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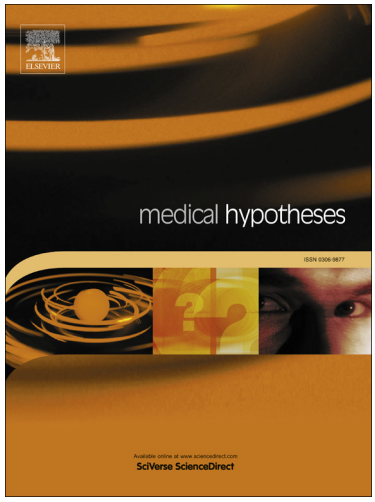

Fragrance compounds: The wolves in sheep's clothings

Seema Patel

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Fragrance compounds: The wolves in sheep's clothings

Seema Patel[1*]

[1]Bioinformatics and Medical Informatics Research Center, San Diego State University, San Diego-92182, USA

Short running title: Dangers of synthetic fragrance exposure
Keywords: Synthetic fragrance; Endocrine disruptors; Gynecomastia; Breast cancer; Depression

***Corresponding Author:**

Dr. Seema Patel
Bioinformatics and Medical Informatics Research Center
San Diego State University
5500 Campanile Dr San Diego, CA 92182
Email: seemabiotech83@gmail.com

Abstract

In the past few decades, synthetic fragrance compounds have become ubiquitous components of personal care and household cleaning products. Overwhelming consumerism trends have led to the excess usage of these chemicals.

It has been observed that this fragrance-laden unhealthy lifestyle runs parallel with the unprecedented rates of diabetes, cancer, neural ailments, teratogenicity, and transgender instances. The link between fragrances as and the multiplicity of pathogens remained latent for decades. However, now this health hazard and its role in homeostasis breakdown is getting attention. The adverse effects of the fragrance constituents as phthalates, paraben, glutaraldehyde, hydroperoxides, oil of turpentine, metals, nitro musks, and essential oils, among others are being identified. The endocrine-immune-neural axis perturbation pathways of these chemicals are being proven.

Despite the revelations of cause-effect nexus, a majority of the vulnerable populations are unaware and unmotivated to avoid these 'slow poisons'. Hence, the the researchers need to further validate the toxicity of fragrance compounds, and raise awareness towards the health risks

In this regard, a number of pathologies triggered by fragrance exposure, yet proven only scantily have been hypothesized. Analysis of the health issues from multiple facets, including the pivotal 'stressors- extracellular acidosis- aromatase upregulation- estrogen hyperproduction- inflammation' link has been proposed. Fragrance compounds share configurational similarity with carcinogenic environmental hydrocarbons and they provoke the expression of the cytochrome group monooxygenase enzyme aromatase. This enzyme aromatizes androgens to form estrogen, the powerful signaling hormone, which underlies the majority of morbidities. This holistic review with a repertoire of preliminary evidences and robust hypotheses is expected to usher in deserving extent of research on this pervasive health risk.

Introduction

Human metabolism generates noxious odors, which are emitted through sweats, sebum, and breath. Biochemically, these odors are composed of fatty acids, steroids, amino acids, and biogenic amines (Liberles, 2014). In fact, all living organisms and organic materials decompose to produce offensive odors (Paczkowski and Schütz, 2011). To mask them, fragrances have been used since ages. All ancient cultures (Greece, Rome and others) have profusely used perfumes, the concoction of various plant-based (flowers, leaves, fruits, resins, seeds, spices, barks etc.) and selective animal glandular products (musk, civet, ambergris etc.) (Herz, 2011). Olive oil, almond oil, coconut oil, grape seed oil have been the carriers for the natural fragrances. Some popular plant resins included frankincense, myrrh, benzoin, *Myroxylon pereirae* (balsam of Peru), and *Cistus* sp.-derived labdanum (Lardos et al., 2011). Popular essential oils included rose (Rosa sp), cinnamon (*Cinnamomum cassia*), anise (*Pimpinella anisum*), marjoram (*Origanum majorana*), lavender (*Lavandula* sp.), frankincense (Boswellia sp.), tree moss (*Evernia furfuracea*), lemongrass oil (*Cymbopogon schoenanthus*), sandalwood oil (*Santalum album*), jasmine absolute (*Jasminum* spp.), ylang ylang oil (*Cananga odorata*), clove oil (*Eugenia caryophyllus*), cedarwood oil (*Cedrus atlantica/deodara*, juniper (*Juniperus virginiana*), neroli oil (*Citrus aurantium* amara flower oil), narcissus absolute (*Narcissus* spp.), and patchouli oil (*Pogostemon cablin*), among a myriad others. These oils carried subtle warm, spicy, vanilla, pungent, pine-like appealing scents. For their ability to suppress the unpleasant body odors they have been embraced widely. Chromatography and mass spectroscopy (gas chromatography-ion trap-tandem mass spectrometry (GC-IT-MS/MS)) analyses have enabled the identification and characterization of the plant essential oils and animal-derived oils. These components include linalool, geraniol, citral, limonene, coniferyl, morinol, nerol, citronellol, linalyl acetate, cinnamic aldehyde, atranol, chloroatranol, lanolin alcohol (from lanolin) etc. However, a shift in the composition of the fragrance materials have occurred in the last hundred years, as the 'Chemistry Era' picked momentum. Natural constituents are replaced by chemicals for their better stability. Currently-used synthetic perfumes as colognes use alcohol (1-decanol) as carrier medium instead of plant oil. Rancidity (oxidation of the oil) is an issue with perfume shelf-life as some compounds autoxidize on air exposure. To prevent rancidity, stabilizing chemicals are added to the perfume mixture. Also to adjust color, viscosity, and intensity, other ingredients are added. These constituents include fixatives, coloring

agents and preservatives such as phthalates, parabens, colophonium (an alcohol soluble resin), hydroxyisohexyl 3-cyclohexene carboxaldehyde, sorbitan sesquioleate, phenoxyethanol, salicylaldehyde, glutaraldehyde, hydroperoxides, trimethylbenzenepropanol, dipropylene glycol, benzyl benzoate, oil of turpentine, metals (nickel sulphate, cobalt chloride), 2-hydroxy-5-octanoylbenzoic acid, capryloyl salicylic acid, β-lipohydroxy acid, methylchloroisothiazoline/methylisothiazoline, methyldibromoglutaronitrile trimethylbenzenepropanol) etc. (Boberg et al., 2010; Özen and Darcan, 2011; Yang et al., 2015).

These compounds occur in almost all personal care products (perfume, body soap, hand wash, shampoo, sunscreen, deodorant, hair spray, nail polish/ remover, lotion/mist), and household cleaning/fragrant agents (room/ car freshener, laundry/ dish detergents, dryer sheets, incense sticks, scented candles, essential oil diffusers, fragrant pens) (Dodson et al., 2012). Chemical-based fragrance usage is widespread, from aeroplane, motel room, restaurants, restrooms and every place in between them. The overpowering and pleasant scents spanning from pumpkin, apple, cinnamon, vanilla, lemon, to lavender, effectively suppress the offensive body odors and musty, moldy, urine, garbage stinks of indoors. However, these fragrance compounds are wolves in sheep's clothing. They are short-term solutions with a long-term health perils.

Evidences are emerging that the fragrance compounds are endocrine disruptors, capable of upsetting the hormonal signaling systems. The pathologies triggered by them can manifest in any form such as neuropathies (depression autism), neoplasms (breast cancer, prostate cancer), endocrinopathies (gynacomastia), organ damage (hepatotoxicity), among others. A survey found that the scented consumer goods emit more than hundred toxic volatile organic compounds (VOCs) such as limonene, α- and β-pinene, ethanol, acetone etc. (Potera, 2011). Such fragrance products severely degrade indoor air quality (Uhde and Schulz, 2015). This review aims to shed light on this critical heath risk posed by the fragrance-laden household products, in order to generate research interest and public awareness.

Pathologies related to synthetic perfumes

Neural issues

Perfume or any strong smell is a known cause of headache and migraine (Burstein and Jakubowski, 2005). Migraine causes irritability, loss of appetite, fatigue, depression, or the quest for solitude (Burstein and Jakubowski, 2005). Young students attributed perfume as one of the few other factors as causal of sleep deprivation (Altun et al., 2012). Reed diffuser fragrance are cocktails of essential oils and other chemicals as glycol ethers, 3-methoxy-3-

methyl-1-butanol, petroleum distillates, ethanol and isopropanol. Exposure to the fumes (in the form of ingestion, inhalation, contact) led to nausea, vomiting, eye irritation and coughing in majority of the patients (Panchal et al., 2016). Depression is a mental state of low spirit, mood swings, and other cognitive and emotional impairment. Major depressive disorder (MDD) is the severe and persistent form of depression, that can be fatal (Kupfer et al., 2012). Depression is more frequent in women, for the cyclic hormonal fluctuations (mostly during premenstrual, postpartum, menopausal) they undergo (Albert, 2015). In a bid to restore cheerful mood, they often resort to antidepressants or transdermal estrogens/testosterone. Dysregulation of neural homeostasis occur by the disturbance of hypothalamic-pituitary-adrenal (HPA) axis. Link between hormones and neurotransmitters (serotonin, dopamine, norepinephrine, glutamate, gamma-aminobutyric acid (GABA)) is obvious as they share common receptors and pathways via the HPA axis (Jin and Yang, 2014). Hippocampus, amygdala, corticotropin-releasing factor, glucocorticoids, brain-derived neurotrophic factor, and CREB (cAMP response element binding protein) play key roles in this pathway. Pesticides from organophosphates, organochlorine, and carbamate class disrupt the immune and hormonal signaling, leading to a gamut of health hazards (Mathew et al., 2015; Toe et al., 2013). Aroma compounds are similar to pesticides in perturbing hormones and manipulating neurotransmitters.

Human skin and organs have numerous odorant receptors (approximately 400) (Malnic et al., 2010). The exogenous odor molecules bind to these olfactory receptors belonging to G-protein coupled receptor (GPCR) family (Spehr and Munger, 2009). These receptor proteins occur on cell surfaces including that of neurons (Gottfried and Wilson, 2011). Olfactory perception varies between genders and among individuals (Nováková et al., 2013). Estradiol and progesterone communicate odorant-evoked signals via the estradiol and progestin receptors. Studies have found that olfactory neurons expressing the olfactory receptors also express the estrogen receptors, which explains the link between smell and the sex hormones. Even in animal models, smell has been found to influence social behaviors like solitary nature or gregariousness (Brennan, 2010). Vomeronasal organ, the vascularized region of olfactory system interacts with circulating peptide or steroid hormones, modulating behavioral activities (Kang et al., 2009). Studies have found that females are significantly more cacosmic (experiencing illness on exposure to environmental chemicals like pesticide, automobile exhausts, terpene paints, rubber carpet, including perfumes) than males (Bell et al 1993). The pathologies associated with the pollutants inhalation included nasal allergies, asthma, breast cysts, hypothyroidism, sinusitis, migraine, food sensitivities, irritable bowel, anxiety, depression, among others (Bell et al., 1994; Caress and Steinemann, 2009). A study found that multiple sclerosis (MS) patients have

less optimal olfactory ability (Zivadinov et al., 1999). It might be due to the damaged olfactory neurons, as characteristic of the inflammatory autoimmune disease. Figure 1 illustrates the mechanisms discussed above.

Skin and airway hypersensitivity

Contact allergy to perfume and other consumer products cause dermatitis and asthma (Dodson et al., 2012). An *in vitro* study revealed that the fragrances such as oak moss, benzyl alcohol, bergamot oil, lime oil, orange oil, α-amyl cinnamic aldehyde and laurel leaf oil can be stimulated by ultraviolet (UV) A or B. The photo-activation can generate toxic compounds and can cause hemolysis (Placzek et al., 2007). Incense smoke liberates fumes of toxic gases as CO, CO_2, NO_2, SO_2, benzene, toluene, xylenes, aldehydes, PAHs (polycyclic aromatic hydrocarbons) along with particulate matters (higher than cigarettes) that mediate airway diseases as well as contact dermatitis (Lin et al., 2008). Dermal or inhalation exposure to the sensitizing fragrance leads to skin and bronchial sensitization which impairs the quality of life. Pustular contact dermatitis and urticaria due to fragrances have been proven. Patch test have shown positive reactions to a number of perfume constituents (Devos et al., n.d.; Nardelli et al., 2013).

Breast cancer and polycystic ovary syndrome

Breast cancer, the chief cause of female cancer mortality is of heterogeneous origin, occurring in more than five phenotypes (luminal A, luminal B, HER2 over-expressing, normal-like and basal-like) (Pazaiti and Fentiman, 2011). In estrogen positive type breast cancer, estrogen binds to its receptors, promoting breast epithelial cell proliferation and duct growth (Chung et al., 2012; Ferramosca et al., 2012; Tung et al., 2010). Progesterone binds to its receptors for milk-producing alveoli development (Conneely et al., 2007). Both these hormones are controlled by anterior pituitary lactogenic hormone (prolactin) (Raheem et al., 2010). Out of the multiple culprits, fragrance compounds with estrogenic properties (parabens, phthalates, nitro musks) have been major players in the breast carcinogenicity (Taylor et al., 2014). These compounds penetrate blood stream through skin, resulting in disruption of endocrine homeostasis (Darbre, 2009). The detailed mechanism has been discussed later in another section. Considering the level of malignancy, the carcinogenic cosmetics are certainly not worth-using. A review investigating the nexus between haircare products and breast cancer risk in African American women found solid cause-effect evidences (Stiel et al., 2016). Aromatase P450 (estrogen synthetase or estrogen synthase) is a monooxygenase-type enzyme, coded by gene CYP19 in chromosome 15, and it is responsible for steroidogenesis, including the biosynthesis of estrogens (Auvray et al., 2002). This enzyme catalyzes the conversion of the C19 steroids (androstenedione, testosterone, and 16-α-hydroxyandrostenedione) to estrone, estradiol-17β and estriol

(Auvray et al., 2002). Increased aromatase activity leads to hyperproduction of androgens or their increased aromatization into estrogen (Auvray et al., 2002). The over-expression of aromatase promotes the expression of the hormonal receptors, enhancing estrogen activity. Consequently, the pathologies like hyperplasia of female breasts tissues and polycystic ovary syndrome (PCOS) take place (Barker et al., 2009; Demura et al., 2007; Zhao et al., 2014). High aromatase activity induces the elaboration of growth factors like transforming growth factor beta 1 (TGF-β), epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF). These growth factors further stimulate aromatase activity, completing a vicious cycle (Su et al., 2011). This enzyme is found in gonads, brain, blood vessels, bone, skin, adipose tissue, placenta, among other tissues (Cui et al., 2013). Several anticancer drugs are aromatase inhibitors (anastrozole, letrozole etc.) (Barker et al., 2009; Lee, 2016). Figure 2 illustrates the mechanisms discussed above.

Gynecomastia

High rate of androgen aromatization into estrogen is responsible for male gynecomastia, the proliferation of breast glandular tissue (ductal epithelial hyperplasia, ductal elongation and branching) (Cuhaci et al., 2014; Czajka-Oraniec et al., 2008). This abnormal condition of increased subareolar nodule size and pain is fuelled by high estrogen activity, which causes psychological distress in the patients. Exogenous or endogenous estrogen, along with growth hormone (GH) and insulin-like growth factor 1 (IGF-1) leads to the lump formation or fatty tissue growth. Medications like the antihypertensive, acid reflux drugs, antidepressants (diazepam), alkylating agents, and substance abuse drugs, the fragrance-laden toiletries are drivers of gynecomastia. Tamoxifen or raloxifene therapy, surgical correction or radiotherapy can resolve this condition.

Reproductive issues and teratogenic effects

Several of the synthetic fragrances (such as nitro musks) being lipophilic, make their way into female adipose tissues. Their occurrence in breast milk has been detected. Through the milk, the pollutants are passed on to the suckling infant (Taylor et al., 2014). Transplacental diffusion of galaxolide, polycyclic musk into umbilical cord blood and exposure to fetus was reported (Zhang et al., 2015). A study has reported that these synthetic musks reduce the growth of juvenile and larval stages of the freshwater mussel (*Lampsilis cardium*) (Potera, 2007). It raises the question if these chemicals can cause developmental defects in human neonates too The link between air dye application during pregnancy and malignancies in the child has been established (Saitta et al., 2013).

A study connects the unprecedented rise in sex organ anomaly in newborns (like the undescended testicles and hypospadias) to compounds like phthalates, present in cosmetic products (Barrett, 2005). A study reports that a majority of perfumes are capable of fetal neuromodulation, even at femtomolar concentrations, via the pregnant mothers (Bagasra et al., 2013). The exposure of male rats to *Boswellia papyrifera* and *Boswellia carterii* smoke followed by sperm analysis revealed significant decrease in the sperm count, motility, speed and other abnormalities (Ahmed et al., 2013). From these publications, the detrimental effects of fragrance materials on human reproductive system are conspicuous.

Autism spectrum disorders (ASDs) are a set of neural aberration in parieto-frontal mirror neuron system, hampering behavioral and social aspects (Faras et al., 2010; Perkins et al., 2010). One key cause of this disease is the prenatal exposure to chemicals (perfumes and medicines) by transplacental diffusion and postnatal exposure through breast milk (Bagasra et al., 2013; Taylor et al., 2014; Zhang et al., 2015).

Transgender issues

Transgenderism can be of many forms, together grouped as lesbian, gay, bisexual, and transgender (LGBT) populations. Gender issues and non-conformity to sexual identity of birth (gender dysphoria) can arise at any time of life span. These changes are psychologically-distressing, resulting in depression, suicidal tendencies and mortality. LGBT populations face numerous additional health risks requiring clinical interventions. For example, they are at heightened risk of sexually transmitted diseases (STDs) such as AIDS, syphilis, gonorrhea, and infections by chlamydia, human papillomavirus, hepatitis A, among others. Individuals opt for surgical and hormonal gender-reassignment therapies to fit their orientation/alignment. The causes of gender transformation have been sparsely studied. Synthetic fragrance compounds are one of the likely culprits in gender manipulations via the imbalance of sex hormones. Some key perfume ingredients in this regard has been discussed.

Phthalate (a constituent of many synthetic perfume) exposure of mothers during pregnancy can cause poor masculinity in the male child (Percy et al., 2016; Swan et al., 2010). Testicular feminization (*e.g.* Reifenstein's syndrome) might also be linked to it. Phthalates can activate a subset of peroxisome proliferator-activated receptors (PPARs), which act as nuclear hormone receptors (Latini et al., 2008).

Liver, and thyroid toxicity

Adverse impact of fragrance compounds on liver has been observed. Polycyclic musks imbibed into blood can reach liver and block the activity of multidrug efflux transporters. The impeded activity of the pumps and

channels can lead to the pooling of toxic chemicals, and subsequent organ damage (Potera, 2007). A mussel model study found that the synthetic musks inhibit the activity of multidrug efflux transporters essential for ejecting out toxins (Luckenbach and Epel, 2005). In fish model, nitro musks interfered with xenobiotic metabolism ability of cytochrome P450 isoforms (Schnell et al., 2009). As these enzymes are crucial to metabolize drugs, their manipulation is likely to cause hepatotoxicity. When exposed to toluene, a component of fragrance, liver enzyme profile can be perturbed and chemical hepatitis can result (Malaguarnera et al., 2012). A rodent study has shown that a fragrance ingredient α-iso-methylionone (AIM) alters hematological profile, manifested in reduced aspartate aminotransferase (AST), and increased cholesterol, creatinine, and total protein level (Politano et al., 2012). Also, the increment in liver, kidney and spleen weights were observed (Politano et al., 2012). Thyroid and bone marrow-related adverse effects were observed at 500 mg/kg/d dosage of the compound (Politano et al., 2012). Figure 3 illustrates the mechanisms discussed above.

Discussion

It is deplorable and alarming that awareness of the threats of perfume allergy is very low. Tricked by aggressive advertisement and to improve aesthetic appeal, people are exposing themselves are to multiple chemical fragrance compounds. Further, it is a matter of concern that an alert individual cannot escape the perils of fragrances by mere lifestyle revision, and avoidance of the chemicals. Like the harms of passive smoking, passive exposure to the perfumes occurs in a number of public places. In realization of the dangers of peanut allergy to vulnerable individuals, peanut was pulled off from the food platter in passenger planes (Waggoner, 2013). Similar awareness and action is needed for perfumes as well. Exposure to strong fragrances can provoke asthma like symptoms. Because the chemicals are perceived as a stress, and in response to it, angiotensin II, the vasoconstrictor will be elaborated by the body. An aware individual does not deserve to get the brunt of someone else's reckless lifestyle choices. Also, the cleaning staff in public places must be trained so as to ensure prevention of perfume abuse i.e. excess usage.

Hormonal disturbance is the core cause of all pathologies (Ranabir and Reetu, 2011). Just for a superficial sensory appeal, one should not agitate it, as consequences are likely to be unforgiving. Unfortunately, the current consumerist culture and media marketing strategies are only fuelling their prevalent use (Kaličanin and Velimirović, 2016). It is high time, the youth realizes the dangers of perfumes. It is much safer to stay away from them, than risking hormonal disturbance, gynecomastia, cancers, depression, autistic children and an array of other agonies.

The cause-effect relation between perfumes and health deterioration is rather straight-forward. Aroma compounds are substrate for aromatase enzyme. Aromatic hydrocarbons (such as benzene and PAHs) are degraded by aromatase, and perfume compounds are a form of hydrocarbons (Paakki et al., 2000). So, high exposure of aroma compounds increases aromatase expression, which enhances tissue-specific estrogen biosynthesis, leading to a wide array of inflammatory diseases, as mentioned before. One way to prevent these pathologies can be by refraining from the usage of aromatase substrates (in the form of judicious dietary, cosmetics, medication choices and environmental exposure). High aromatase activity is proportional to high estrogen activity, which might explain better infection fighting ability in females of reproducing age. On the other hand, low aromatase activity translating into low estrogen, as characteristics of males and older females explains poor resistance to infections. Despite the strong immunity conferred by estrogen, its inflammatory attribute makes it an ambiguous signaling molecule. The isoforms of the estrogen receptors (Erα and ERβ), despite containing the same motifs .i.e. N-terminal DNA binding domain and C-terminal ligand binding domain, have different amino acid substitutions, which modulate estrogen function differently. It is not yet clear which isoform of the ER is expressed following the fragrance compound exposure. Investigating this ambiguity can shed light on the inflammation mechanisms. The link of aroma compounds and thyroid must be further probed, as thyroid is very critical endocrine regulator. It has come forth that aromatase often co-expresses with thyroid-stimulating hormone (TSH) (Caglar et al., 2015). Diabetes is a common inflammatory disease and aromatase overdrive is responsible for it. It is suspected that fragrance compounds make endocrine system go haywire and lead to diabetes (Williams, 2012). The correlations between perfume exposure and resultant pathologies often vary at regional and epidemiological basis, which so far has undermined their health risks.

Also, it important to know that the less volatile fraction of the perfumes contain phthalate, which renders the older products more toxic (Orecchio et al., 2015). The terpenes like limonene and linalool are prone to oxidation, and behave as dermal allergens. Patch testing with the oxidized terpenes have shown the incidences of allergic contact dermatitis (Audrain et al., 2014).

In fact, the hazardous effects of these synthetic compounds go beyond human health. A study found traces of musk fragrances such as galaxolide, tonalide, cashmeran, and UV-filters in marine species (mussel, clam, flounder, herring and mullet) and macroalgae, which constitute seafood. These bioaccumulated xenobiotics will ultimately reach to the human body via the food chain (Cunha et al., 2015). Polycyclic musks tonalide, galaxolide, and their

degradation product was detected at a dose of 0.26 - 1.0 µg/L in the water and trouts of a German river (Lange et al., 2015). Stable fragrance compounds like amberketal, ambrofix, amyl salicylate, benzyl salicylate, bourgeonal, isobutavan, dupical, hexyl salicylate, isobutavan, lemonile, pelargene, peonile, mefranal, myraldene, okoumal, oranger crystals, tridecene-2-nitrile, ultravanil were identified in the surface water of the city of Venice and its lagoon, occurring at the concentration from 30ng/L- 10µg/L (Vecchiato et al., 2016). Sewage discharges was the source of the estrogenic compounds (Vecchiato et al., 2016). It is important to remember that these xenobiotics will ultimately make way into human body as potable or shower water.

Perfume manufacturers do not disclose the ingredients and quantity of the fragrance compounds in the name of 'trade secret'. Though they ought to abide by ethics, for profit and the goals of high market share, they forgo those. With the help of unscrupulous advertisements and sponsored research reports, they keep luring naive and unaware consumers. A survey reports that the products advertised as organic, natural, green, eco-friendly also emit an array of hazardous chemicals (Potera, 2011). It is appalling that even if people know the threats, they continue using these toxins, resonating the "death wish" concept discussed in the popular TV series "Mad men". Almost everybody knows the health risks of oil spill exposure. The constituents have been linked to genotoxic, immunotoxic, and endocrine toxicity (Laffon et al., 2016). Chemically, perfume components are not much different from these vicious PAH compounds. This analogy should be a "wake up call". One should realize that every time an individual gets exposed to a perfume, he/she agitates his/her hormonal signaling, risking cancer development. Even essential oil generally traded to be "plant-based, so safe" are not free of risks, as they can cause phototoxicity and skin irritations (Placzek et al., 2007). The fragrance compounds so ubiquitous in modern times initiate vicious cycles of 'exposure – pathologies – drugs', which must be understood, information disseminated and terminated. Based on the review work and hypotheses, it can be stated that perfumes and other fragrance compounds in day-to-day consumer products are 'slow killers with fatal punch'.

Conclusion

Growing recognition of the widespread use of fragrances in modern society is alarming. These pleasant-seeming deleterious compounds are the causal factors of a wide array of immune-neural-hormonal health issues. Allergy, irritation, migraine, asthma, depression, high blood pressure, diabetes and other symptoms should not be trivialized. Unheeded, and continued, the fragrance compounds can lead to gynaecomastia, cancers, gender manipulation, teratogenicity. Creating public awareness is essential to avoid grave health consequences. Toxicology

research on perfumes must be prioritized, just like other urgent topics like 'antibiotics-drug resistance' and 'pesticide-food safety'. This review 'though barely scratches the surface" of the enormous health threats of 'synthetic fragrances' is expected to evoke alertness.

Conflict of interest

There is no conflict of interest in submission of the manuscript.

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Legends to the Figures

Fig. 1. Fragrance compounds manipulating neurotransmitters for neuropathologies

Fig. 2. Fragrance compounds as the drivers of breast cancer and other endocrinopathies

Fig. 3. Fragrance compounds inhibiting efflux transporters leasing to hepatotoxicity

Fig. 1.

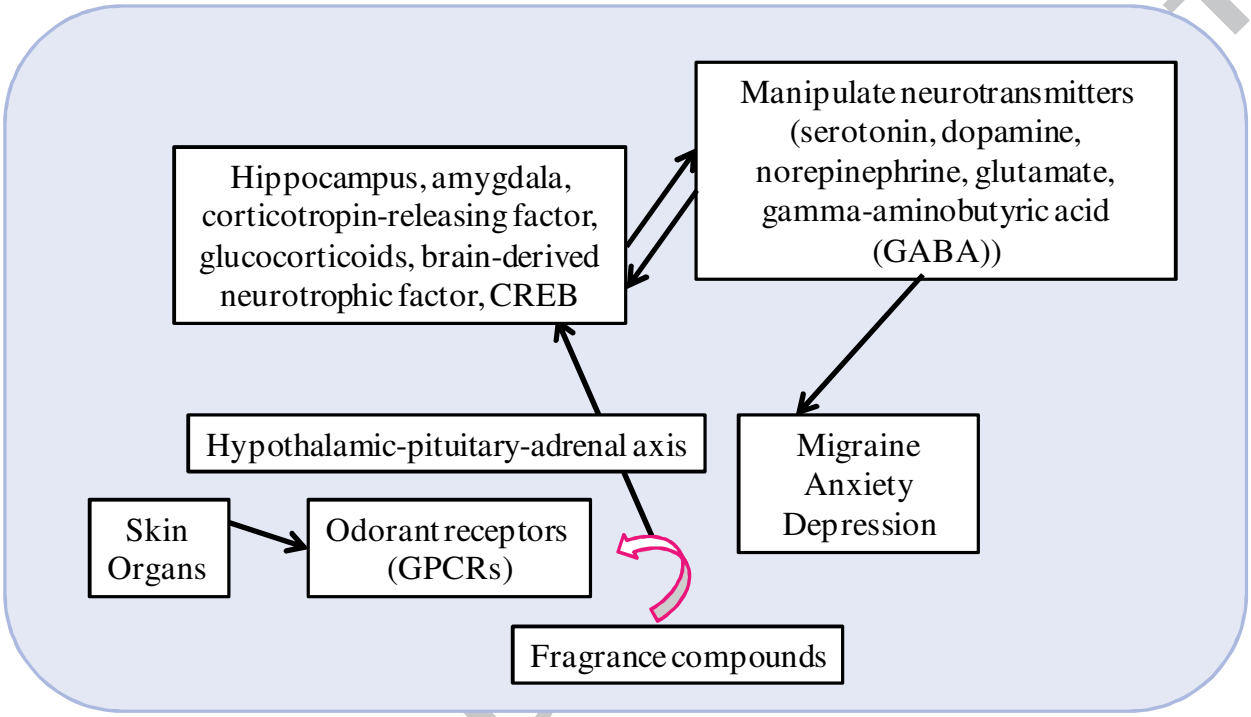

Fig. 2.

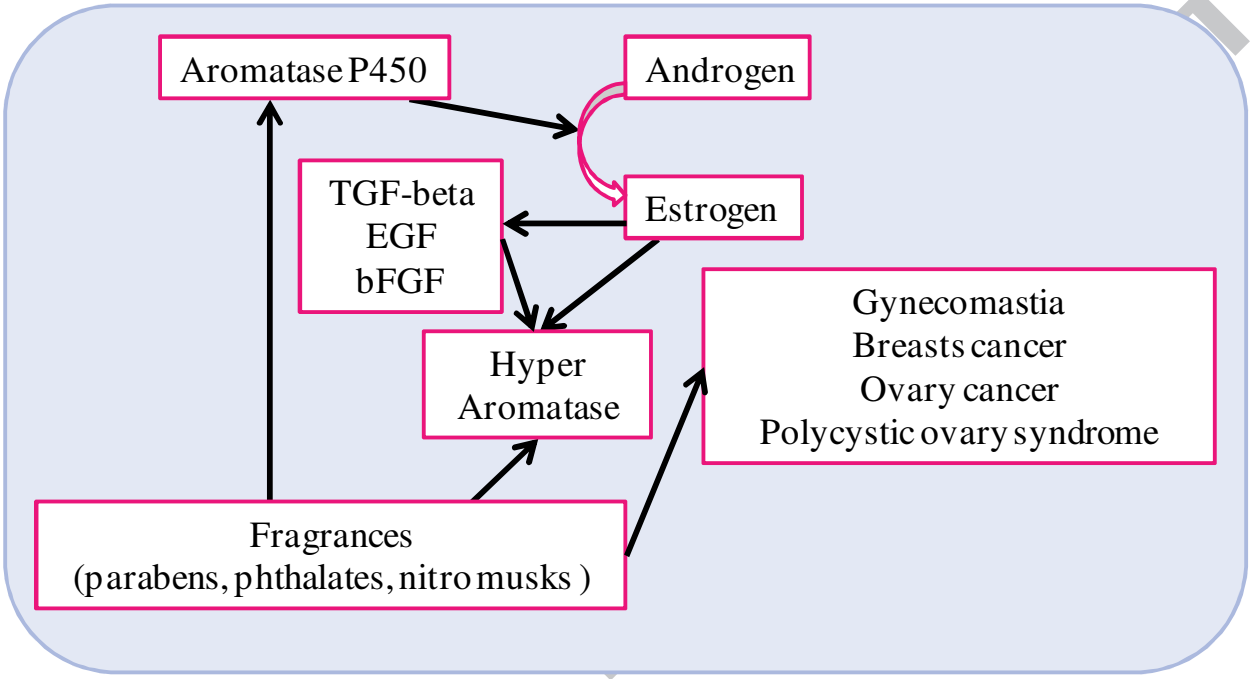

Fig. 3.