation of this evaporating and condensing substance the term “vaping — vapor inhalation” is used to smoke the electronic cigarette (1).

As users draw air from the e-cigarette, a sensor detects this airflow and vaporizes the e-liquid in the cartridge by heating it. This air, also called an aerosol, provides users with nicotine, and when users exhale, some of this aerosol is released into the ambient air. The temperature of the e-cigarette aerosol ranges from 40°C to 65°C. Although it varies from brand to brand, it can be puffed 10 to 250 times with a cartridge, which number corresponds to approximately 5-30 cigarettes. Also, automatic or manual type battery has an important role in e-cigarette use. Users of the automatic battery device use the e-cigarette as if it is a tobacco cigarette, that is, the e-cigarette is always ready for smoking. In e-cigarettes with a manual battery, it is necessary to press a button that activates the device to make the e-cigarette ready for use.

Many e-cigarette models have a voltmeter that allows the user to choose the amount of aerosol produced and, accordingly, the amount of nicotine taken by inhalation. It is also available in disposable e-cigarettes. Many other e-cigarettes are designed to be prefilled or manually refillable and reusable).

2. E-liquid components and their characteristic features

In addition to the nicotine concentration in e-liquid, e-cigarette or e-liquid has other components and characteristics that may affect nicotine exposure. These features generally affect nicotine exposure by changing the e-cigarette use behavior, making nicotine more delicious, or increasing the delivery of nicotine to the user. In addition, it has been demonstrated that e-liquid (e.g. PG/VG ratio, flavor) and other characteristics of e-cigarette (type, brand, electric power) contribute significantly to the variant of nicotine yield in the aerosol (11). The level of nicotine in e-liquid is also an important factor in determining nicotine delivery (12).

2.1. Flavors

In today's market, there are various e-liquids with distinctive aromas which contain many different types of sweetening agents for e-cigarettes. In addition, there is a refillable tank in e-cigarette that distinguishes it from tobacco cigarettes. In 2009, the United States banned the use of artificial or natural flavors (other than tobacco or menthol) in cigarettes due to the concern that the flavored tobacco with different flavors promotes smoking among children and young people by the Law on the Prevention of Tobacco Smoking and Tobacco Control in the US. As a matter of fact, some of the flavors mimic tobacco (only tobacco or tobacco-menthol flavor), while others imitate

cigars, while others mimic different types of food (fruit, dessert, sugar flavored) or drinks (alcohol or coffee flavored). In a study conducted, it reported that as of January 2014, there are 466 e-liquid brands (each with its own website) and 7764 different flavors in the US. In the 17 months after the research, approximately 11 new e-cigarette brands and 242 new flavors were launched (13). New e-cigarette brands are constantly introduced to the market, and the exact number of e-liquid brands available in the market as of 2017 is unknown.

The various numbers of the flavors and failure to disclose the ingredients contained in the product labels create a problem for the researches. Therefore, research on the effects of the special additives contained in these flavors on nicotine intake is limited. Studies have shown that different flavors mask the harmful effects of nicotine, encouraging users to start e-cigarettes or continue increasing their use, and these flavors also cause changes in the aerosol to increase nicotine delivery (1). It also contains chemicals that cause irreversible lung disease. For example, diacetyl which is a common safe food sweetener used to provide a buttered or creamy taste (2,3-butanedion), when aerosolized, and inhaled by the workers cause acute onset bronchiolitis obliterans, an irreversible obstructive pulmonary disease (14). The Flavor Extract Manufacturers Association (FEMA), which evaluates the safety of food ingredients, has identified 1037 flavoring substances as potential hazards for respiration due to their potential volatility and respiratory irritant properties. While the common e-cigarette flavors in this list are not limited to these; diacetyl, acetoin, 2,3-pentandion (butter flavors), camphor, cyclohexanone (menthol flavors), benzaldehyde (cherry or almond flavors), cinamaldehyde (cinnamon flavor), cresol (skin or drug flavor), butyraldehyde (chocolate flavor) and it also contains isoamyl acetate (banana flavor) substances.

The delicious flavors and the variety of flavors available have been shown as motivating factors for starting or continuing e-cigarette use, especially among young people and smokers. As flavors, it has been determined that those with menthol, sugar or fruit flavors are more preferred than those with tobacco flavors. At this point, it has been revealed that users believe that e-cigarettes with fruit, sugar or menthol flavors are less harmful than tobacco-flavored e-cigarettes (15).

In general, products containing flavors are harmful as they facilitate the use of e-cigarettes. Thus, in an in vitro study on human bronchial epithelial cells exposed to non-flavored e-cigarette vapor produced from the e-cigarette device; toxicity indicators such as metabolic activity, cell viability and cytokine release were compared. It was found that the effects of different e-liquids, which are the same in terms of nicotine level, base (PG only) and device vapor transmission settings, differ from each other. However, when flavors are also added to e-liquids, the situation is different. For example, it has been determined that the levels of toxicity indicators of e-liquid with a special strawberry flavor are higher than that of other e-liquids. This reveals that some additives in flavors contribute to the toxicity of the vapor received by inhalation (16). The chemicals of the flavors in many e-liquids have been analyzed and in many of these e-liquids, aldehydes which cause irritation in the mucosal tissue of the respiratory tract have been identified. In addition, if these chemicals of the flavors are inhaled, it has been determined that they are at a high level (10-40 mg/mL), which may cause a potentially toxic effect in the respiratory tract (17).

The high number of flavored e-liquids commercially available makes it difficult to understand whether these flavors have an effect on their concentration and properties in aerosols. However, at this point, focusing on the common chemicals (vanilla, ethyl vanillin, menthol, fruit esters in fruit flavored e-liquids) instead of the different flavors found in e-liquids can help to understand the effects on aerosol. One of the most frequently used flavors in e-liquids is menthol.

2.2. Nicotine

Nicotine is an alkaloid found in plants such as tobacco in the Solanaceae family, which is easily absorbed by the body with dermal, oral or inhalation exposure, and can easily pass through many biological membranes, including the blood brain barrier and placenta. Nicotine, a pharmacologically active component of tobacco smoke, is generally considered to be the main factor involved in the development of cardiovascular diseases, lung diseases and lung cancers (1). Nicotine is an important factor in the development and maintenance of tobacco habit at least as break this habit. Nicotine products used in quitting tobacco habit are nicotine bands, nicotine gums, subcutaneous and nicotine-containing apparatus and nasal sprays. In addition to these, there are also electronic cigarettes marketed as an alternative for quitting the tobacco habit. Nicotine concentrations in these refillable e-liquids range from 0-36 mg/mL (Table 1).

Table 1. Amounts of nicotine released from nicotine sources (1)

Source of Nicotine	Amount (mg)
1 whole cigarette	10-30
1 cigarette butt	5-7
1 cigar	15-40
1 gram chewing tobacco	6-8
1 piece nicotine gum	2-4
1 nicotine patch	8-100
1 IQOS heets stick	15-18
1 mL e-liquid with freebase nicotine	1-24
1 mL e-liquid with nicotine salt	1-100

Some users prefer solutions with intense nicotine, and adjust their e-liquids to nicotine with high concentration. Studies on nicotine absorption in e-cigarette use differ greatly from each other. Therefore, it is still unclear whether e-cigarette vapor causes more nicotine exposure than tobacco cigarettes (18). The physiological effects of nicotine throughout the system are the ability to influence the release and metabolism of neurotransmitters, as well as increased blood pressure, increased pulse rate, increased free fatty acids in the plasma, blood sugar mobilization, and increased catecholamine concentrations in the blood (18). Nicotine acts as an agonist chemical that binds to a receptor and activates this receptor to

produce a biological response at most nicotinic acetylcholine receptors (1).

2.2.1. Freebase nicotine

Nicotine, which is generally used in e-liquids and cigarette, is also called “freebase nicotine”, due to its freeform in these products. In the beginning of the 1960's, Philip Morris began using ammonia to make nicotine in tobacco to freebase form. With this way it was aimed that producing low-efficiency (tar or nicotine) cigarettes with the nicotine beat required to make customers "addicted" to the cigarette continuously (1). In fact, becoming nicotine's to a freebasenicotine form is not a complicated process. A base, such as ammonia, accepts a proton from a positively charged nicotine carboxylic acid salt (for example a malate or a tartrate) in tobacco. Thus, a proton bound ammonia (NH_3) turns into a cation (NH_4^+), so that the positively charged nicotine acid salt is separated from a proton to become neutral. This neutral, proton-free nicotine is in the form of a "freebase" as it is no longer bound to another molecule (or anions) in the form of a salt.

Free nicotine is highly volatile. James F. Pankow from Oregon Health and Science University emphasized that increasing the particle ratio of nicotine in the freebase form would lead to an increase in the amount of nicotine passing into the gas phase. The nicotine that has gone into the gas phase can accumulate quickly and easily in the respiratory tract. It’s by nature of the freebase form, it crosses the blood-brain barrier more easily, making nicotine more "accessible" for smokers and therefore stronger beat (1).

The absorption of nicotine from biological membranes depends on pH. Nicotine provides a more comfortable passing through the mucous membrane at high pH, especially when it does not have any charge. At physiological pH values, nicotine is protonated by 69%. Nicotine has a low polarity and is easily soluble in low polarity environments, so it is well absorbed through the skin and easily penetrates the brain tissue through the blood-brain barrier (1).

2.2.2. Nicotine salt

It is a form of nicotine found in tobacco leaves as naturally, including freebase nicotine and other organic components. Nicotine salts are composed of nicotine and organic acid (consisting of molecules containing organic radicals containing the ionizable -COOH group such as lactic acid and propionic acid), as well as these salts are effectively transferred to the blood. Nicotine salt’s feature of rapidly increasing in plasma levels, it gives much more satisfaction to the users than freebase nicotine (1). In 2015, PAX Laboratory patented the nicotine salt formulation which they produced for use in JUUL, an e-cigarette device brand. In these compact low-temperature devices, e-liquids with 59 mg/mL nicotine (in the form of nicotine salt) are used in each e-liquid capsule (cartridge) to achieve the power of a traditional tobacco cigarette. On the other hand, in the e-liquid industry, the standard nicotine content (mostly in freebase form) generally varies between 0-24 mg/mL.

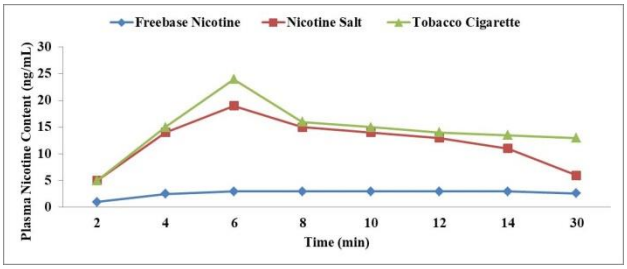

Figure 3. Time dependent change of blood-nicotine levels

The nicotine salt used with different ingredients in JUUL capsules has been the key to the rapid increase in popularity of this product. The main ingredients of e-liquid in this device is the nicotine benzoate salt, a nitrogenous base, in which the freebase nicotine reacts with the benzoic acid to form the nicotine salt. While the amount of benzoic acid in JUUL is approximately 45 mg/mL or 4.5%, the amount of nicotine is 59 mg/mL or 5.9% (1).

When the organic acid/nicotine salts are given to the user separately to be inhaled, neither strong basic nicotine nor free acid do not reach the lungs directly. For this reason, nicotine salt is given by combining with organic acid. This allows nicotine salt to be inhaled and provides easier transmission/efficiency to the lungs than freebased nicotine. This is a desired condition for e-cigarettes, and it also provides nicotine to be offered to the user in a more acceptable pH range. These organic acids, also known as free hydrogens, are positively charged and show an interest in the nitrogen center of nicotine. This interest is important for stabilizing the nicotine molecule for long-term activity and defending nicotine against oxidative deterioration (Figure 3). Indeed, the binding of a cationic salt to the electronegative nitrogen center of the nicotine molecule prevents oxidative damage that it may be exposed to compared to a salt-free formulation. However, there are many nicotine salts available and only certain salts can be used for e-cigarettes. Nicotine salt to be used in e-cigarettes must have two important properties. The first of these is that the nicotine to be used should be volatile with glycol and glycerin at approximately the same temperature, and the other is that it is in the form of acid (such as those found in food and medicinal substances) that can be accepted by the human body. As the nicotine salt samples; Nicotine levulinate, pyruvate, benzoate and nicotine salicylate can be given.

The benefits of the main salt combinations are not yet fully defined. However, although the effects of these different salt combinations on the consumer differ, research on these chemicals is still ongoing. Based on the available data and feedback, it was determined that the three main salt combinations described below provide an experience similar to the freebase e-cigarette experience.

2.2.2.1. Nicotine benzoate (benzoic acid)

Benzoic acid is a colorless, crystalline, solid and simple aromatic carboxylic acid which is described by the chemical formula $C_7H_6O_2$. Its name has long been derived from the name of benzoin gum, the only known source of benzoic acid (1). Benzoic acid occurs naturally in many plants and serves as an intermediate in the biosynthesis of many secondary metabolites. Benzoic

acid salts are used as food preservatives, and benzoic acid is an important precursor to the industrial synthesis of many other organic substances. Nicotine benzoate lowers the pH of the freebase nicotine, providing a soft and pleasant taste of nicotine beat, especially at high nicotine concentrations. Studies show that benzoic acid significantly improves the stability of the nicotine molecule and therefore can better preserve the aroma and flavor of e-liquid (19).

2.2.2.2. Nicotine levulinate

Levulinate acid has the ability to potentially desensitize the upper respiratory tract by allowing the vaporized nicotine to be inhaled deeper into the lungs. Some literature sources state that levulinic acid may increase the binding of nicotine to neurons that normally do not respond to nicotine (19).

2.2.2.3. Nicotine pyruvate

Studies show that pyruvic acid helps nicotine uptake, especially at low nicotine doses. Studies on e-cigarettes have revealed that inhalation of nicotine pyruvate gives its user a better sense of satisfaction due to its well toleration by causing a rapid increase in plasma nicotine concentrations (1).

In addition to all these kinds of salts, there are acids such as nicotine salicylate, nicotine tartrate, nicotine glucuronide and nicotine citrate.

As a result, the patented formulation of nicotine salt enables more effective delivery of nicotine. Therefore, the user can also consume more nicotine with the nicotine salt through the respiratory system compared to the freebase nicotine. Freebase nicotine has a harsh and unpleasant taste. Otherwise, nicotine salt forms are less harsh and have a less unpleasant taste.

2.2.3. Inhalation of nicotine salt in e-liquid

Inhalation of an e-liquid containing nicotine salt or nicotine freebase differs from each other. The reason of this is that e-liquid with nicotine salt has high levels of nicotine in its content. However, when the user use a device that works at low power and has high nicotine level, the user does not feel that is using an e-liquid with a high nicotine level despite the body reaching the nicotine saturation rapidly. For this reason, e-liquid manufacturers do not recommend the use of nicotine salt in low power (sub ohm) devices, as the nicotine beat will be high. Therefore, instead of low power devices, devices that produce less steam but have higher ohmic coil resistance are used.

With the nicotine salt, the effect of nicotine increased, the time of effectiveness shortened, and the stability of nicotine increased. However, to list the negative aspects of the nicotine salt; the reduction of the impact of nicotine beat on the throat, limited information about benefit/harm, high production cost and low compatibility with the devices can be counted (Table 2).

2.2.4. Nicotine level

One of the most important aspects of e-cigarette use is that these devices are designed with the ability to deliver nicotine to the lungs. The amount of nicotine that can be delivered to the lungs varies between an e-cigarette and a tobacco cigarette, and also varies between e-cigarettes from different companies. As a matter of fact, while some studies on the amount of nicotine delivered to the lungs, it has been found that nicotine in e-cigarettes is lower than tobacco cigarettes. On the other hand in many other studies, it has been revealed that nicotine in e-cigarettes is equivalent or higher than to tobacco cigarettes (12).

Table 2. Differences between freebase nicotine and nicotine salt

Freebase Nicotine	Nicotine Salt
Freebase nicotine molecule is more volatile than nicotine salt, but shows less compatibility with human mucosa.	The inhalable form of nicotine salt for human cell membranes is more biocompatible than the inhalable form of freebase nicotine.
In the same time, it is almost impossible to achieve the level of freebase nicotine in the blood to the level of an tobacco cigarette.	This nicotine absorption is very fast compared to the tobacco cigarette, and reaches the maximum level of saturation in the blood comparable to a tobacco cigarette for the same time.
Freebase nicotine is a less stable compound than nicotine salt.	Nicotine salt is a much more stable compound than freebase nicotine.
Freebase liquid nicotine is more prone to oxidation than nicotine salt, which reduces the storage time of freebase nicotine.	Storage period of nicotine salt is long. The nicotine salt has been reported to produce a much smoother throat hit depending on the pH level. Nicotine salt can be attractive for hardcore smokers who want quick and strong effect from nicotine.
The user must use a powerful device to produce a remarkable amount of steam.	There is no need to balance e-liquid with nicotine salt with a powerful device, so it can be used with a relatively small device and at a cheap cost.
The user uses e-liquid, which is more expensive and contains a large amount of freebase nicotine.	It saves more money because the user uses less e-liquid.

Studies with automatic cigarette machines have shown that e-cigarettes deliver less nicotine to the lungs in each puff than in regular tobacco cigarettes. However, the nicotine level in the serum is higher in the experienced e-cigarette user compared to the inexperienced e-cigarette user, and even in the serum of the experienced e-cigarette user, this rate is almost as much as in normal smokers (12). In a study with experienced e-cigarette users, a saliva cotinine (the main metabolite of nicotine) level was found to be 322 ng/mL. The average saliva cotinine level was found to be 113 ng/mL in tobacco smokers, while it was reported as 2.4 ng/mL in non-smokers (20).

E-cigarettes contain liquid and concentrated nicotine in the cartridge part where e-liquid is located. Cases where this concentrated nicotine is accidentally swallowed by the user have been reported. Indeed, when nicotine is inhaled, swallowed, or in contact with the skin, it may pose a danger to the health of vulnerable individuals, such as children, adolescents, pregnant women, nursing women, people with heart disease and the elderly.

Nicotine shows rapid absorption in the lungs, skin and mucosa, and the lethal dose ranges from 10 to 60 mg (or 0.5-1.0 mg of nicotine per kilogram of body weight) (21).

In some e-cigarettes, the liquid nicotine concentration is 100 mg/mL and this rate is a potential lethal dose. Even some e-liquids sold without nicotine have been found to contain nicotine.

2.2.5. Nicotine pharmacokinetics of electronic cigarettes

It is in the literature that e-cigarettes are used by cigarette smokers to replace cigarettes containing tobacco (1). Today, it is generally accepted that the harmful effects of smoking are due to exposure of some of the 6500 or more chemical components in the particle and vapor phases of cigarette smoke (1). These chemicals, which are either contained in tobacco's own leaf or by products formed as a result of pyrolysis and combustion of tobacco, are taken into the body by inhaling cigarette smoke. In addition, e-cigarettes produce aerosol, which is much less toxic than a normal cigarette, compared to smoking (22). Therefore e-cigarette using significantly reduces exposure to chemical toxins compared to smoking. Because of e-cigarettes have a less toxic exposure profile than traditional cigarettes, are recommended. E-cigarette play an important role in helping smokers reduce or quit smoking, or in reducing harm caused by exposure to tobacco.

In recent years, pharmacokinetic studies have been conducted on electronic cigarettes. Pharmacokinetic studies provide information on the absorption, distribution, metabolism and excretion of a drug or chemical compound over time.

Nicotine pharmacokinetics studies aim to reveal nicotine absorption in humans. With nicotine pharmacokinetics studies, it was aimed to measure the nicotine amount in the blood depending on time and dose by taking samples from the blood plasma before and after using the cigarettes at the time intervals determined in the study. While nicotine level in blood plasma was 15-20 ng/mL (23) as a result of smoking, nicotine level in blood plasma was found as 3.5ng/mL as a result of first generation electronic cigarette use. With smoking, nicotine level in plasma reaches its highest level within 5 minutes. However, the same period lasts at least 20 minutes for those using e-cigarettes (24). In most studies on new generation e-cigarettes, plasma nicotine levels have been found to be higher than the levels observed in the first generation e-cigarettes. In comparison with a new generation e-cigarette and a cigarette in terms of plasma nicotine levels, it has been found that plasma nicotine levels with smoking are still significantly higher than the new generation e-cigarette with an average of 18 ng/mL. In the same study, the highest plasma nicotine value in the new generation e-cigarette was 11.9 ng/mL (25). However, data from other studies reveal that new generation (second and third generation) e-cigarettes provide near or even higher levels of nicotine than the cigarette, with the highest average plasma nicotine value reaching 43.6 ng/mL (26).

2.3. Propylene glycol and Vegetable glycerin

Propylene glycol is an organic compound with the chemical formula $CH_3CH(OH)CH_2OH$, and a viscous, colorless liquid with an almost odorless but slightly sweet taste. Propylene glycol containing two alcohol groups; it can be mixed with a wide range of solvents, including water, acetone and chloroform. In general, glycols are not irritating, have very low volatility and very low toxicity.

Propylene glycol (PG) is a commonly used ingredient in many cosmetic products, topical skin preparations, drugs and foods, and also used in the industrial field is made of propylene oxide. Propylene glycol is also one of the main ingredients used to form the e-cigarette aerosol.

Glycerin is a colorless, odorless, sweet taste, non-toxic viscous substance. It is widely used in food industry as a sweetener and moisturizer in pharmaceutical formulations. Vegetable glycerin is a substance that creates a visible cigarette vapor, added to nicotine solutions, which are often used in e-cigarettes. While glycerin is produced by heating palm or coconut oil, it can also be produced from animal fat and soap by a fatty acid decomposition process.

E-liquids contain two basic elements that cover most of the volume of e-liquid, including propylene glycol (PG) and vegetable glycerin (VG), to suspend nicotine and different sweeteners, and to spray aerosolized particles when they reach a sufficient temperature (18). Nicotine, flavors and other ingredients are added to this basic structure. In addition, this propylene glycol and vegetable glycerin (PG/VG) ratio in e-liquid affects nicotine yield, and determines the toxicity of aerosol produced from e-cigarette.

Although the American Federal Drug Administration (FDA) recognized both PG and VG as generally safe for oral consumption, the effects of repeated inhalation of aerosolized PG and VG are still well unknown. In a study, it was reported that exposure to aerosole with acute PG and VG does not have a significant effect on pulmonary function, but chronic exposure may be likely to cause lung dysfunction.

In another study, the content of e-liquids of 10 commercial e-cigarettes was analyzed after the aerosolization process, and it was found that each e-liquid has a different PG/VG ratio or contains only PG or only VG.

The fact that PG and VG have different boiling points (PG = 186.6°C, VG = 286.9°C) is due to the molecular weight (PG = 76, VG = 92) that significantly affect the aerosolization rate at different temperatures (27). In the human respiratory model, e-liquids containing 16 mg nicotine and PG or VG were used to measure the accumulation of particles of e-cigarettes. E-liquids were used with only one puff nasal ventilation ($1.2 m^3/s$) and one puff mouth ventilation ($1.688 m^3/s$) via a cigarette machine, and the particle size and concentration in the aerosol was observed. It has been determined that the particle size accumulated by single puff is much smaller than the particle size accumulated by continuous e-cigarette exposure. In the study conducted using the human respiratory model, it is thought that 9-17% of the total volume of the aerosol is associated with venous absorption areas such as the head and respiratory tract, and 9-18% is associated with arterial absorption, such as alveoli (27).

2.4. pH

Nicotine is generally in the form of free nicotine, also called as freebase nicotine, which is non-ionized at high pH, can be absorbed easily and quickly, is bioavailable, non-protonated. This non-ionized nicotine can easily pass

through biological membranes. The disintegration constant (pKa) for nicotine is 8.02, and at this pH half of the nicotine is in a non-ionic freebase form that can be absorbed more easily. Buffer solutions prepared to make nicotine more alkaline increase the absorption of nicotine. In addition, buffering may occur as a natural result of the absorption area. An example of this can be given saliva in the mouth containing bicarbonate. The presence of bicarbonate serves to buffer nicotine. In addition, dissolution of the cigarette smoke which contains nicotine in lung fluid (pH: 7.4) facilitates absorption (28).

Preclinical research has revealed that the pH of the environment is important in the physiological response to absorption of different nicotine doses. At this point, the absorption of the nicotine from mucous or dermal increases linearly with pH. The tobacco industry, who wants to take advantage of this, also increases the pH of the product content to increase the absorption of nicotine. The pH values of e-liquids vary widely among different brands (pH = 4.78-9.60). E-liquids without nicotine were found to have lower pH (neutral or acidic), while the pH of e-liquids with a large proportion of nicotine was greater than 9 (29). In addition, although e-liquids of different brands contain the same amount of nicotine, pH values may vary. Therefore, e-liquids belonging to different brands listed with the same nicotine amount provide different nicotine yields to their users at different pH values. In a study, the pH of 36 different e-liquid samples was measured and these pH values were found between 5.1-9.1 (30).

As a result about the components and characteristics of e-liquids; various properties and components of e-liquids can affect nicotine delivery. When all other factors are kept constant, e-liquid with high nicotine concentration causes more nicotine delivery. Flavors make it easier to increase the exposure of users to nicotine by ensuring that nicotine-containing e-cigarettes are started or continued and by masking the bad effects of nicotine (1).

3. The Main Features of the E-Cigarette Aerosol

E-cigarettes are very popular in nowadays due to its considered as safe (29). However there is very little data on the acute and chronic effects of inhalation of the aerosol emitted by e-cigarettes (31). The reason for the lack of the data is that the properties and dynamics of this aerosol released from the e-cigarette after entering the respiratory system are unknown.

Aerosols released in e-cigarettes have specific properties. The inhaled aerosol is highly concentrated and contains very small particles of sub-micrometer size. The e-cigarette aerosol, commonly referred to as "vapor-steam", is essentially; containing propylene glycol (1,2-propanediol, PG), vegetable glycerin (propane-1,2,3-triol), nicotine, water, sweeteners (if present in e-liquid), preservatives, and also consists of e-liquid droplets by-products of thermal decomposition of some of these components. These droplets are surrounded by a mixture of decomposed substances in air and vapor. At this point, the physical properties of the components in the aerosol are important. As a matter of fact, most of the e-liquid components have a high boiling point (PG: 180°C and VG: 300°C) and therefore have low volatile properties. The high boiling point of vegetable glycerin or propylene glycol allows the aerosol to reach a high temperature, but this can also cause the release of toxic substances contained in the aerosol.

Propylene glycol and VG are hygroscopic, which causes the volume of e-liquid droplets to grow by absorbing water vapor in humid air in the environment (32). When comparing the smoke of tobacco cigarette and aerosol of e-cigarette in terms of accumulation of particles and effects on health, it has long been known that particles in inhaled cigarette smoke cause many undesirable health problems. The particles in the smoke of the tobacco cigarette consist highly and often carcinogenic organic substances. Although these particles actively accumulate in bronchial bifurcations (carinal areas), the development point of lung cancer is also known as the same anatomical region. However, unlike regular cigarettes, vapors and droplets released from e-cigarettes are much less toxic, but it does not mean that e-cigarettes are completely safe for human health. Because the data available on the physical properties of the e-cigarette vapor after being taken into the body are not sufficient, more studies are needed to determine the potential accumulation points in the respiratory system. In a study, it was revealed that the coagulation and hygroscopic growth of the droplets in the e-cigarette aerosol caused more accumulation in the respiratory system compared to normal cigarette particles. It is stated that slower and deeper inhalation of the e-cigarette aerosol increases droplet accumulation due to the stronger spreading effect in the pulmonary region (33). In addition, the effect of the average droplet size on the local accumulation of e-cigarette aerosols has been tested, while it has been found that the accumulation in the bronchial and pulmonary regions remains unchanged, while the increased particle size has been found to accumulate in the main respiratory tract (33).

Particle size affects the area of accumulation in the respiratory system. In this case, small particles easily move up to the lower respiratory tract, delivering more nicotine to the alveoli. In general, it has been found that the particle sizes of vegetable glycerin are larger than the particle sizes of propylene glycol. The presence of nicotine or different flavors in the aerosol had no effect on the distribution of particles in the aerosol (27). As a result of mathematical modeling for determining accumulation points; It is generally estimated that the accumulation is between the 16-23 generation of the lung, that is, in the small respiratory tract, including the alveoli (34).

Despite similar accumulation points and shapes in the bronchial bifurcation region of e-cigarette and normal cigarette, e-cigarette droplets are expected to be less toxic since they do not contain mutagenic compounds that result from burning of the cigarette. Accordingly, it is claimed that the risk of lung cancer with e-cigarette use is significantly reduced for both active use and passive exposure (35).

3.1. The Role of the Form of Inhalation

Since e-cigarettes are also used quite frequently among those who have smoked or still smoke tobacco cigarettes, the way inhaled e-cigarette's aerosol among users is habitually similar to the way it inhales tobacco cigarette smoke. Typically, in both types of cigarettes, aerosol or cigarette smoke is first taken into the mouth, called

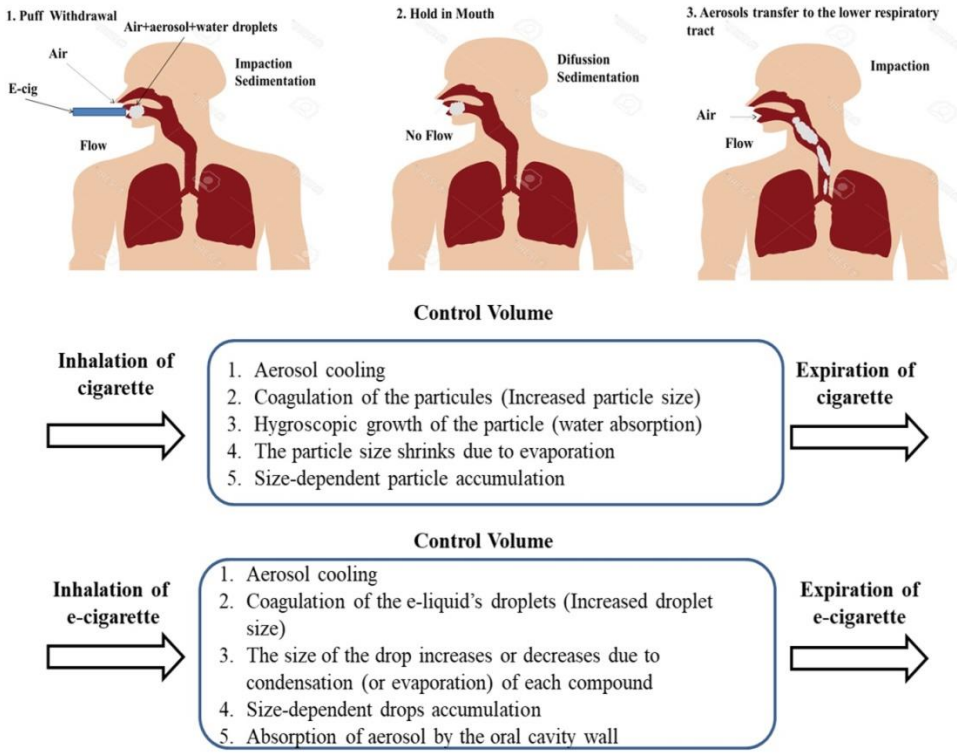

Figure 4. The first image (on the top) shows that three phases of inhalation of e-cig aerosols, which is puffing, retention of the aerosol in the mouth and inhalation of aerosol. The second image (below) shows that a comparison of thermodynamic and mass transfer effects after inhalation of smoke of a tobacco cigarette and aerosol of e-cigarette (1).

"puff", and then this vapor held in the mouth for a few seconds is inhaled into the lungs (Figure 4). E-cigarette vapor or cigarette smoke draw on (puffing) and mouth retention periods provide a certain period of time for initial aerosol properties to change due to thermodynamic and mass transfer effects (33).

Despite similar inhalation patterns of normal cigarettes and e-cigarettes, the aerosol dynamics occurring in the respiratory system differ from each other due to the different properties of the aerosols contained in both types of cigarettes. Smoke caused by burning tobacco in cigarettes is composed of thin solid and semi-volatile particles in the air, while the e-cigarette vapor consists of liquid droplets suspended in its mixture of steam and air. E-cigarette droplets are formed by the condensation of the vapor produced by heating the e-liquid, and it contains e-liquid components and by-products in different proportions (32).

In a study, CT scans of the upper respiratory tract geometry during inspiration through inhalers with different internal aerodynamic resistance have been demonstrated (36). Higher airflow obstruction reduces this flow, so the inhaled aerosols in the oral cavity have a lower rate and longer residence times. Both effects (a change in oral geometry and a decrease in airflow) affect the dynamics of the aerosol particles and the accumulation of the aerosol in the oral cavity and organs (32).

4. Use of E-cigarette

While the use of electronic cigarettes by children in the US is increasing day by day, this increase rate is quite low compared to the use of traditional tobacco products. Surveys made include young people's e-cigarettes; reveals that he has learned from internet advertising, television, friends or family members (37). High school students in the US stated that they preferred e-cigarettes because they thought it was more safe than tobacco cigarettes in general (38).

E-cigarette use is increasing day by day, not only among young people, but also among adults. It has been demonstrated in the last six years that the rate of adults who have switched from normal smoking to e-cigarette use has increased 10 times and that nearly four million Americans use e-cigarettes (39). It can be said different from the young people that adults use e-cigarettes as an alternative tool to tobacco cigarette, to try to quit smoking, and which they think e-cigarette is safer than normal cigarettes (4).

4.1. E-cigarette in the Global Market

The main reason why e-cigarettes have an increasing importance in the world market stems from the fact that manufacturers market e-cigarettes as an aid to quit smoking tobacco.

Public health professionals working to reduce tobacco consumption are increasingly concerned about the impact of e-cigarette on public health, especially as the popularity, prevalence, and sales graph of e-cigarette use is increasing among young people. The e-cigarette industry is growing at an astounding pace, and it is

predicted that it will be in a position to catch the tobacco industry in the next 10 years. While there were more than 200 e-cigarette brands on the market in 2013, it was estimated by economists that e-cigarette sales would raise to $3 billion in the same year. As of 2017, over 650 e-

cigarette brands, and the global e-cigarette industry had reached $10 billion (1).

4.2. Marketing of E-cigarette

E-cigarette manufacturers publish advertisements on television, internet and social media in order to encourage e-cigarette use. The biggest marketing strategies in the e-cigarette industry; The health benefits of e-cigarettes compared to normal cigarettes can be counted as the effect of reducing or quitting smoking, minimum passive exposure to vapor and the ability to perform e-cigarettes even in places where normal smoking is prohibited. As a matter of fact, in addition to these marketing strategies, in 2012, a big e-cigarette company made an advertisement film with famous stars to be broadcast on television and the internet, and it was tried to be stated that these cigarettes are modern and eye-catching (1). Consequently, it is revealed that these marketing strategies are successful when the e-cigarette sales figures are examined.

Despite all these marketing strategies, the use of e-cigarettes carries with it a great concern. Among the main causes of this concern; the lack of data on the effect of e-cigarette on smoking cessation, the potential of creating nicotine addiction in non-smoker adolescent and children, e-cigarette may pollute tobacco-free environments, reducing the attempts of smoking cessation with use of traditional cigarettes and e-cigarette together, e-cigarette can be normalized, and a potential to create a new air pollution in environments where smoking is prohibited can be listed (1).

4.3. Regulation of E-Cigarette by National/International Organizations

The American pharmaceutical and food agency has proposed a law that regulates the use of e-cigarette used as a tobacco product. With the proposed law, the sale of electronic cigarettes to the adolescents includes an arrangement similar to the ban on the sale of traditional tobacco products to the adolescents.

E-cigarette use is supported by many health institutions in the UK. As a matter of fact, it has been suggested that e-cigarette should be included in medical products. However, it is not possible to support e-cigarette use globally in reducing the harm of consumption of traditional cigarettes. Those who intend to quit smoking by the health ministry are advised to use only approved smoking cessation drugs, such as nicotine replacement therapy (NRT), until additional safety information is available.

Due to lack of evidence that is safe for use in some countries, such as particularly in Turkey, Canada, Mexico, Singapore, Brazil, Argentina and Colombia e-cigarette sales have been banned completely. In February 2014, the European Parliament published the EU Tobacco Products Statement on the regulation of e-cigarettes (including solution content, advertisements and marketing strategies), safety and quality standards as a nicotine-containing product along with its increasing market and market (1).

CONCLUSION

In this review is given general information about the e-cigarette history, its working mechanism, development and marketing, parts and feature of it, ingredients, nicotine and nicotine's pharmacokinetics, regulation of the countries.

Electronic cigarettes or e-cigarettes (e-sig), also known as electronic nicotine delivery system, are devices designed to deliver aerosolized nicotine with a minimal tool, which is considered to be relatively safer than tobacco. The main purpose of electronic cigarettes is to give the user the feeling of smoking without using tobacco. Therefore, one of the most important aspects of e-cigarette use is that these devices are designed with the ability to deliver nicotine to the lungs. An e-cigarette has four general parts, which are the battery, the heating element (atomizer), the chamber where the steam is held, and the cartridge containing the solution. Although the popularity of e-cigarette increase day by day over the worldwide, there is not sufficient research and data of these devices on human health which proves it is safe. Due to this reason health care professionals concerned about e-cigarettes becoming a new tobacco cigarette by getting very popular among young and adults.

According to the many users as results of marketing, e-cigarette is much safer than the tobacco cigarette, and it helps reduce or quit the tobacco cigarette. However more than 460 different e-cigarette brands are currently sold in the markets and a new one is added every day. Although the amount and components of nicotine contained in each of these varies, many electronic cigarettes also offer different artificial flavor options to the user. Due to these reason effects of e-cigarette and inhalation of its ingredients researches cannot give exact data. Despite that ingredients are in the GRAS list, effects on human health after the inhalation of them are still unknown. In the meantime, e-cigarette's popularity and using by many vapers is not only giving harm to the user, but also polluted the air. Acute and chronic effects of e-liquids and aerosols still undetermined, so more meticulous researches should be done before any solid conclusions can be drawn about the dangers, or usefulness of e-cigarettes.

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