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History repeats itself: Role of characterizing flavors on nicotine use and abuse

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Abstract

The popularity of e-cigarettes has skyrocketed in recent years, and most vapers use flavored e-cigarette products. Consumption of flavored e-cigarettes exceeds that of combustible cigarettes and other tobacco products among adolescents, who are particularly vulnerable to becoming nicotine dependent. Flavorings have been used by the tobacco industry since the 17th century, but the use of flavors by the e-cigarette industry to create products with “characterizing” flavors (i.e. flavors other than tobacco or menthol) has sparked a public health debate. This review addresses the possibility that characterizing flavors make nicotine more appealing, rewarding and addictive. It also discusses ways in which preclinical and clinical studies could improve our understanding of the mechanisms by which flavors may alter nicotine reward and reinforcement.

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Keywords

e-cigarettes; Characterizing flavors; Nicotine reward; Nicotine reinforcement; Adolescents

1. Introduction

E-cigarettes arrived on the market in the early 2000s (National Academies of Sciences, 2018), and their popularity has since sky-rocketed. E-cigarettes are available in over 15,000 distinct flavors, including ‘cotton candy’, ‘tropical blue slushie’ and ‘crazy berry’ (Hsu et al., 2018). Flavors offer users the ability to customize their products and increase their opportunities for experimentation, both of which are cited as important reasons for e-cigarette use (Kong et al., 2015; Soule et al., 2016; Zare et al., 2018). The availability of such a massive variety of sweet and attractive flavors has played a role in e-cigarettes’ exploding popularity. From 2018 to 2019, as many as 3.2% of US adults (~8 million) and

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19% of US middle and high school students (~5.3 million) were current e-cigarette users (Bao et al., 2019; Cullen et al., 2019a). This rise in e-cigarette use is not confined to the US. In 2016, 6.5% of adolescents in Mexico had tried e-cigarettes, despite a ban on the importation, distribution, and sale of e-cigarettes (Zavala-Arciniega et al., 2019). Similarly, in 2017, surveys of 28 EU member countries found that ~8 million Europeans regularly used e-cigarettes and that as many as 63 million people had tried them (Laverty et al., 2018).

While e-cigarettes may be a useful smoking cessation tool (Berry et al., 2019; Hajek et al., 2019; Masiero et al., 2019), they are also not harmless (Kaur et al., 2018; Wang et al., 2019). The benefits and risks of e-cigarettes are reviewed elsewhere (Cooke et al., 2015; Hajek et al., 2014; Zulkifli et al., 2018). Instead, this review will focus on the role of 'characterizing' flavors in nicotine and e-cigarette use. A 'characterizing' flavor is defined as a 'clearly noticeable smell or taste other than one of tobacco, resulting from an additive or a combination of additives, including, but not limited to, fruit, spice, herb, alcohol, or candy which is noticeable before or during the consumption of the tobacco product' (Talhout et al., 2016). Although menthol is an extremely popular flavoring in both tobacco and e-cigarettes, we will not include it in our discussion. Menthol has significant impacts on nicotine pharmacology, sensory effects, and use patterns, all of which have been widely reviewed elsewhere, as well as in this special issue (Giovino et al., 2004; Kamatou et al., 2013; Rosbrook and Green, 2016; Villanti et al., 2017a,b; Wickham, 2015). By limiting our review to non-menthol characterizing flavors (e.g. fruit, candy, licorice) and sweeteners, we will address a topic that has received limited attention (Feirman et al., 2016; Huang et al., 2017; Klus et al., 2012; Talhout et al., 2016) but has recently come under a great deal of regulatory scrutiny (Carpenter et al., 2005b; Glantz, 2019; Lewis and Wackowski, 2006).

2. The history of tobacco flavorings in the tobacco industry

Flavorants have been a component of tobacco products since the 17th century, when essential oils like orange and bergamot were added to products (Klus et al., 2012). Additives were regularly used between the 17th and 20th centuries to impart appealing aromas and tastes onto tobacco products and to alter their physical properties. For example, in 1912, a study in the Lancet reported that tobacco companies were using glycerol and oils to sweeten and moisten products (The toxic factor in tobacco, 1912). Glycerol is still added to cigarette tobacco at levels ~1–5% during processing, both as a humectant to prevent tobacco leaves from crumbling and as a flavoring material or solvent (Carmines and Gaworski, 2005). Although the advent of e-cigarettes was nearly a century away, it seems that the industry was keenly aware that these additives could influence the composition of tobacco smoke.

Nicotine is widely accepted as the primary reinforcer in tobacco products, including e-cigarettes (De Biasi and Dani, 2011). Still, characterizing flavors might modulate reinforcement or even serve as reinforcers themselves. In the 1980s and 90s, tobacco companies made a concerted effort not only to improve the flavor profiles of their products, but also to understand how the flavors "worked". Major companies like R.J. Reynolds and Philip Morris were spending between $14 and $20 million per year in chemosensory research during these decades (Brown & Williamson Tobacco Corporation Ltd; Kohnhorst, 1985; "Philip Morris U.S.A. R&D Strategic Plan", 1993). Although industry research can be

largely qualitative and is not subject to peer review, internal documents reveal key insights into how companies understood the science of flavorant appeal. In 1992, Philip Morris tested several flavors among young adult (18–34 years old) smokers and found that participants were more excited about, curious about, and socially accepting of tobacco products with characterizing flavors (Unknown, 1992). Industry researchers also began investigating specific mechanisms by which characterizing flavors could enhance user experience. In one industry-funded experiment, researchers investigated how flavor volatiles (e.g. phenyl ethyl alcohol, isoamylacetate) could alter nerve responses that contribute to the irritating effect of nicotine and, ultimately, planned to use that information to design "flavor systems for … new products" (Carchman and Southwick, 1990).

Generally, the tobacco industry found that smokers reacted positively to fruit and sweet flavors (Kapuler & Associates, 1984; Unknown, 1992). However, their research also identified specific populations, namely teenagers and women, who would be most susceptible to these products (Carpenter et al., 2005, Carpenter et al., 2005a,b; Cummings, 1999; Kapuler and Associates, 1984; Vila, 1978). These findings shifted the priority of many tobacco companies toward the development of products with characterizing flavors like honey and apple cider, specifically to appeal to these groups (Cummings, 1999; Hoffman et al., 2016).

Characterizing-flavored cigarettes entered the market in the 1970s, but it wasn't until the early 2000s that they sparked public controversy in the US. Three major flavored products emerged – Camel Exotic Blends, Kool's Smooth Fusions, and Salem's Silver label. Camel Exotic Blends released at least 18 different flavors between 1999 and 2006, including berry, lime, coconut, toffee, and bourbon. From 2003 to 2004, overall cigarette sales fell, but R.J. Reynolds Camel brand experienced a 9.8% increase in sales that coincided with the introduction of new flavors to their Exotic Blend line (Cheddar, 2004; Lewis and Wackowski, 2006). Similarly, after the Family Smoking and Prevention Act (FSPTCA) banned the use of characterizing flavors in cigarettes in 2009, cigarette sales declined, but sales of flavored products that remained on the market, like little cigars and cigarillos, soared, rising 482% from 2000 to 2011(CDC, 2011; Kostygina et al., 2014).

Recounting this history draws attention to the similarities between research investigating flavored tobacco products and current research on e-cigarette flavorants. As we shift the discussion to the 21st-century, we will revisit the theme that characterizing flavors might attract specific and potentially vulnerable populations. We will then explore the current evidence on whether characterizing flavors increase e-cigarette abuse liability and describe specific mechanisms through which characterizing flavors might impose their reward-enhancing effects.

3. Characterizing flavors might attract specific and potentially vulnerable populations

3.1. Characterizing flavorants might have sex-specific effects

In general, men are more likely to use e-cigarettes (Barnett et al., 2015; Choi et al., 2012; Hedman et al., 2018; Saddleson et al., 2015; Soule et al., 2016; Sutfin et al., 2013). However, research suggests that women are more likely than men to use characterizing flavored products and/or to value flavor availability (Chen et al., 2018; Dawkins et al., 2013; Delnevo et al., 2015; King et al., 2013; Kistler et al., 2017; Piñeiro et al., 2016; Schneller et al., 2019b; Smith et al., 2016; Soneji et al., 2019; Villanti et al., 2013). This sex-difference is subtle, but consistent. For example, one study found that the presence of 'appealing flavors' was reported by 89.23% of women as a reason for e-cigarette use, compared to 74% of men (Xiao et al., 2019). Similar to cigarette companies, e-cigarette manufacturers are adapting to specifically attract female users (Doxey and Hammond, 2011; Moodie et al., 2014; Richardson et al., 2014; Yao et al., 2016). For example, e-cigarette distributors have created products with 'feminine' attributes, such as pink packaging and 'jeweled' vaporizers (Yao et al., 2016).

The hypothesis that there will be sex differences in flavored e-cigarette use is partially influenced by the history of characterizing flavors being "made for" and marketed towards women (Anderson et al., 2005; Carpenter et al., 2005a,b; Carpenter et al., 2005; Doxey and Hammond, 2011; Kapuler and Associates, 1984; Moodie et al., 2014; Richardson et al., 2014; Vila, 1978; Yao et al., 2016). However, this hypothesis is further encouraged by evidence that began accruing in the 1990s, which suggests females are more sensitive to the sensory aspects of cigarette smoking as opposed to the pharmacological effects of nicotine (Perkins, 1999; Perkins et al., 2001a; CDC, 2001). This earlier research allows one to hypothesize a new theory in the e-cigarette era: if women are driven by the sensory experience of vaping and not motivated as much by nicotine's pharmacological effects, perhaps women will consume more vapor 'for the flavor' without carefully titrating their nicotine dose. There is some opposition to this idea of sex-dependent nicotine-induced effects (Kleykamp et al., 2008). However, in a clinical trial, women consumed lower doses of nicotine via e-cigarettes when not assigned a preferred flavor, whereas men successfully titrated their nicotine dose regardless of flavor-assignment (Oncken et al., 2015). Unfortunately, the aforementioned study only used 'menthol' flavoring, and clinical studies which include *ad libitum* vaping sessions have thus far not been large enough to adequately investigate sex differences. Therefore, the ability for characterizing flavors to interfere with nicotine titration, specifically in women, can only be addressed with more research.

As mentioned, observational research tends to show that females display a slightly higher preference for flavored-e-cigarettes than males (Chen et al., 2018; Dawkins et al., 2013; Delnevo et al., 2015; King et al., 2013; Kistler et al., 2017; Piñeiro et al., 2016; Schneller et al., 2019b; Smith et al., 2016; Soneji et al., 2019; Villanti et al., 2013; Xiao et al., 2019). However, the most convincing animal study to-date found that male rather than female mice were susceptible to the nicotine reward-enhancing effect of farsenol, a major chemical component in green-apple flavoring (Avelar et al., 2019). The hypothesis that women (or

females in animal studies) would be more sensitive to characterizing flavorants was based on the suggestion that they are more sensitive to the sensory components of smoking. Therefore, it is important to point out that in the study by Avelar et al. farsenol was injected intraperitoneally (i.p.) and the potentially rewarding *sensory* contributions of farsenol were absent. Still, this research is crucial in that it proves that flavor volatiles are pharmacologically active molecules. In fact, the reward-enhancing effects of farsenol were accompanied by sex-specific changes in expression of α4 and α6 nAChR subunits in the ventral tegmental area (VTA) and substantia nigra pars reticulata (SNr), and by a functional upregulation of α6β2β3 nAChRs in the VTA (Avelar et al., 2019). Furthermore, following 5 days of farsenol treatment, male mice displayed an increase in baseline dopaminergic (DAergic) firing in the VTA, which was hypothesized to be the result of decreased GABAergic baseline firing on inhibitory interneurons in the SNr (Avelar et al., 2019). Although the relative responses of these neurons to acute nicotine treatment were unchanged (~1.5–2 fold increase), the VTA DAergic firing frequency during nicotine treatment was about 6X greater in farsenol-treated males than it was in saline-treated males as a result of the increased baseline.

Moving forward, scientists must consider both the neuropharmacological and sensory contributions of flavorants, ideally simultaneously. In basic research, e-cigarette vapor systems might be preferred to achieve this goal. In clinical research, it will be essential to study groups large enough and diverse enough to investigate potential sex differences in e-cigarette behaviors and preferences in the lab.

3.2. Characterizing flavors might have age-specific effects

Adolescents have consistently reported high rates of flavored e-cigarette use (63–66%) and a consistent low use of tobacco-flavored e-cigarettes (4.8–5.1%) (Clarke and Lusher, 2017; Corey et al., 2015; Cullen et al., 2019a; Morean et al., 2018; Schneller et al., 2019b). On the other hand, adults regularly rate ‘tobacco’ in the top 3 flavor categories (Morean et al., 2018; Schneller et al., 2019b; Villanti et al., 2013; Yingst et al., 2017). Initially, this led to a concern that characterizing flavors were only popular with young e-cigarette users and only served to attract adolescents toward nicotine use. However, adults have been using flavored e-cigarettes at relatively high rates since 2012 (54%) (Cullen et al., 2019a, 2019b; Smith et al., 2016) and these rates have only increased, with 84% of adult e-cigarette users reporting flavored product use between 2015 and 2016 (Schneller et al., 2019a) (the most recent data for this age group). Despite universal popularity of characterizing flavors, adolescents and young adults are more interested in and have greater intentions to try flavored tobacco products than adults (Ashare et al., 2007; Manning et al., 2009; Pepper et al., 2016; Soneji et al., 2019) (with few exceptions: Pepper et al., 2013; Shiffman et al., 2015). This puts young people at a unique risk to initiate e-cigarette use due to characterizing flavors. In fact, a striking 80–98% of adolescents and 60–95% of young adults initiate e-cigarette use with a flavored e-cigarette, compared to 44% of 25+ adults (Harrell et al., 2017; Villanti et al., 2017a,b). The following paragraphs discuss potential mechanisms, ranging from increased susceptibility to marketing to increased susceptibility to ‘sweetness’ that could explain why so many adolescents initiate e-cigarette use with characterizing flavors.

Products with characterizing flavors are perceived as less harmful across all ages (Chen et al., 2018; Feirman et al., 2016; Huang et al., 2017; Manning et al., 2009), but this perception may be more pronounced in younger populations (Czoli et al., 2016; Ford et al., 2016; Huang et al., 2017; Pepper et al., 2016). When people feel safer using a product, uptake increases accordingly (Chaffee and Cheng, 2018; SAMHS, 2013). Adolescents who report believing that fruit-flavored e-cigarettes are less harmful are also more likely to be interested in trying fruit-flavored e-cigarettes (Pepper et al., 2016). Furthermore, a study conducted in college-aged students found that the fMRI activity within the nucleus accumbens (NAc) was significantly greater while viewing advertisements for sweet vs. tobacco flavored e-cigarettes (Garrison et al., 2018). This increase in NAc activity was correlated with poorer memory for health warnings that appeared on the advertisements for sweet-flavored products, providing a possible mechanism by which characterizing flavors can reduce perceptions of harm in young people (Garrison et al., 2018). Alternatively, an increased sensitivity to marketing could explain the susceptibility of adolescents towards these products. Young people are more likely to buy heavily marketed cigarette brands, whereas adults are more likely to buy generic brands (CDC, 1994). In addition, most adolescents (73.8%) report exposure to e-cigarette advertising (Wagoner et al., 2019) and say that they think certain e-cigarette advertisements are marketed to them, or even to people younger than them (McKelvey et al., 2019). Although surveys find non-trivial rates (~14.2%) of adolescents reporting “appealing advertisements” as a reason for e-cigarette use among adolescents, similar rates are reported among adults (Rodu and Plurphanswat, 2018; Soneji et al., 2019; Wagoner et al., 2019). Still, the marketing content that does reach adolescents appears to be working. At least two analyses of nationally representative data sets suggest that marketing exposure significantly predicted e-cigarette experimentation and use among youth who had never used tobacco products before (Chen-Sankey et al., 2019; Mantey et al., 2016). Although we highlight them here, neither reduced harm perceptions nor marketing sensitivity fully explain the social and psychological phenomena that lead younger populations to e-cigarette use. For example, adolescents have reported peer pressure, curiosity, and cessation as reasons for e-cigarette use, among others (Kong et al., 2015; Pokhrel et al., 2015; Xiao et al., 2019).

E-cigarettes with characterizing flavors are consistently rated as sweeter than those with menthol or tobacco flavoring (Goldenson et al., 2016; Kim et al., 2016; A. M. Leventhal et al., 2019a; Mead et al., 2019). In addition, some sweeteners (e.g. sucrose, sucralose, ethyl maltol) have been detected in e-liquids (Fagan et al., 2018; Kubica et al., 2014; Miao et al., 2016), and it is common among “Do-It-Yourself” users to add sweeteners to their e-liquid mixes (No Author, 2017, 2016).Therefore, the ability of ‘sweetness’ to alter nicotine reward and reinforcement should be considered. Here, again, there is a theory that adolescents might be disproportionately affected by a characteristic of flavored e-cigarettes. Children have a strong innate preference for sweetness that tapers off with age (Desor and Beauchamp, 1987; Enns et al., 1979; Mennella et al., 2011; Zandstra and De Graaf, 1998). For example, the preferred sucrose level in adolescents (aged < 16) is more than double that of older subjects (Monneuse et al., 1991). The flavorants used by the vape and tobacco companies are the same as those that children grow up eating via candy and sugary drinks (Brown et al., 2014). Following repeated pairing of these flavorants with highly palatable

and caloric foods, these flavorants will have already established positive associations (Beauchamp and Cowart, 1985; Fanselow and Birk, 1982; Harris et al., 2004; Mennella et al., 2016). Furthermore, adolescents' heightened preference for sweetness is associated with a heightened preference for the foods and flavors paired with sweetness (Cooke and Wardle, 2005; Hoffman et al., 2016). Considering all of this, it is possible that heightened preferences for sweetness (and for the characterizing flavors associated with sweetness) could spill over and contribute to a heightened preference for flavored e-cigarettes/nicotine. This theory was first addressed in the context of flavored combustible cigarettes, and was explored at length in a review by Hoffman and colleagues (Hoffman et al., 2016).

Of course, the real problem is not that adolescents like flavors or sweetness, but that a higher percentage of adolescents might be exposed to nicotine. Adolescent nicotine uptake is associated with negative developmental consequences and an increased probability of becoming a dependent smoker in adulthood (England et al., 2017, 2015; Goriounova and Mansvelder, 2012; USHHS, 2016; Omelchenko et al., 2016; Walker and Loprinzi, 2014; Yuan et al., 2015). Alarmingly, for the first time since the 1990s, adolescent tobacco product use has increased. Many argue that characterizing flavors contribute to this unprecedented increase in adolescent tobacco use and flavors should be banned to reverse this trend. A common counterargument is that flavored e-cigarettes attract only the subset of adolescents who were already susceptible to tobacco use or are 'high sensation seekers' (Kim and Selya, 2019). High sensation seekers are more likely to gravitate toward novelty and are more likely to smoke cigarettes than low sensation seekers (Kopstein et al., 2001; Zuckerman, 1994). This argument is related to a major theory of drug use susceptibility called the 'common liability' theory (reviewed at length by Vanyukov and colleagues: Vanyukov et al., 2012), which postulates that certain individuals are predisposed to drug addiction due to biological under-pinnings (e.g. drug metabolism, genetic variation, etc.) that are out of their control. In support of this idea, one study found that a correlation between the availability of flavored tobacco products and increased trial intentions only occurred among participants that were categorized as 'high sensation seekers' (Manning et al., 2009). However, this fails to explain why total adolescent tobacco use is on the rise. We know this increase is driven by flavored e-cigarette uptake since rates of using other tobacco products have not changed (CDC, 2019), and 80–98% of adolescents initiate e-cigarette use with a flavored e-cigarette (Harrell et al., 2017; Villanti et al., 2017a,b). Together, these data indicate that the common liability hypothesis does not sufficiently explain the uptake of e-cigarette use by youth. Instead, flavored e-cigarettes are likely the main contributor to the current increase in overall tobacco use.

Another concern among public health officials is that the increase in flavored e-cigarette uptake will lead to increased combustible cigarette use over time. Smoking is still the leading cause of preventable death in the developed world, with smoking related disease leading to 480,000 lives lost per year (Creamer et al., 2019; USHHS, 2014). A recent meta-analysis showed a strong and consistent association between initial e-cigarette use and subsequent cigarette smoking initiation (Soneji et al., 2017). In addition, flavored e-cigarette use (rather than e-cigarette use generally) has been associated with higher rates of vaping and increased risk of subsequent cigarette initiation (Barrington-Trimis et al., 2018; Chen et al., 2016; Dai and Hao, 2016; Leventhal et al., 2019b). One theory is that if adolescents

initiate with flavored e-cigarettes, their first exposure to nicotine is more likely to be pleasant. Individuals who report a positive first-experience with smoking are more likely to go on to become regular smokers (Chen et al., 2003; DiFranza et al., 2007; Mantey et al., 2017; Rodriguez and Audrain-McGovern, 2004; Sartor et al., 2010; Urbán, 2010). However, not all research suggests that flavors are associated with a progression to combustible use (Audrain-McGovern et al., 2019). Furthermore, as stated earlier, data from 2019 only show an increase in e-cigarette, not combustible smoking, among adolescent populations (CDC, 2019). Therefore, the role of flavored e-cigarettes on the ability to cause progression to combustible cigarettes is still unclear.

3.3. Characterizing flavorants affect nicotine reward, reinforcement, and consumption

As discussed, characterizing flavored e-cigarettes are well liked by users independent of age. Moreover, characterizing-flavored e-cigarettes appear to be rewarding even in the absence of nicotine. At least one study has found that e-cigarette flavor is rewarding when injected intraperitoneally into mice, and flavored e-cigarettes without nicotine receive higher appeal ratings than e-cigarettes containing nicotine in clinical studies (Avelar et al., 2019; DeVito et al., 2019; Leventhal et al., 2019c; Leventhal et al., 2019a; Pullicin et al., 2019). This phenomenon extends outside of the lab, with the majority (up to ~60%) of adolescents reporting vaping “just flavor” (Krishnan-Sarin et al., 2015; Miech et al., 2017; Morean et al., 2016). If characterizing flavors are rewarding in their own right, it is reasonable to surmise that ‘flavor reward’ and ‘nicotine reward’ could interact in some way to make vaping more reinforcing and potentially increase total nicotine consumption.

There are subtle, but important, differences between reward and reinforcement. Reward refers to the ability of environmental stimuli to elicit an approach response whereas reinforcement refers to the ability of stimuli to strengthen and increase repetitions of learned stimulus-response behaviors (White, 1989). A flavor could make nicotine more enjoyable and approachable, i.e. more rewarding. Alternatively, a flavor could enhance the association between action (i.e. vape) and effect (i.e. physiological response to nicotine). Most likely, the addition of characterizing flavors to e-cigarettes will affect both nicotine reward and reinforcement. In the following paragraphs we review the emerging literature that investigates roles of characterizing flavors on nicotine reward and reinforcement. In addition, we will consider how the unique properties of flavored nicotine might lead to increased nicotine consumption.

Clinical studies measure reward by asking participants to subjectively rate a variety of flavored e-cigarettes. Generally, nicotine containing e-cigarettes with characterizing flavors (e.g. fruit and desserts) are more rewarding (i.e. receive higher ratings) than unflavored and tobacco-flavored e-cigarettes (Audrain-McGovern et al., 2016; Goldenson et al., 2016; Jackson et al., 2020; Kim et al., 2016; Leventhal et al., 2019a). However, two studies failed to find this flavor-dependent increase in the hedonic value of e-cigarettes (DeVito et al., 2019; Mead et al., 2019). All studies that found characterizing flavors were more subjectively rewarding (compared to unflavored or tobacco-flavored e-cigarettes) used relatively low concentrations of nicotine (6–12 mg/mL nicotine) (Goldenson et al., 2016; Jackson et al., 2020; Kim et al., 2016; Leventhal et al., 2019) or catered nicotine

concentration to individuals' current nicotine use (Audrain-McGovern et al., 2016). In contrast, studies which did not report a reward-enhancing effect of characterizing flavors used higher nicotine concentrations (18–24 mg/mL nicotine) (DeVito et al., 2019; Mead et al., 2019). It is likely that e-cigarettes with these high nicotine concentrations were aversive. In fact, a study conducted by Leventhal and colleagues measured negative appeal ratings in the presence of just 6 mg/mL of nicotine (Leventhal et al., 2019a). Furthermore, most adults and adolescents report using products with nicotine concentrations less than 18 mg/mL (Morean et al., 2016; Yingst et al., 2015). It should be noted that JUUL products, which have been extremely popular and in 2018 were estimated to make up ~68% of e-cigarette sales in the US, have a much higher nicotine concentrations (e.g. ~60 mg/ml) (Omaiye et al., 2019a; Zaleski, 2018). However, JUUL products use nicotine-salt rather than free-base nicotine, and the relationship between dose and reward in nicotine-salt products has not yet been investigated. Age and e-cigarette user experience might also partially explain differences in these data. The studies using younger populations (aged 18–35 years old) were more likely to find a reward-enhancing effect of characterizing flavors (Audrain-McGovern et al., 2016; Goldenson et al., 2016; Leventhal et al., 2019a) compared to studies using older adults (DeVito et al., 2019; Mead et al., 2019). Finally, 'experienced vapers' found nicotine-containing characterizing flavored e-cigarettes more rewarding (Kim et al., 2016), whereas 'inexperienced vapers' with similar age demographics did not (Mead et al., 2019). In conclusion, current evidence suggests that characterizing flavors positively affect subjective reward ratings at lower doses of nicotine, possibly due to a leftward shift of the dose-response curve. At this point, however, there is insufficient evidence to suggest that characterizing flavors ameliorate perceived aversiveness on the opposite arm of the notorious inverted U dose-response curve. There might also be subtle contributions of age and e-cigarette user status on flavor-enhanced e-cigarette reward.

Measuring reinforcement requires subjects to perform an operant task (e.g. press a button). These tasks can be of varying difficulty. The easiest "schedule of reinforcement" only requires 1 response in order to receive a reward. If every future reward also requires 1 response, then the ratio is "fixed". This schedule of reinforcement is called "Fixed Ratio 1" (FR1). From here, there are two common ways to increase the effort required to obtain the reinforcer. One is to increase the number of responses required to receive a reward (e.g. FR10 = 10 responses to receive 1 reward). Alternatively, the number of responses required after each reward is earned could be progressively increased (e.g. 1, 5, 25, 125 …), according to a Progressive Ratio (PR) schedule of reinforcement. In the only clinical study to-date that has measured the reinforcement of flavored e-cigarettes using an operant task, participants worked approximately four times harder in order to earn puffs from their preferred flavored e-cigarette (either green apple or chocolate) than they worked for puffs from an unflavored e-cigarette. Flavored e-cigarettes were valued so highly that participants, despite being 12 hours into nicotine withdrawal during the task, still chose to work for puffs from a flavored e-cigarette, which came at a significantly higher behavioral cost (10 puffs for 250 responses for the unflavored e-cigarette vs. 10 puffs for 1375 responses for the flavored e-cigarette) (Audrain-McGovern et al., 2016).

Several groups have used animal models to test the hypothesis that characterizing flavors alter nicotine reinforcement by pairing intravenous nicotine self-administration (nicotine

IVSA) with oral delivery of characterizing flavor cues, with varying results (Chen et al., 2011; Palmatier et al., 2019). Nicotine IVSA was not enhanced by characterizing flavors at high doses of nicotine (e.g. 15, 30, 60 μg/kg/infusion) (Chen et al., 2011; Palmatier et al., 2019). In fact, Chen and colleagues found that intra-oral flavor cues (e.g. cocoa or grape Kool-Aid) *inhibits* acquisition of nicotine self-administration, unless social interaction or a social cue is present (Chen et al., 2011). However, Palmatier and colleagues showed that a licorice flavor cue could enhance nicotine self-administration, but only at doses much lower than those tested in the aforementioned study (e.g. 7.5 μg/kg/infusion (Palmatier et al., 2019)). Similar to findings in the human subjective reward literature, characterizing flavors' ability to enhance nicotine reinforcement appears to be limited to low doses of nicotine. 'Sweetness' has also been shown to enhance nicotine reinforcement. Intra-oral sucrose (10%) increased the number of nicotine infusions earned by male rats across several schedules of reinforcement (FR1-FR5) and saccharin enhanced responding for nicotine, but only at a low effort (FR1) schedule of reinforcement (Wickham et al., 2018). Therefore, it is likely that the caloric-value of sucrose and not just 'sweetness' played a role in enhancing the value of nicotine. Intra-oral sucrose and saccharin led to increased phasic DA release in the nucleus accumbens (NAc). Unfortunately, Wickham and colleagues did not measure phasic dopamine in response to nicotine in combination with sweeteners, so the sweeteners' ability to enhance a nicotine-induced dopamine response in the NAc remains unknown (Wickham et al., 2018).

Observational data suggest an association between the use of characterizing flavors and increased e-cigarette consumption (Chen, 2018; Huang et al., 2017; Morean et al., 2018). In general, vapers are sensitive to their preferred nicotine dose and will alter e-cigarette use (e.g. longer/shorter puff duration, more or less puffs, etc.) to self-titrate to their preferred nicotine dose (Dawkins et al., 2016; Lopez et al., 2016; St. Helen et al., 2017; Talih et al., 2015). However, at least three clinical reports show that characterizing flavors can increase (or, at the very least, alter) nicotine consumption, as measured by an increase in the number of puffs taken, increased volume of e-liquid used, and longer duration of 'puffs' during *ad libitum* vaping sessions (Audrain-McGovern et al., 2016; Jackson et al., 2020; St. Helen et al., 2018). Again, inconsistency in this field might be due to factors such as different nicotine concentrations, age, and user-status (Audrain-McGovern et al., 2016; DeVito et al., 2019; Jackson et al., 2020; St. Helen et al., 2017, 2018).

In adults, while flavors may lead to increased e-cigarette consumption, several reports suggest that it is also associated with decreased combustible cigarette use (Chen, 2018; Chen et al., 2018; Litt et al., 2016). This has the potential to reduce harm in this population. In contrast, flavored e-cigarette use in adolescence is associated with increased frequency of vaping (Morean et al., 2018), which has been shown to predict future combustible cigarette use (Barrington-Trimis et al., 2018; Chen et al., 2016; Dai and Hao, 2016; Soneji et al., 2017; Vogel et al., 2019). This complicates the broader "cost-benefit" implications of these data. Perhaps increased e-cigarette use benefits current-smokers who are reducing combustible cigarette use, but it could harm other populations (e.g. never-smokers, former-smokers, and adolescents) who might increase their overall exposure to nicotine. In addition, most cigarette smokers who take up e-cigarettes, use both cigarettes and e-cigarettes (i.e. are dual-users) (CDC, 2016; Patel et al., 2016) and the benefit that dual-use might have on

health is not clear. Regardless of the implications, more research needs to be conducted in this area both in and outside the laboratory, with careful consideration of the complexity of e-cigarette user preferences in the 'real world' (e.g. use of multiple flavors, user preferred nicotine concentrations, dual use of e-cigarettes and cigarettes, etc.).

3.4. Potential mechanisms for the effects of characterizing flavorants on vaping

3.4.1. Pharmacological effects of characterizing flavorants—As we observed earlier in this chapter, flavor volatiles are not inert chemicals, in fact many have intrinsic pharmacological effects. The most comprehensive survey of e-cigarette flavoring chemicals to-date quantified flavor volatiles in 277 e-cigarette refill liquids (Omaiye et al., 2019b). Since more than one hundred of flavor volatiles were identified in the e-liquids, Table 2 focuses on the top 5 most common flavorants and is meant to illustrate the vast number of potential pharmacological effects of e-cigarette flavor volatiles.

Several e-cigarette flavorants have monoamine oxidase (MAO) inhibitor activity (Ben Saad et al., 2017; Guzmán-Gutiérrez et al., 2012; Kim et al., 2012; Truman et al., 2019; Xu et al., 2015; Zhao et al., 2009). Vanillin, for example, inhibits MAO-A with a potency that far exceeds that of harman, one of the major MAO inhibitors found in tobacco smoke under the same test conditions (IC_{50} = 17 μM vs. 0.31 μM) (Truman et al., 2019). Persistent activity of monoamines in the synapse, due to MAO inhibition, can increase nicotine reward (Kapelewski et al., 2011). In addition, linalool is able to alter the activity of cytochrome P450 enzymes in rats including CYP2A enzymes that are responsible for nicotine metabolism, albeit at considerably high doses (Nosková et al., 2016).

Whether flavorants are delivered in high enough concentrations to affect the brain and behavior of vaping humans remains up for debate. Flavored combustible tobacco products probably never transferred meaningful concentrations of flavor volatiles to alter pharmacology; however, the story might be different for vapers. Let's consider the possibility of exposure to vanillin (one of the most common flavorants) in a smoker compared to a vaper. A commercial filtered cigarette weighs ~940 mg and cigarette companies report levels around 0.005% vanillin in conventional tobacco products (German Cancer Research Center, 2012; Malson et al., 2001); whereas, several studies have found vanillin in e-liquids at concentrations as high as 30 mg/mL (Behar et al., 2018; Tierney et al., 2015). Vanillin is reported to transfer into mainstream smoke at ~63.2% efficiency into cigarette smoke (Green et al., 2016) and at ~93% transfer efficiency into e-cigarette vapor (Behar et al., 2018). Assuming these values, a pack-a-day smoker would be exposed to less than 1 mg of vanillin in a day. If an e-cigarette user vapes ~3 mL/day (Smets et al., 2019), at 30 mg/mL and assuming 93% transfer into vapor and 100% absorption by the lungs, they will have consumed ~83.7 mg/day. Perhaps at this rate of delivery, a pharmacological effect of vanillin is possible.

Flavoring chemicals have also been shown to react with e-cigarette solvents and to combust at high temperatures (i.e. pyrolyze), forming products with different chemical properties (Erythropel et al., 2019; Khlystov and Samburova, 2016). Therefore, when studying potential pharmacological effects of flavorant chemicals it is important to consider the chemicals that will be inhaled by users, as opposed to what is present in the e-liquid before

consumer use and pyrolysis. Most flavoring chemicals have a low molecular weight and high volatility. Therefore, the dominant proportion of them transfer into the e-cigarette vapor intact (Klus et al., 2012). Still, it is important to consider and to continue to study the transfer rate of these chemicals. Only in doing so, can our research accurately estimate a realistic 'vaping experience' and determine if and how flavorants are interacting with nicotine pharmacology.

3.4.2. Characterizing flavorants might affect the processing of sensory stimuli associated with vaping—Flavor is perceived through a combination of olfactory, gustatory, and tactile stimuli (Auvray and Spence, 2008; Spence, 2015). Tactile stimuli are incorporated into flavor perception via activation of chemosensory nerve endings in the mouth, nose and airways which contribute to sensations such as the burning effect of chili oil, or the cooling effect of menthol (Auvray and Spence, 2008). As mentioned, although nicotine is the primary reinforcing agent in cigarette smoking, decades of research have proven that the sensory aspect of smoking is also crucial to smoking behavior and nicotine dependence. For example, study participants are more likely to report subjective enjoyment from smoking a denicotinized cigarette than from receiving intravenous (IV) nicotine (Rose, 2006), blocking the airway sensory experience of smoking with anesthesia can reduce smoking satisfaction (Rose et al., 1984), and sensory stimulation with alternative irritants (e.g. citric acid) can reduce cravings for cigarettes (Westman et al., 1995). In this section, we will discuss the potential ability of characterizing flavors to alter vaping/nicotine reward via sensory mechanisms.

A chemosensory sensation that is particularly salient in cigarette smoking is a scratchy sensation at the back of the throat, known as a 'throat hit'. Throat hit results from the stimulation of nicotinic cholinergic and TRP receptors lining the oropharynx and lungs (Goldenson et al., 2016; Kichko et al., 2015; Pokhrel et al., 2015). Smokers and vapers report liking this sensation (Cohn et al., 2020; Pokhrel et al., 2015) and vapers cite it as a reason for using certain e-cigarette products (Chen and Zeng, 2017; Etter, 2016; Pokhrel et al., 2015). Early e-cigarette products (e.g. cig-a-likes) failed to mimic the throat hit sensation (Farsalinos et al., 2014; Hajek et al., 2018). However, newer generation e-cigarettes, device settings (e.g. voltage, resistance, etc.), solvent ratio, and higher nicotine content have led to products which can provide this sensory experience (Farsalinos et al., 2015; Goldenson et al., 2016; Mead et al., 2019; Smith et al., 2019; Wagener et al., 2017). Surprisingly, when e-cigarettes are studied in the lab, throat hit or 'harshness' is more often correlated with negative sensory experiences and decreases in overall product appeal ratings. Instead, it seems that perceived sweetness has higher value in e-cigarettes and leads to greater sensory experiences (DeVito et al., 2019; Goldenson et al., 2016; Kim et al., 2016; A. M. Leventhal et al., 2019a; Mead et al., 2019; Pullicin et al., 2019).

'Sweetness' is a sensory phenomenon that was mentioned earlier in the section titled "Characterizing flavors might have age-specific effects." While it is true that adolescents are more sensitive to sweetness, all humans are programmed to enjoy and to seek out sweetness. In clinical studies of e-cigarettes, in which mainly adults participate, 'flavor-enhanced sweetness' and 'liking' are usually correlated to reward (DeVito et al., 2019; Goldenson et al., 2016; Kim et al., 2016; A. M. Leventhal et al., 2019a) (although see Mead et al., 2019;

Pullicin et al., 2019). Interestingly, although sweeteners are regularly used in e-cigarette liquids, characterizing flavor volatiles, not added sweeteners, appear to drive perceptions of sweetness and liking scores of e-cigarettes (Rosbrook et al., 2017). Sweetness certainly plays a role in e-cigarette reward, but we should be careful not to overestimate its role or to assume that the two modes of reward (i.e.. natural and drug-induced) will interact in an additive manner. This model is possibly too simplistic, especially when we are interested in the rewarding properties of human vaping, which can be influenced by countless environmental and social factors such as age, usual flavor preference, and smoking status (Leventhal et al., 2019a; Mead et al., 2019).

An alternative sensory mechanism by which characterizing flavors could alter nicotine salience is by ‘masking the harshness’ of nicotine. The tobacco industry worked off of this assumption for many years, with documents claiming that tobacco flavor additives (e.g. “vanilla bean, peach, apricot, licorice, cocoa, and many others”) act as masking agents against “objectionable off flavors” (Fries and Brother and Triest; Kostygina et al., 2014; Unknown, 1966). While there is plenty of evidence that menthol reduces irritation caused by nicotine inhalation and leads to increased liking and nicotine consumption (Biswas et al., 2016; DeVito et al., 2019; Fan et al., 2016; Garten and Falkner, 2004; Henderson et al., 2017), evidence that characterizing flavors have this ‘masking’ ability is more sparse. Animal models of drug taking in which bottles of drug are provided to an animal with or without a sweetener (e.g. saccharin) have shown that sweeteners increase nicotine consumption (Smith and Roberts, 1995; Wickham et al., 2018). Since characterizing flavors are perceived to be sweet and to enhance sweetness (Frank and Byram, 1988; Labbe et al., 2007; Rao et al., 2018; Smith et al., 2019), we might expect them to have the same ability. In fact, a study from the flavor field found that a “fruity-ester” volatile (e.g. ethyl hexanoate) can both increase rated sweetness and decrease rated bitterness of sweet and bitter tasting solutions, respectively (Isogai and Wise, 2016). Anecdotally, vapers report that characterizing flavors mask the harshness of the “cigarette taste” (Chen et al., 2019; Soule et al., 2016). Finally, the addition of a characterizing flavor to nicotine-containing e-cigarettes suppressed an ‘unappealing’ sensation (Kim et al., 2016; Leventhal et al., 2019c), otherwise reported by study participants.

The sensory aspects of vaping introduce an interesting paradox. Most studies find that people ‘like’ sweet e-cigarettes and dislike ‘harsh’ e-cigarettes. However, nicotine is the agent responsible for creating the ‘throat-hit’ sensation (Goldenson et al., 2016; Leventhal et al., 2019a). If nicotine is the primary reinforcing agent in e-cigarettes, why then is the sensory ‘throat hit’ not correlated with liking? It seems that there is a delicate balance between nicotine delivery and sensory “pleasantness” which maximizes vaping reward. Clinical studies often use commercial products without determining flavorant identity or concentration (see Table 1), despite the fact that the concentrations of flavoring chemicals can vary dramatically from product to product (Omaiye et al., 2019b; Tierney et al., 2015). Certainly, the varying concentrations of flavor volatiles could impact the neuropharmacological effects of e-cigarettes. However, it is also possible that the ability of flavored e-liquids to mask harsh sensory effects and to enhance sweetness will depend on the concentration of flavoring chemicals, the ratio of flavorants to nicotine, or even on the presence of specific flavorants.

3.4.3. Characterizing flavorants might alter the pharmacokinetics of nicotine

—Pharmacokinetics describes the rate at which four main processes occur following drug intake: absorption, distribution to tissues, metabolism, and elimination. The research in this area is limited. However, the only study that tested the ability of characterizing e-cigarette flavorants to alter nicotine pharmacokinetics found that rate of nicotine absorption and participants' heart rate increase (associated with rapid nicotine delivery:Haass and Kübler, 1997) were higher in a strawberry e-liquid condition compared to a tobacco-flavored condition (St. Helen et al., 2017). The researchers noted that the strawberry e-liquid (pH = 8.29) was slightly more acidic than the tobacco flavor e-liquid (pH = 9.10). The difference in e-liquid acidity was proposed as a potential mechanism for the increase in the rate of nicotine absorption.

To understand how the acidity of e-cigarette vapor could affect nicotine absorption, one has to understand the basics of nicotine chemistry. Nicotine has two nitrogen groups in its chemical structure; thus, it can exist in three forms – Nic (unprotonated, aka "free-base"), $NicH^{+}$ (monoprotonated), or $NicH^{++}$ (di-protonated). The acidity of the residing solution or matrix (e.g. e-liquid or e-vapor) determines the ratio of protonated to unprotonated nicotine, such that more basic matrices will have more unprotonated Nic or 'free-base' nicotine (CDC, 2010; Perfetti, 1983). Free-base nicotine has two unique properties which make it particularly important for nicotine deposition and absorption. First, free-base nicotine is more volatile and is therefore more likely to be in the gaseous state upon heating. As a result, basic smoke or vapor will more readily deposit in the mouth and the upper airways (Dollery et al., 1975; Henningfield et al., 2004). This phenomenon can be observed by comparing the absorption of cigars (which have a very basic smoke) to the absorption of the more acidic American blend cigarettes. While cigar smoke is readily deposited and absorbed in the mouth, if cigarette smokers limit their inhalation and hold American blend smoke in their mouths, almost no nicotine absorption can occur (Armitage et al., 1975; Gori et al., 1986). This does not mean that nicotine absorption from a more acidic matrix is impossible. Instead, the smoke's particulate matter will bypass the mouth and upper airways and reach the lungs, where smoke is buffered to physiological pH and some of the nicotine is made available for absorption (Dani et al., 2014; Pankow, 2001). Somewhat counter-intuitively, even though acidic vapor must travel further, it ends up being absorbed into the blood-stream faster due to the vast surface area and structural complexity of the alveoli in the lungs (Patton, 2004). The second property of free base nicotine that makes it especially important in nicotine pharmacokinetics is that only uncharged free-base nicotine can freely move through lipid bilayers. The protonated forms of nicotine cannot be absorbed unless converted to free-base nicotine (such as after buffering in the lung) (Pankow, 2001; Pankow et al., 1997). In conclusion, this chemistry suggests that a more acidic nicotine vapor would be absorbed more quickly and reach a maximum concentration in the blood (C_{max}) sooner (due to the rapid uptake via the lung); however, there would be less nicotine bioavailable (due to more protonated nicotine in the matrix), which would lead to less systemic exposure to nicotine. In contrast, a more basic nicotine vapor would be absorbed by the buccal mucosa of the mouth and upper airways, leading to a more gradual rise of nicotine concentration in the blood towards its C_{max} (because there is less surface area in these tissues than there is in

the lung). However, more nicotine would be in the unprotonated/bioavailable form and would ultimately lead to a greater systemic nicotine exposure.

In the aforementioned study, St. Helen and colleagues further explored their hypothesis that the acidity of strawberry was affecting pharmacokinetic outcomes by looking at a separate data set in which the study participants vaped their usual e-cigarettes during an *ad libitum* session (St. Helen et al., 2017). The 'usual' e-liquids were categorized into basic (pH > 7) and acidic (pH < 7) e-liquids. The acidic regular e-liquids led to an earlier T_{max} and an increased C_{max} (normalized for retained nicotine dose), although neither were significant. Note that the time at which a drug reaches its C_{max} is known as the T_{max} (T = time). Furthermore, when the group looked at rates of absorption (AUC/retained nicotine dose), the basic e-liquids tended to show slower rates of absorption (St. Helen et al., 2017). Interestingly, there was no difference in systemic nicotine exposure between basic and acidic vapors. It is possible that the lung had sufficient buffering capacity that a roughly equivalent amount of nicotine was ultimately absorbed.

There has long been controversy around the ability of smoke/vapor pH to affect nicotine pharmacokinetics. Tobacco companies have spiked "low nicotine" products with ammonia, with the idea that even though these products contained less nicotine by weight, more of the nicotine would be in the free-base, bioavailable form (Phillip Morris and Trimmer, 1962; Stevenson and Proctor, 2008). However, both tobacco industry affiliates and at least one independent research study suggest that at least up to a pH of 8.0, nicotine absorption and bioavailability are not affected by pH (Dixon et al., 2016; Klus et al., 2012; Seeman, 2007; Shao et al., 2013). E-cigarette liquids have reported pH values ranging from 4.3 to 9.1 (Lisko et al., 2015; St. Helen et al., 2017). At the extremes of this range, the pH values of e-liquids are unprecedented. The pH of other tobacco product smokes only ranges from 5.5 to 7.5 (Benowitz et al., 2009; Brunnemann and Hoffmann, 1974). Therefore, more research is needed to understand how pharmacokinetics and nicotine bioavailability are affected at these extremes. While St. Helen and colleagues' findings support the theoretical effects of pH on nicotine pharmacokinetics laid out above (e.g. acidic e-liquids having smaller T_{max}, larger C_{max}), this pilot study included only 14 (predominantly male) individuals. The only other corroborating evidence at this point is a patent which describes the ability of different acids in e-liquids to impact nicotine's C_{max} (Bowen and Xing, 2015). The rate of drug delivery (T_{max}) to the brain is correlated with strength of reward and reinforcement (Benowitz et al., 2009; Henningfield and Keenan, 1993). Therefore, if more acidic vapors lead to a faster rate of absorption and peak concentration of nicotine in the blood/brain, it could have important implications on the abuse liability of certain e-cigarette products. It will be important to continue to monitor the pH of e-cigarette vapors/liquids and to determine a standardized method to compare pH between studies.

3.4.4. Characterizing flavors could alter vaping topography—Topography describes *how* a user vapes (e.g. length of puff, flow rate, time between puffs, etc.). Previous research has described a very reliable topographical pattern among combustible cigarette smokers (e.g. 10–15 puffs that last about 1.8 s each, for a 5–8 min period) (Benowitz et al., 2006; Zacny and Stitzer, 1994). In contrast, vaping patterns are far less consistent. For example, puff duration has been found to vary between 1.4 and 5.2 s (Dawkins et al., 2016;

Spindle et al., 2015; St. Helen et al., 2016). This is most likely due to the nearly infinite number of ways for vapers to customize their experience. Users can select different devices, use different concentrations of nicotine ranging from 0 to 87.2 mg/ml (National Academies of Sciences Engineering and Medicine, 2018), and can select from over 15,000 available flavors (Hsu et al., 2018). Each of these flavor and device combinations could deliver different volatiles with different pharmacological and sensory properties (e.g. harshness, sweetness), which could ultimately alter vaping topography.

Very few have tested the effects of characterizing flavor on vaping topography (Audrain-McGovern et al., 2016; Jackson et al., 2020; Robinson et al., 2018; St. Helen et al., 2018). As mentioned earlier in the section titled “Characterizing flavorants affect nicotine reward, reinforcement, and consumption”, a small clinical study (n = 14) found that participants took longer puffs (sec) when they were using a strawberry flavored e-cigarette compared to when using a tobacco flavored e-cigarette (St. Helen et al., 2018), and two additional studies found that participants took more puffs from a ‘fruit’ flavored e-cigarette during *ad libitum* vaping sessions. One particularly interesting study was conducted outside of the laboratory using RIT wPUM™ monitors (Robinson et al., 2018). This technology allows researchers to track topographical features (e.g. flow rate, volume, duration) for puffs over a longer period (i.e. weeks instead of hours) and in a “natural” environment. A within-subject analysis was performed comparing individuals’ vaping topography during a one-week period of vaping a tobacco flavored e-cigarette to a one-week period of vaping a berry flavored e-cigarette. Although no differences in any topographical measures were detected, the data were not conclusive. The authors hoped that the RIT wPUM™ monitors would allow them to measure naturalistic vaping. However, the technology may not be advanced enough for this to be practically true. The monitors are relatively large and are bound to alter the vaping experience to an extent. Participants had to remember to turn monitors on before starting to vape, had to remember to bring them along during the day, and had to be willing to use the bulky equipment in public. These inconveniences probably affected participant compliance and led to incomplete data collection. The large variability in the mean daily volume and mean daily puff count measurements supports this concern (Robinson et al., 2018).

At this point, we have a poor understanding of the effect of flavorants on vaping topography. Research in this area is faced with difficulties that are on display in the studies above. Embracing a naturalistic approach seems ideal in order to determine how individuals are actually vaping. However, here, researchers deal with major compliance issues that make data difficult to interpret. E-cigarette characteristics, such as device-type and nicotine concentration, have been shown to affect topography (St. Helen et al., 2016). Therefore, if too much control is exerted over participants in clinical studies (flavor selection, device selection, nicotine concentration selection), the resulting data might not represent reality. Ultimately, both strategies are imperfect and both are needed as we attempt to better understand the role of flavors on vaping topography. Future topographical research can hopefully draw connections between potential changes in topography and the mechanisms that underlie them. For example, in the study by St. Helen and colleagues, participants may have taken longer puffs of the strawberry e-cigarette because it was more acidic and did not contribute as much to an unpleasant sensory ‘throat hit’. While this was implied, it was not directly tested. Designing experiments to connect the pharmacological, pharmacokinetic and

sensory effects of flavored e-cigarettes to the behavior of smokers (e.g. puff length, puff frequency, etc.) is an important, and currently absent, part of our understanding of flavored e-cigarettes.

3.4.5. Characterizing flavorants can become secondary or conditioned reinforcers—Over time, the cues associated with nicotine delivery (e.g. taste, feel, sight) become rewarding, even in the absence of nicotine. At this point, the cue has become a conditioned reinforcer. The relationship between nicotine and its conditioned reinforcers is reciprocal. Conditioned reinforcers make nicotine more reinforcing and conversely, nicotine can increase responding for non-pharmacological cues (e.g. tones, lights, etc.). While extensive animal research has determined that non-pharmacological cues gain reinforcing value of their own over time (Barret and Bevins, 2013; Caggiula et al., 2002a, 2002b, 2009; Caggiula et al., 2002b; Chaudhri et al., 2006), there is a more limited body of research suggesting that characterizing flavors specifically can act as conditioned reinforcers.

We have already touched on the ability of flavors to act as conditioned reinforcers when we discussed the ability of a characterizing flavor (e.g. licorice), sucrose and saccharin to enhance responding for nicotine during IVSA experiments in rodents in the section titled “Characterizing flavorants affect nicotine reward, reinforcement, and consumption” (Palmatier et al., 2019; Wickham et al., 2018). Sucrose and saccharin are inherently rewarding. However, licorice is not inherently rewarding. Mice had to be trained (via repeated pairing with sucrose) to have a learned flavor preference for licorice in order for it to enhance nicotine reward. A control group that did not receive the prior flavor conditioning for licorice (i.e. did not like licorice flavor before it was paired with nicotine) failed to acquire nicotine self-administration (Palmatier et al., 2019).

As described above, another characteristic of conditioned reinforcers is that cues become rewarding on their own, in the absence of nicotine. Both previously mentioned nicotine IVSA studies addressed this characteristic of conditioned reinforcement in their investigations. Follwing nicotine self-administration, Palmatier and colleagues allowed rats to continue to self-administer for a 1.0% licorice root solution, but now I.V. saline was delivered instead of I.V. nicotine. Rats continued to show a preference for the sipper that delivered licorice root solution for at least 1 day. However, it should be noted that the experimenters had already trained the rats to prefer licorice by pairing it with sucrose. The preference rats displayed for the licorice flavor following its pairing with nicotine was similar to that established via sucrose-pairing at the beginning of the experiment. Unfortunately, rats that were conditioned to develop a licorice flavor preference and then went on to self-administer saline were not included in this arm of the experiment and could not serve as a control. This makes the role of nicotine- vs. sucrose-pairing in the maintenance of the flavor preference unclear (Palmatier et al., 2019). A similar experimental design was employed to determine if saccharin could become a conditioned reinforcer of nicotine. Following 5 days of nicotine/saline IVSA paired with intra-oral saccharin, Wickham and colleagues executed a ‘Conditioned Reinforcer (CR) test’. In this test, mice nose poked to receive only saccharin. The researchers surmised that if the earlier nicotine-saccharin pairing made saccharin into a conditioned reinforcer, rats from the I.V. nicotine group would self-administer more saccharin during the ‘CR test’. There was not a significant

enhancement of responding at the CR nose-port in the I.V. nicotine group compared to the I.V. saline group during the 'CR test'. This was interpreted by the researchers as a failure of nicotine to alter the conditioned reinforcing value of saccharin. However, these data are somewhat complicated since saccharin has reinforcing value of its own. The researchers observed the reinforcing value of saccharin earlier in their experiments when they found rats would self-administer intra-oral saccharin on two low effort schedules of reinforcement without I.V. nicotine delivery (Wickham et al., 2018). In addition, although rats were trained to self-administer nicotine using levers, the operant behavior was switched to nose-poking during the CR test. It is possible that this could have interfered with the animals' understanding of the task.

We are beginning to investigate and understand the role that characterizing flavors and sweeteners might play as conditioned reinforcers following nicotine pairing. For example, it appears that e-cigarette flavorants enhance responding for nicotine. However, there are still significant gaps in the literature. First of all, both pre-clinical investigations on the topic limited their study to male rats. As such, nothing is known about potential sex differences in the development of characterizing flavors as CRs. In addition, there is an entire body of research which is in direct contrast to the hypothesis that characterizing flavors will lead to conditioned flavor preferences, known as 'conditioned taste aversion' (CTA). CTA has been shown to occur in rodent models when characterizing flavors are paired with bitter or unpleasant flavors (Limebeer and Parker, 2000; Parker, 1984). Nicotine is bitter and conditioned taste aversions have been readily developed to flavors previously paired with nicotine in animal models (Chen et al., 2011; Korkosz et al., 2006; Laviolette et al., 2002; Wilmouth and Spear, 2004). On the other hand, flavor- and odor-cues become positively associated with nicotine reward in human smokers. These cues (i.e. flavors) can become independently rewarding and reinforcing (Brauer et al., 2001; Perkins et al., 2001b; Pickworth et al., 1999; Rose et al., 2010; Westman et al., 1995). Due to this dichotomy, the field might face challenges if researchers do not carefully optimize experiments and create better translational animal models. One factor to consider is the inherent neophobia that animal models have toward novel 'characterizing' flavors. Although humans also experience flavor neophobia (De Cosmi et al., 2017), for years before a person vapes, their selected flavor will be paired with thousands of varied natural rewards (i.e. foods that have sweetness and caloric value) and will already be preferred. A potentially important step in creating valid animal models might be to create learned flavor preferences or to screen animals for their flavor preferences prior to their pairing with nicotine, such as was done by Palmatier and colleagues (Palmatier et al., 2019).

4. Conclusions

The number of current adolescent tobacco users in the US increased in 2019 for the first time in decades, an effect driven by the rise in (mostly flavored) e-cigarette use (CDC, 2019). Flavored e-cigarette use is associated with increased vaping (i.e. increased nicotine exposure), which is concerning given that nicotine disrupts crucial neural development that occurs throughout adolescence (England et al., 2017, 2015; Goriounova and Mansvelder, 2012; Omelchenko et al., 2016; Walker and Loprinzi, 2014; Yuan et al., 2015). In addition, e-cigarette use, and flavored e-cigarette use predicts a transition to smoking combustible

tobacco products (Barrington-Trimis et al., 2018; Chen et al., 2016; Dai and Hao, 2016; Leventhal et al., 2019b; Soneji et al., 2017) which is still the leading cause of preventable death in the developed world (Creamer et al., 2019; U.S. HHS, 2014). However, this risk in the adolescent population needs to be considered in balance with the potential benefit to society if flavored e-cigarettes could help adults quit smoking. While observational reports are mixed (Al-Delaimy et al., 2015; Berry et al., 2019; Biener and Lee Hargraves, 2015; Gomajee et al., 2019; Rigotti et al., 2018; Weaver et al., 2018; Zhu et al., 2017; Zhuang et al., 2016), four out of the five randomized clinical trials (RCTs) from the last five years suggest that e-cigarettes improve smoking cessation outcomes (Carpenter et al., 2017; Hajek et al., 2019; Halpern et al., 2018; Masiero et al., 2019; Tseng et al., 2016). E-cigarettes themselves seem to be effective smoking cessation aids. However, at this point, it is unclear if characterizing flavors provide an added benefit. Observational data suggest that flavored e-cigarettes help individuals reduce and quit smoking (Chen, 2018; Chen et al., 2018; Tackett et al., 2015). However, the topic has not been properly addressed in an RCT with treatment seeking individuals.

This field of research needs to move ahead strategically in order to better understand the role of characterizing flavors in nicotine and e-cigarette reward and to protect consumers of all ages. There should be an emphasis to include female subjects both in clinical and preclinical studies. This is paramount, given that women are potentially more susceptible to a preference for flavors, as well as for experiencing the sensory attributes of vaping. Unfortunately, many studies have not been able to measure possible sex differences. This might partially be explained by the fact that less women than men vape (Barnett et al., 2015; Choi et al., 2012; Hedman et al., 2018; Saddleson et al., 2015; Soule et al., 2016; Sutfin et al., 2013) and women could be harder to recruit for clinical studies. However, many preclinical studies have also used only male subjects, which is not justifiable. In addition, care must be taken to create translatable animal models. Although the flavorant farsenol, and likely several more unstudied flavor volatiles, have pharmacological effects on their own (Avelar et al., 2019), other work found that a flavorant could only affect nicotine-taking after animals were trained to prefer the flavor (Palmatier et al., 2019). In order to best mimic the human experience of vaping, researchers should consider using animals with a flavor preference prior to nicotine-pairing. This will allow both intrinsic pharmacological effects of flavorants and the potentially important contextual effects of a preferred flavor to be studied simultaneously, as they would in human vapers. Finally, flavor volatiles should be appreciated as pharmacologically active chemicals with potential effects within the central nervous system (CNS) and therefore researchers in basic and clinical research should take the time to evaluate the types and concentrations of flavorants in their experimental solutions, whenever possible.

Even with these precautions, our understanding of flavor volatiles' true effects on nicotine reward and consumption will be complicated by many hurdles. First, it is unclear if the concentration of volatiles that passes through the brain blood barrier of vapers is physiologically relevant. Second, pre-clinical models have had to rely on e-liquids injection or delivering flavors separately from nicotine. While we can learn important information from these methods, we should strive for a better understanding of the effects of the chemical composition that vapers are actually exposed to, i.e. in e-cigarette vapors. The final

hurdle is one of exponential proportions. The most comprehensive study of e-cigarette liquids found 155 chemical volatiles in 277 e-liquids, with an average of about 25 chemicals/e-liquid (Omaiye et al., 2019b). Assuming all combinations are possible, there are approximately $4.774401753992 \times 10^{28}$ mixtures of flavor volatiles available on the market. Even if the scientific community spends decades understanding what flavor volatiles do individually, we might never fully appreciate the complexity of the mixtures that humans are exposed to during vaping and how these will interact with nicotine reward.

This review highlights two main concepts that are relevant for the research on flavorants in e-cigarettes. First, characterizing flavors target specific populations, women and the particularly vulnerable adolescent population. These are not new revelations. Rather, research in the 1900s and early 2000s made this clear; yet, we are forced to re-discover these phenomena in the context of e-cigarettes. Second, there are a wide variety of mechanisms, ranging from sensory contributions to pharmacokinetics to neuropharmacological activity, that could contribute to increased nicotine use and abuse. As of 2020, we have only begun to scrape the surface of our understanding.

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HIGHLIGHTS

- Flavored e-cigarettes are widely popular, but particularly among women and adolescents.
- Flavorings have been used in tobacco products since the 17th century.
- Evidence suggests that flavors enhance nicotine reward and might increase consumption.
- Flavor volatiles are pharmacologically active chemicals inhaled by vapers.

Table 1

Summary of behavioral findings in 'characterizing' flavored e-cigarette literature.

E-cigarette Flavor/s (volatiles)	Species	Route of administ-ration	Nicotine/Flavorant Concentration/ Dose	Main Findings	Reference
"Green apple" (farsenol)	Adult mice (α c4 - mCherrya6- GFP mice; C57BL/6 J background)	Intraperitoneal (i.p.) injection	Nicotine: 0.5 mg/kg; free-base Farsenol: 0.1–10 mg/kg	- rewarding in male mice (dose-dependent), - β2* nAChR antagonist (DhJ3E) blocked farnesol- induced CPP in male mice. - enhanced nicotine CPP in male mice. - increased baseline firing frequency of VTA dopamine (DA) neurons in male mice - decreased baseline firing frequency of SNr GAB A neurons in male mice - upregulates a6*-containing nAChRs (physically and functionally) in VTA DA neurons of male mice	Avelar et al. (2019)
"Sweet flavors" = Peach, Watermelon, blackberry, Cotton candy, cola, sweet lemon tea	Humans (N = 20, age 19–34) 45% women	Inhalation	Nicotine: 0, 6 mg/ml; free-base (measured in the e-liquid) Flavorant(s): unknown	- "Sweet" e-cig produced greater appeal ratings (compared to tobacco-, menthol- and unflavored e-cigs)	Goldenson et al. (2016)
"Cherry", "Chocolate"	Humans (N = 132, age 18–45) 51% women	inhalation	Nicotine: 18 mg/ml; free-base (measured in e-liquid) Flavorant(s): Unknown	- Cherry and chocolate were rated sweeter than unflavored e-cigarettes, but were not better liked - Sweetness was positively associated with and irritation, bitterness, and sourness were negatively associated with liking	Mead et al. (2019)
"Sweet Flavors" = Blueberry, Strawberry, Peach, Watermelon, Blackberry	Humans (N = 101, age 18–35) 35% women	inhalation	Nicotine: 0, 6 mg/ml; free-base (measured in the e-liquid) Flavorant(s): Unknown	- Sweet flavors (and menthol) were more appealing than tobacco flavors - Sweet flavors (and menthol) suppressed nicotine's unappealing qualities in non-smokers. Never smokers had largest preferences for non-tobacco flavors	(Leventhal et al., 2019a)
"Cherry Crush", "Vivid Vanilla", "Pina Colada", "Peach Schnapps"	Humans (N = 31, age >18; average = 34*) 42% women *age range not provided	inhalation	Nicotine: 12 mg/ml; free-base (measured in e-liquid) Flavorant(s): Unknown	- Pina Colada was perceived as the sweetest and was most liked - Sweetness had the greatest positive impact on liking (followed by 'coolness (sensory)' and harshness had the greatest negative impact on liking	Kim et al. (2016)
"Cherry"	Humans (N = 19, age 21–35) 32% women	inhalation	Nicotine: 0, 6, 12 mg/ml; free base (measured in e-liquid) "Cherry": 4.7% or 9.3% vol/vol	- The concentration of cherry flavoring did not significantly affect (but tended to increase) perceived intensities of sweetness	Pullicin et al. (2019)
"Fruit" = Blueberry, Strawberry, Peach, Watermelon, Blackberry	Humans (N = 100, age 18–34) 35% women	inhalation	Nicotine: 0, 6 mg/mL; free-base (measured in the e-liquid) Flavorant(s): Unknown	- Appeal of fruit (vs. tobacco) flavors were mediated by its "sweetness", "smoothness" and bitterness- reducing" effects	(Leventhal et al., 2019c)]
"Green apple", "Chocolate"	Humans (N = 32, age 18–30) 38% women	inhalation	6,12,18 mg/ml; free-base (measured in e-liquid) Concentration dependent on participants' usual brand and smoking rate Flavorant(s): Unknown	- Subjective reward was higher for the flavored (vs. unflavored) e-cigarettes - Participants worked ~4X harder to receive puffs of a flavored e - Participants took 2X more flavored puffs than unflavored	Audrain- Mc Govern et al. (2016)

E-cigarette Flavor/s (volatiles)	Species	Route of administ-ration	Nicotine/Flavorant Concentration/ Dose	Main Findings	Reference
				puffs (both were simultaneously available) during a 90-min *ad libitum* session	
"Green apple"	Humans (N = 49, age 16–20) 37% female	inhalation	Nicotine: 6, 12 mg/ml Flavorant(s): unknown	- Green apple flavored e-cigarettes were better liked (compared to unflavored and menthol-flavored). - Participants took more puffs from and used more e-liquid from a green apple flavored e-cigarette (compared to unflavored and menthol-flavored).	Jackson et al. (2020)
"Chocolate", "Grape"	Female adolescent Rats (Sprague-Dawley)	Nicotine - intravenous (i.v.) Flavorants - oral	Nicotine: 15–30 [ig/kg/infusion; free base Chocolate: 0.5% Hersey's Unsweetened Cocoa Grape: 0.1% Unsweetened Grape Kool-Aid *Note: 0.4% saccharin was added to all oral solutions	- Adolescent female rats would not self-administer nicotine with contingent delivery of oral flavo rant, unless provided social interaction during the self-administration session	Chen et al. (2011)
"Licorice" - (licorice root extract)	Male adult rats (Sprague-Dawley)	Nicotine - intravenous (i.v.)	Nicotine: 7.5 [ig/kg/infusion; free base Licorice: 0.1%, 1.0% (vol/vol)	- licorice (1.0%) enhanced responding for nicotine in male rats that were conditioned to "prefer" licorice before the self-administration paradigm across several schedules of reinforcement (FR2-FR10)	Palmatier et al. (2019)
Saccharin, sucrose	Adult male rats (Sprague Dawley)	Nicotine - intravenous (I.V.) injection Flavors - intra-oral	Nicotine: 0, 30 [μg/kg/infusion; free base Saccharin: 0.32% Sucrose: 10%	- Saccharin enhances nicotine self-administration at FR1 schedule of reinforcement - Sucrose enhanced nicotine self-administration at several schedules of reinforcement (FR1-FR5)	Wickham et al. (2018)
Strawberry	Humans (N = 14, age 19–59) 20% women	inhalation	Nicotine: 18 mg/ml; free base (measured in the e-liquid) Flavorant(s): Unknown	- C_{max} for the strawberry e-liquid was 22% higher compared to the tobacco e-liquid (not statistically significant) - $AUC_{0 \rightarrow 180}$ was significantly higher with the strawberry e-liquid compared to the tobacco e-liquid - The pH of e-liquids may influence rate of nicotine absorption. - Longer average puff duration when using strawberry e-liquid compared to tobacco e-liquid	St. Helen et al. (2017) St. Helen et al. (2018)
"Cherry" and "Chocolate"	Humans (N = 14, age 19–59) 20% women Humans (N = 88, age, age 18–55) 50% women	inhalation	Nicotine: 18 mg/ml; free base (measured in the e-liquid) Flavorant(s): Unknown Nicotine: 0,18 mg/ml; free base (measured in the e-liquid) Flavorant(s): Unknown	- Participants assigned sweet flavors (i.e. chocolate and cherry) reduced cigarettes smoking rates less than those assigned menthol and tobacco flavors - The highest vaping rates were observed in participants assigned tobacco- and cherry- (compared to chocolate and menthol) flavors	Litt et al. (2016)
"Arctic Blast"	Adult mice (C57BL/6)	inhalation	Nicotine: 12–30 mg/ml; free-base (measured in the vapor) Flavorant(s): Unknown	- Arctic blast-flavored vapor did not enhance nicotine discrimination (compared to unflavored vapor)	Lefever et al. (2019)
"Fruity aromas" (ethyl butyrate, isoamylacetate) "Dessert/Confection aromas" (ethyl maltol, vanillin)	Humans (N = 20, age 18–25) 40% women	Propylene glycol/ Vegetable glycerin tasting solution = oral Flavorants = inhalation	Nicotine: n/a Ethyl butyrate: 4.75, 9.75 (%w/w) Iso-amyl acetate: 13, 30 (%w/w) Ethyl maltol: 15, 30 (%w/w) Vanillin: 25, 50 (%w/w)	- Fruity aromas increased rated sweetness of the tasting solution - Dessert/confection aromas increased rated pleasantness of the tasting solution - Ethyl maltol decreased rated bitterness of the tasting solution	Rao et al. (2018)

E-cigarette Flavor/s (volatiles)	Species	Route of administ-ration	Nicotine/Flavorant Concentration/ Dose	Main Findings	Reference
"Berry"	Humans (N = 34, age 18–63) 6% women	inhalation	Nicotine: 6, 12, or 18 mg/ml; free base (measured in e-liquid) Concentration dependent on participants' preference Flavorant(s): Unknown	- A significant proportion of participants altered their puff flow rate (ml/s) when vaping the "berry" flavor (compared to tobacco); however, the direction of this effect was bi-lateral	Robinson et al. (2018)
Sucralose "Strawberry", "Vanilla", "Watermelon" and "Cherry"	Humans (N = 32, age 18–45) 50% women	inhalation	Nicotine: nominally 12 mg/ml, (actual range = 13.3–14.7 mg/ml) Sucralose: 0, 1% (wt/vol) Characterizing flavor ants: unknown	- flavor volatiles, not sucralose, played a larger role in sweetness and liking scores - Liking and sensory qualities of vaping depend on olfaction	Rosbrook et al. (2017)

Table 2

The five most common e-cigarette flavor volatiles and their reported pharmacological activities.

Flavor Volatile	Pharmacological Activity	Proposed Mechanisms of Action
Ethyl Maltol	Sedative and anti-convulsant (Aoyagi et al., 1974)	
	**Increases cellular activity and downstream signaling (Rowell et al., 2020)	- **phospholipase C activation, endoplasmic reticulum Ca^{2+} release, store-operated Ca^{2+} entry (SOCE), and protein kinase C (PKCa) phosphorylation (Rowell et al., 2020)
Ethyl Butanoate/ Ethyl Butyrate	Significantly decreases blood oxygen level-dependent (BOLD) response in the VTA and hypothalamus when administered alongside glucose tasting solutions compared to water controls (van Opstal et al., 2019)	
Vanillin	**Increases cellular activity and downstream signaling (Rowell et al., 2020)	- **phospholipase C activation, endoplasmic reticulum Ca^{2+} release, store-operated Ca^{2+} entry (SOCE), and protein kinase C (PKCa) phosphorylation (Rowell et al., 2020)
	Neuroprotective (Dhanalakshmi et al., 2016; Jayant et al., 2016; Lee et al., 2018; Makni et al., 2012)	- decreases lipid peroxidation and NO_2; elevates the activities of antioxidative enzymes and of GSH (Makni et al., 2012) - enhances cell proliferation in the DG of adolescent mice (Cho et al., 2016) - activates TRPV1 receptors (Jayant et al., 2016) - prevents the reduction of ID1 expression (Lee et al., 2018)
	Anti-depressant (Ben Saad et al., 2017; Xu et al., 2015)	- olfactory sensory input (Xu et al., 2015) - prevents depression-induced changes in protein expression (Xu et al., 2015) - anti-oxidant and anti-inflammatory activity (Ben Saad et al., 2017) - anti-MAO activity (Truman et al., 2019; Xu et al., 2015).
	Reduces insulin resistance (Park et al., 2011) Stimulates peripheral sensory receptors	- activates fat oxidation, potentiates leptin signaling (Park et al., 2011) - TRP receptor activation (Jayant et al., 2016; Lübbert et al., 2013;Vennekens et al., 2008)
Linalool	Anxiolytic (Coelho et al., 2013; Zhang et al., 2016)	- antagonism of T-type channels (Kaur et al., 2019) - prevents stress-induced changes in gene and protein expression (Yoshida et al., 2017; Zhang et al., 2016)
	Reward-related effects	- Increases striatal DA release (Okuyama et al., 2004)
	Neuroprotective (de Lucena et al., 2020; Sabogal-Guaqueta et al., 2016; Xu et al., 2017a, 2017b)	- anti-inflammatory and antioxidant effects (de Lucena et al., 2020; Godinho et al., 2018b; Sabogal-Guaqueta et al., 2019, 2016; Xu et al., 2017a, 2017b) - alleviates disruption of monoaminergic systems (de Lucena et al., 2020) - alleviates disruption of cholinergic systems (Xu et al., 2017b) - Prevents disruption of protein expression (Xu et al., 2017b) - Enhances mitochondrial function (Sabogal-Guaqueta et al., 2019)
	Sedative/anti-convulsant (Deng et al., 2018; Elisabetsky et al., 1999; Linck et al., 2009; L F Silva Brum et al., 2001; Sugawara et al., 1998; Zhong et al., 2019)	- inhibits glutamate binding (Elisabetsky et al., 1999) and signaling (L F Silva Brum et al., 2001; L. F. Silva Brum et al., 2001) - alters neurotransmitter protein concentrations (Deng et al., 2018; Zhong et al., 2019)
	Anti-depressant (Guzman-Gutierrez et al., 2012; Kim et al., 2012; Zhao et al., 2009)]	- MAO-inhibitor activity (Kim et al., 2012) - Regulates of monoamine transporter activity (Zhao et al., 2009)
	Anti-ischemic (Barrera-Sandoval et al., 2019; Park et al., 2016; Sabogal-Guaqueta et al., 2018)	- anti-inflammatory and antioxidant effects (Barrera-Sandoval et al., 2019; Park et al., 2016) - Prevents disruption of a healthy phospholipid profile (Sabogal-Guaqueta et al., 2018)
	Antinociceptive (Batista et al., 2010, 2008; Peana et al., 2006; Tashiro et al., 2016)	- Inhibits nitric oxide (NO) formation (Peana et al., 2006) - Activate at ionotropic glutamate receptor (AMPA, NMDA and kainate) receptors (Batista et al., 2008)

Flavor Volatile	Pharmacological Activity	Proposed Mechanisms of Action
		- activates hypothalamic orexin neurons (Tashiro et al., 2016) - olfactory sensory input (Tashiro et al., 2016)
Ethyl Acetate	Sedative/anti-convulsant (Herrera-Ruiz et al., 2007)	- Enhances GABA signaling (Herrera-Ruiz et al., 2007)
	Protective against cognitive dysfunction (Godinho et al., 2018a; Huang et al., 2016; Jara-Moreno et al., 2018; Seung et al., 2018)	- Antioxidant and anti-inflammatory (Godinho et al., 2018a; Huang et al., 2016; Kim et al., 2018; Seung et al., 2018) - Prevents disruptions in protein expression (Ha et al., 2018; Kim et al., 2018; Okesola et al., 2019; Seung et al., 2018) - Alleviates disruption cholinergic system (Ha et al., 2018; Kim et al., 2018; Okesola et al., 2019) - Alleviates disruption of monoaminergic systems (Okesola et al., 2019) - Enhances mitochondrial function [(Huang et al., 2016; Kim et al., 2018) - Regulates the JNK/AKT pathway [(Ha et al., 2018; Kim et al., 2018)
	Alters metabolism	- High dose increased metabolic activity of CYP2A enzymes and was a weak inhibitor of CYP2C6 in rat liver (Noskovâ et al., 2016)
	Has reward-related effects	- Increased ICSS response rates at low concentrations[†] (Yavich et al., 1994; Yavich and Zvartau, 1994)
	Anti-depressant[§]	- Regulates monoamine transporter activity[§] (Zhao et al., 2009)
	Protective against cognitive dysfunction[§] (Godinho et al., 2018a; Huang et al., 2016; Jara-Moreno et al., 2018; Seung et al., 2018)	- Antioxidant and anti-inflammatory[§] (Godinho et al., 2018a; Huang et al., 2016; Kim et al., 2018; Seung et al., 2018) - Prevents disruptions in protein expression[§] (Ha et al., 2018; Kim et al.,2018; Okesola et al., 2019; Seung et al., 2018) - Alleviates disruption of monoaminergic systems§ (Okesola et al., 2019) - Prevents disruptions in protein expression[§] (Ha et al., 2018; Kim et al., 2018; Okesola et al., 2019; Seung et al., 2018) - Alleviates disruption cholinergic system§ (Ha et al., 2018; Kim et al., 2018; Okesola et al., 2019) - Alleviates disruption of monoaminergic systems§ (Okesola et al., 2019) - Enhances mitochondrial function§ (Huang et al., 2016; Kim et al., 2018) - Regulates the JNK/AKT pathway§ (Ha et al., 2018; Kim et al., 2018)
	Sedative/anti-convulsant[§] (Herrera-Ruiz et al., 2007)	- Enhances GABA signaling[§] (Herrera-Ruiz et al., 2007)

[†] ethyl acetate is one component of glue thinner that was used in these experiments.

[**] these flavorants were one of 3 constituents contained in a ‘banana pudding’ e-liquid.

[§] ethyl acetate fraction of a plant extract.

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