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Medical aromatherapy revisited—Basic mechanisms, critique, and a new development

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Abstract

Objective: According to a series of recent meta-analyses and systematic reviews, aromatherapy has shown to be effective in treating patients with different medical conditions. However, many of the clinical studies are of rather low methodological quality. Moreover, there is much conceptual ambiguity with regard to what aromatherapy actually constitutes.

Method: In this paper, we discuss the conditions under which aromatherapy is most likely to be of medical value by outlining the workings of the olfactory system and the necessary requirements of odors to be therapeutic. We then introduce an aromatherapeutic inhaler that was tested in a series of studies involving 465 participants.

Results: This inhaler (AromaStick®) produced large to very large effects across a variety of physiological target systems (e.g., cardiovascular, endocrine, blood oxygenation, and pain), both short term and long term.

Discussion: Inhalation of volatile compounds from essential oils yields almost immediate, large, and clinically relevant effects as long as the scents are delivered highly concentrated from an appropriate device. The changes caused in the body seem side effect-free and can be sustained when inhalation is repeated.

KEYWORDS

AromaStick®, aromatherapy, clinical effects, inhaler, olfactory system

1 | INTRODUCTION

Every ancient culture used scents either for hygienic or remedial purposes. For example, Hippocrates (460–370 BC) introduced scents to treat hysteria, which he regarded as symptoms caused by movements of the womb (King, 1993). Records show that the therapeutic use of distilled oils was already applied in the 10th Century AD (Forbes, 1970). According to estimations, there are about 350,000 plant species, among which approximately 17,500 are aromatic plants (Tisserand & Young, 2014). Of these, some 400 are commercially processed for their aromatic raw materials. However, after the introduction of clinical efficacy testing in the 1950s and the rise of pharmacotherapy dominating Western medicine, aromatherapeutic approaches were almost exclusively restricted to alternative medical approaches. Until recently, conventional medicine regarded aromatherapy as pseudoscientific due to a lack of compelling empirical evidence supporting its effectiveness. In the last decade or so, this situation has changed, and there is growing medical interest in aromatherapy. Clinical studies as well as meta-analyses show that some of the former reservations against the medical use of essential oils can no longer be upheld.

There is no doubt that essential oils have very specific pharmacologic properties, which may be actively used to elicit specific physiological responses (Edris, 2007; Hongratanaworakit, 2004). For example, certain odors (e.g., peppermint oil) may alter the endogenous opioid pathways of the brain and therefore reduce pain or anxiety (Bushnell, Ceko, & Low, 2013; Ching, 1999; Villemure, Slotnick, & Bushnell, 2003). Other odors (e.g., eucalyptus or thyme) have remarkable antibacterial, antifungal, anti-inflammatory, immunomodulatory, or antioxidant effects (Brochot, Guilbot, Haddioui, & Roques, 2017; Caceres et al., 2017; Divband, Shokr, & Khosravi, 2017; Hans, Grover, Deswal, & Agarwal, 2016; Jaradat, Adwan, K'aibni, Shraim, & Zaid, 2016; Kenia, Hoghton, & Beardsmore, 2008; Schönknecht, Krauss, Jambor, & Fal,

2016; Zhou et al., 2016). Recent meta-analyses and systematic reviews support the notion that aromatherapy may exert clinical symptom relief when compared with placebo or standard treatment. For example, in a meta-analysis examining different types of pain management, aromatherapy was superior to placebo in treating postoperative, obstetrical, and gynecological pain (Lakhan, Shaefer, & Tepper, 2016). A systematic review investigating the effects of aromatherapy on dysmenorrhea showed that the alleviating effect on menstrual pain was larger with aromatherapeutic interventions than with placebo interventions (Song, Lee, Min, Fike, & Hur, 2018). In a meta-analysis of randomized controlled trials on stress reduction, aroma inhalation yielded favorable effects compared with no treatment, but this effect mainly showed in subjective self-reports (Hur, Song, Lee, & Lee, 2014). An evaluation of aromatherapy on sleep quality including randomized controlled trials and quasi-experimental trials revealed that it was effective in both healthy and unhealthy individuals, especially when used as inhalation rather than massage therapy (Hwang & Shin, 2015). By contrast, a systematic review investigating aromatherapy for treating depressive symptoms found stronger relieving effects for massage aromatherapy than for inhalation aromatherapy (Sánchez-Vidaña et al., 2017).

Together, these findings demonstrate that therapeutic use of essential oils may exert clinical effects. In general, aromatherapy may be applied for a variety of medical conditions, but it appears to be most effective for medical conditions whose underlying mechanisms involve emotional and attentional information processing (Villemure et al., 2003), as well as the activity of the autonomous nervous system (Haze, Sakai, & Gozu, 2002).

Unfortunately, many of the clinical studies are of rather low methodological quality. For example, a systematic review of cancer patients found some effects of aromatherapy massage for long-term pain, anxiety, and quality of life but concluded that these did not translate into clinical benefit due to the low quality of the studies (Shin et al., 2016). In the above cited analyses, up to 50% of the screened studies were reported to be of insufficient quality regarding the key outcomes, the mode of administration, or the assessment protocols. There are additional reasons that may either benefit or harm the evaluation of aromatherapeutic interventions. One critical factor pertains to the lack of accuracy of what aromatherapy constitutes. Most importantly, there is much confusion regarding the definition of aromatherapy. Working with essential oils per se is not sufficient to make a clinical claim. In the medical context, applying them topically or even internally is actually phytotherapy. In contrast, working with volatile compounds of essential oils by inhalation is aromatherapy (Tisserand & Young, 2014). This mix-up and conceptual ambiguity even in high-ranked research papers exacerbates any objective assessment of the clinical use of essential oils. Many researchers seem at a loss or partially ignorant when testing the specific factors constituting an alleged aromatherapy. Unfortunately, this problem also pertains to studies investigating cellular mechanisms of essential oils. For example, in a study reviewing the evidence from the scientific literature regarding the underlying mechanisms of limonene for treating different diseases, the authors mistook consumption with inhalation and draw conclusions which at best should be regarded as ambiguous with regard to the functional pathways involved (Vieira, Beserra, Souza, Totti, & Rozza, 2018). Likewise, in a study discussing the phytochemical mechanisms of aromatherapeutic oils for the treatment of behavioral and psychological symptoms in patients suffering from dementia, the authors call for more rigorous research. However, this conclusion is made without providing a sound definition of what constitutes aromatherapy (Scuteri et al., 2017). Finally, in a recent systematic review and meta-analysis exploring the effects of aromatherapy on the treatment of psychological symptoms in postmenopausal women (Babakhanian et al., 2018), the authors are caught in the conceptual trap that has made aromatherapy a somewhat dubious intervention by confusing the very functional mechanisms they wish to investigate. When concluding that aromatherapy massage improves psychological symptoms, no differentiation is made whether the causative mechanism is the physical therapy (likely) or the aromatherapy (unlikely), thus adding to the confusion whether aromatherapy has clinical benefits.

From this, it becomes clear that the current knowledge of the effectiveness of essential oils in the clinical context is insufficient. Moreover, much of what passes today for aromatherapy is nothing else but setting and ambience, which at best may be regarded as an unspecific factor. Before we elaborate on this, we will briefly outline the olfactory system to demonstrate how, why, and when aromatherapy is beneficial.

2 | THE PHYSIOLOGY OF THE OLFACTORY SYSTEM

Unlike other sensory systems, scientific interest in the olfactory system has long been marginal and only recently received greater interest. This was overdue because, as mentioned above, the importance of the sense of smell is crucial for human phylogeny.

1. Olfactory receptor genes make up 3% of all genes, rendering them the largest gene family in the human genome (Boron & Boulpaep, 2012).
2. The body contains tens of millions of olfactory receptor cells which can be found in almost every organ, including the skin, the brain, the heart, and the gastrointestinal tract.
3. Not only is olfaction the oldest sense, and therefore probably the most meaningful for survival, it is also the only one that is not subjected to neuropsychological filtering processes: Olfactory stimuli are registered in the rhinencephalon, which directly relays sensory information to the amygdala without projecting to the thalamus (Masaoka & Homma, 2011).
4. The direct link to the brain operates at a transmission speed of about 200 ms and exceeds that of most other physiological senses (Khan & Sobel, 2004), and one single molecule suffices to trigger an action potential on the receptor site (Su, Menuz, & Carlson, 2009).
5. In the nasal cavity, we find not only the olfactory system but also the trigeminal system. Most odorant molecules stimulate both systems simultaneously, which has consequences for the perception of odors and the somatosensory innervations associated with them (Brand, 2006).

6. Contrary to the estimate of about 30,000 scents, humans are claimed to be capable of distinguishing at least one trillion different scents (Bushdid, Magnasco, Vosshall, & Keller, 2014), although this estimate has recently been questioned (Gerkin & Castro, 2015; Meister, 2015). Whatever the exact number of scent discrimination may be, it is obvious that the human olfactory system is quite remarkable and biologically of great importance. This is also illustrated by the fact that a large variety of olfactory receptor neurons found in the nose are organized in quite a complex way. This neuronal network contains an enormous variety of receptor proteins (G protein-coupled receptors), which are encoded by a total of over 350 genes (Fleischer, Breer, & Strotmann, 2009; Gerkin & Castro, 2015).

Obviously, human olfaction is anything but an inferior sensory organ even when compared with color vision, which is generally regarded as the most advanced human sensory organ. For many scents, the threshold of detection is in the parts-per-billion range (Devos, Patte, Roualt, Laffort, & Gemert, 1990). This accuracy of detection has been found to afford humans the ability to differentiate scents that vary only in one molecular component (Laska, Ayabe-Kanamura, Hubener, & Saito, 2000; Laska & Hubener, 2001; Laska & Teubner, 1999). The level of complexity of the olfactory system is also reflected in the way smells shape our experiences. Neurobiological research has shown that smell experience is mediated by higher order (prefrontal) processes (Gottfried, 2006). When odor molecules hit the nasal mucosa, first-order neurons conduct the odor-elicited response to the olfactory bulb. The olfactory tract, a complex structure of olfactory sensory axons joining with second-order dendrites (mitral and tufted cells) located in the olfactory sulcus of the basal forebrain, transmits the information to numerous areas within the frontal and dorsomedial lobe. Collectively, these projections make up the primary olfactory cortex. Higher order projections from each of these olfactory structures converge on the orbital prefrontal cortex, the amygdala, the hypothalamus, the basal ganglia, and the hippocampus (Haberly, 1998; Masaoka & Homma, 2011; Price, 1990). This complex of intertwined neuronal systems causes odors to act on the neuroendocrine system, neurotransmitters, and neuromodulators of various brain centers and is responsible for the modulation of perception, cognition, and behavior (Kiecolt-Glaser at al., 2009).

Taken together, and in addition to the obvious unspecific effect of aromatherapeutic odors (e.g., their pleasantness), the very physiology of olfaction is the reason why essential oils lend themselves as specific therapeutic agents. However, for aromatherapy to be effective, it must fulfill certain criteria over and above what the highly sensitive physiological capacities of olfaction can detect.

3 | AROMATHERAPY: COMMON MISCONCEPTIONS AND IMPORTANT REQUIREMENTS

The term 'aromatherapy' is rife with misconceptions, even within the realm of biochemistry (Singer & Schneider, 2016). It is commonly used as a generic term to describe the use of essential oils on the skin, for massage, or in the ambient air. An even more vague definition includes the use of essential oils added to cosmetic care products. In some countries (e.g., France), aromatherapy even includes the intake of essentials oils, making the whole concept more ambiguous. It is important to note, however, that neither the involvement of an odor nor a treatment is sufficient for the claim that an application is aromatherapeutic. A precise and narrow definition of the term defines aromatherapy as the use of scents for the purpose of provoking psychological or physiological responses. The crucial element of aromatherapy, therefore, is the functional aspect of the used scents (Buchbauer, Jirovetz, Jager, Plank, & Dietrich, 1993). Furthermore, any effect elicited by a scent must be the result of not just the scent itself but also of the method of application, which imperatively addresses the concept of molecule concentration reaching the target system. In the case of inhaled scents, air saturation is a very important factor for eliciting the response. However, this relationship is not linear such that prolonged maximum air saturation ensures maximum effects. Due to the laws of habituation the body's perception of sensory stimuli is regulated in a way as to ensure negative feedback between stimulus intensity and the response intensity. Sustained exposure to a specific odor stimulus inevitably results in the intensity of the stimulus being perceived as reduced. This physiological phenomenon has an important biological function, as it allows one to remain receptive to new stimuli. On the other hand, the intensity of the response is dependent upon the degree of neurological processing, with direct sensory processing linked to a stronger response.

Our ability to detect relatively low levels of scent does not contradict the fact that potential volatility of a scent is unimportant. To the contrary, to ensure a full effect, scents must be delivered directly and at maximum concentrations to the nose. This is one of the reasons why the empirical evidence testing aromatherapeutic interventions is noticeably varied and heterogeneous. Apart from experimental research testing specific properties of the olfactory system even below the threshold of perceptibility by highly standardized apparel such as face masks (Masaoka et al., 2013), the effects of odors are usually tested in an environment that allows generalizability of the results to natural and clinically realistic environments (e.g., the therapeutic context). Depending on the mode of application, there may be major therapeutic differences even if effective scents are administered.

In addition to the technical aspect of odor administration, there are a number of biochemical aspects that account for the effectiveness of aromatherapy.

1. One very important factor is purity of the substance. Many essential oils are diluted with cheap synthetic and semisynthetic monoterpenes (Braun & Franz, 2001; Werner, 2005).
2. Another factor is the use of single note or complex blends. Although most odors tested for aromatherapeutic purposes are single note, the therapeutic benefit may be enhanced by using complex scent compositions. This is because complex scent blends act synergistically (Lis-Balchin, Deans, & Hart, 1997), and

many of the ailments treated are associated with different symptoms, which are more likely to be more adequately treated with complex scent blends. This is also underscored by the principles of phytotherapy that exploit the combined action of a mixture of constituents in order to maximize the number of synergistic or antagonistic interactions that may exist between different phytochemicals (Efferth & Koch, 2011).

3. Although many aromatherapeutic agents are synthesized, there is empirical evidence showing that the brain differentiates between them. For example, a study measuring the brain activity of women found that real body odor samples obtained from friends and strangers were processed by different parts of the brain than their synthetic odor mix counterparts (Lundström, Boyle, Zatorre, & Jones-Gotman, 2008). More importantly, natural scents may be more effective due to their chirality. Synthetic (racemic) substances always contain mirror molecules that may have important pharmacokinetic differences (Szelenyi et al., 1998). Furthermore, the majority of synthetic scents consist of only a few molecules. Natural scents, on the other hand, are complex mixtures of up to several hundred individual substances—which explains why the overall effect of such complex scents is only rarely limited to the actions of just one or some of their components. Natural scents are preferable to synthetic ones for yet another reason. Due to manufacturing processes, many synthetic scents contain traces of contaminants or additives that may be potentially harmful.
4. Unlike pharmacologic agents, natural plant-derived raw materials are difficult to standardize because of factors that are difficult to control (e.g., population-specific taxons, climate, and chemotype variations). Biologically speaking, natural plants will produce varying levels of different essential oils to protect themselves from potential pathogens and therefore sources of raw material will always vary. It may therefore not be ruled out completely that depending on the source of the scents slightly different therapeutic outcomes may ensue.

We may therefore formulate the basic preconditions for an effective aromatherapy as follows: It must (a) involve volatile compounds of essential oils by inhalation, (b) directly and specifically target the nose, (c) in high enough molecule concentrations that are able to trigger physiological changes. In a broader sense, effective aromatherapy must (d) involve natural essential oil compounds of high phytochemical quality, and (e) be potent enough to strongly stimulate the olfactory system without causing habituation.

4 | NEW DEVELOPMENTS: THE AROMASTICK® TECHNOLOGY

Recently, a lipstick-sized nasal inhaler has been developed that delivers scents concentrated and unadulterated to the nose forcing the person to sniff for information acquisition. The sniff is the mode of action that carries messages from the environment into the olfactory system for processing (Sobel et al., 1998). In resting breathing, this is to a far lesser degree the case because only a fraction of inspired air encounters the olfactory epithelium, that is, approximately 5–10% (Keyhani, Scherer, & Mozell, 1995). Furthermore, the neurons in the nose are sensitive to air pressure and this mechanosensitivity is thought to increase the sensitivity of the nose (Mainland & Sobel, 2006; Scott, 2006; Verhagen, Wesson, Netoff, White, & Wachowiak, 2007). Thus, the AromaStick® guarantees full absorption of the scent molecules when put close to one nostril (with the other one closed with a finger) during inhalation and then repeated with the other nostril. Unlike similar devices, the inhaler consists of a wet filter held centrally, almost floating, inside the tube. This allows for the active ingredients to avoid contact with the container, which in turn guarantees a smooth flow of air around the filter. The centrally suspended filter has an additional benefit as it avoids direct contact with the PP material of the primary container, thus minimizing the risk of a chemical reaction between essential oil and material, which potentially could result in undesired vapors. Depending on the purpose of the inhaler, it contains different complex scent compositions of 100% natural essential oil ingredients. The inhaler is designed and fabricated by AromaStick Inc., Sargans, Switzerland. Quality control is done by an independent laboratory. The essential oils are purchased from reputable suppliers complete with certificates of analysis. Freshness of the oils in the finished product is guaranteed by a foil-sealed container. The odor has shown to maintain freshness for at least 24 months according to several stability tests under GLP (good laboratory practice). Once opened, an AromaStick® lasts approximately 6 months. Although not strictly invented for medical purposes, the inhalers have shown to produce large to very large effects across a variety of physiological and psychological target variables.

4.1 | Excursion

Before we introduce the body of evidence for this new method of working with scents, we will address a fundamental issue affecting empirical science as a whole and the conclusions derived from clinical testing in particular: null hypothesis significance testing (NHST). NHST has become the standard for a broad range of clinical testing. However, for more than 70 years, methodologists have warned that the use of significance tests is in many cases not only statistically and logically wrong, but potentially detrimental to the advancement of knowledge (for recent overviews, cf. Branch, 2014; Lambdin, 2012). In fact, contrary to the belief of most researchers, there is no empirical evidence supporting the application of NHST (Armstrong, 2007). Although major steps have been undertaken in the last decades to improve the quality of clinical research, for example, by issuing guidelines such as CONSORT (Moher, Altman, Schulz, Simera, & Wager, 2014), it is surprising that the fundamental problems of NHST are seldom addressed. We will briefly discuss some of the fundamental problems of NHST to illustrate how precarious and misleading the use of significance tests is, whose use in psychology has been dubbed the "dirty little secret."

1. Significant results do not tell anything about the relevance of the underlying effect. Also, they are not comparable across different studies. Many so called "highly significant" results are only of small clinical importance when expressed in terms of the actual size of the effects (Ioannidis, 2005; Lykken, 1968).
2. Any null hypothesis can easily be rejected with sufficiently large or homogenous samples, and statistical tests can arbitrarily be rendered significant regardless of the meaningfulness of the relationship investigated.
3. Many statistical assumptions associated with NHST are misconceived (Hubbard, 2004; Hubbard & Armstrong, 2006; Schmidt & Hunter, 1997; Thompson, 1999). One such fundamental error is the combination of Fisher's evidential statistic (*p* value) and Neyman–Pearson's error estimate (α). Despite common misconceptions, they are not in any meaningful way associated when stating that $p < \alpha$.
4. This causes the illogic that accompanies NHST: To believe that if a set of data is unlikely to occur if the null hypothesis is assumed, one can conclude that it is probably wrong. In other words, when the probability of α is smaller than the criterion applied, chance is deemed unlikely to have produced the result, or formally put: P (Data|H0) → P(H0|Data). Yet both conditional probabilities are unrelated and, in fact, distinct from each other and cannot be reversed (Gigerenzer, Gaissmeyer, Kurz-Milcke, Schwartz, & Woloshin, 2008; Kalinowski, Fidler, & Cumming, 2008).
5. It is rather sobering that many statistical experts and academics are not able to give a correct definition of a so called significant result (Haller & Krauss, 2002; Thompson, 1999).

To circumvent these problems, methodologists advise to focus on effect sizes and confidence intervals because they are far more indicative of the importance of clinical results. Additionally, effect sizes are directly comparable because they are standardized. Fortunately, more and more scientific journals are open to this idea and editors especially of novel journals start questioning the logic of NHST.

5 | EMPIRICAL EVIDENCE FOR THE AROMASTICK® TECHNOLOGY

In the following, the results of a series of different studies involving a total of 465 participants are reported, which aimed at testing the AromaStick®. As outlined in Table 1, the analyses were solely based on the effect size d (Cohen, 2008) and their respective confidence intervals (95%; Borenstein, Hedges, Higgins, & Rothstein, 2009). An overview of the main percentage changes is depicted in Figure 1.

As can be seen, the effects observed were large to very large according to the commonly proposed criteria (Cohen, 2008; Hattie, 2009). In fact, given that the average effect size in most fields is estimated at $d < 0.8$ (Sedlmeier & Gigerenzer, 1989), corresponding to a mean difference of less than a standard deviation, the observed effects are quite remarkable. In accordance with the rule of thumb that a relevant effect should be visible to the naked eye (Cohen, 1992; Edwards, Lindman, & Savage, 1963), we may conclude that this mode of aromatherapy produces changes that are far from clinically meaningless. To the contrary, they attest to the workings of the olfactory system outlined above and the presumption made that the mode of application and molecule saturation of the inhaled air is indeed one of the deciding factors for aromatherapy to be effective.

To put the observed effects in perspective, it is helpful to elaborate on their meaning. For instance, with a Cohen's *d* of 1.5, 93% of the AromaStick® users were above the mean of the control group. In principle, this means that if 100 people go through the AromaStick® treatment, 54.5 more people have a favorable outcome compared with receiving the control treatment. A *d* of 2.8 means that 100% of the AromaStick® treatment group was above the mean of the control group, and there is a 98% chance that a person picked at random from the treatment group had a higher score than a person randomly chosen from the control group (probability of superiority). If 100 people went through the inhaler treatment, 77.5 more people would have a favorable outcome compared with the control treatment. From these examples it becomes clear that treatment with the AromaStick® benefitted a vast majority of its users.

One of the striking observations across the studies is the fact that only a few inhalations sufficed to affect the target systems tested. Equally interesting was the magnitude of the effects. For instance, the reduction of systolic and diastolic blood pressure and heart rate (Schneider, 2016a) proved that the inhalers effectively reduced the activity of the sympathetic nervous system. In fact, they did so even to an extent that was reminiscent of the effects of antihypertensive drugs. That this also showed in individuals who were not under particular stress (Study 4) points to the inhalers' general potency and is in alignment with the fact that very stable and closely regulated systems like blood oxygenation can even be "optimized" over and above normal physiological functioning (Schneider, 2017a). In fact, the direct supply of odor molecules to the nose not only increases the oxygenation effect of deep breathing by a factor of 2.5 but also keeps it at a higher level three times longer.

Where tested, all participants reported improvement in mood and well-being. This was no doubt in part due to the odors' pleasantness but mostly constituted a specific effect of the active profiles of the inhalers. Research has shown that pleasant odors induce mood improvement and decrease pain unpleasantness when pain intensity is attended to. In contrast, paying attention to the intensity of odorous stimuli during pain stimulation decreases pain intensity perception and pain-evoked brain activity (Villemure et al., 2003). Thus, the odor molecules delivered by the AromaStick® inhalers may work in two different ways. In the pain studies (Schneider, 2017b), the individuals suffered from chronic or recurrent pain. Chronic pain patients have shown to suffer extensive alterations in the neurologic pain matrix (Apkarian et al., 2014; Baliki, Geha, Fields, & Apkarian, 2010). Both activity and connections of important pain-processing brain regions may be (permanently) altered, which often causes marked changes in behavior (e.g., increase in anxiety and/or decrease in reward learning, dysfunctional coping with pain). These patients may have a decreased threshold for pain signals, which enhances physiological and psychological reactions associated with discrepant bodily processes (Bendelow & Williams, 2008; Simons, Elman, & Borsook, 2014). They also tend to perceive pain relief or pain reductions as less rewarding (Campbell & Edwards, 2009). Although parameters of pain dynamics in these individuals are much more resistant and less variable,

TABLE 1 Overview of main effects across different AromaStick® studies

Reference	Type of study	Sample	Target variable	ES/CI[a]	Difference[b]	Intervention
Schneider, 2016a (Study 1)[c]	Experimental	Highly stressed individuals	SBP	1.5 0.7 < *d* < 2.3	−12 mmHg	3 Inhalations short-term intervention
			DBP	1.3 0.4 < *d* < 2.2	−8 mmHg	
Schneider, 2016a (Study 2)[c]	Experimental	Highly stressed individuals	SBP	2.5 1.5 < *d* < 3.4	−15 mmHg	
			DBP	1.0 0.4 < *d* < 1.7	−7 mmHg	
			HR	1.1 0.4 < *d* < 1.7	−7 bpm	
			Cortisol	0.8 0.1 < *d* < 1.6	−0.05 µg/dl	
Schneider, 2016a (Study 3)[c]	Experimental	Highly stressed individuals	SBP	1.2 0.4 < *d* < 2.0	−17 mmHg	
			DBP	0.8 0.3 < *d* < 1.5	−7 mmHg	
			HR	1.2 0.4 < *d* < 2.0	−7 bpm	
Schneider, 2016a (Study 4)[c]	Experimental	Healthy individuals	SBP	2.3 1.5 < *d* < 3.1	−16 mmHg	
			DBP	2.4 1.6 < *d* < 3.2	−11 mmHg	
			HR	1.9 1.2 < *d* < 2.7	−11 bpm	
Schneider, 2016a (Study 5)[c]	Field	Borderline hypertensives (responders)	SBP	3.1 1.9 < *d* < 4.3	−10 mmHg	30 months every 2–3 hr daily
			DBP	0.9 0.1 < *d* < 1.8	−6 mmHg	
Schneider, 2016b	Experimental	Healthy individuals	Concentration	1.3 0.5 < *d* < 2.2		One inhalation before each testing block (eight total) ca. 10 min
			Scanning speed	1.0 0.3 < *d* < 1.7	+29% total cognitive performance	
			Accuracy	0.8 0.1 < *d* < 1.5		
Schneider, 2017a	Experimental	Healthy individuals	Blood oxygen saturation (SpO_2)	2.0 1.5 < *d* < 2.5	+1.6% absolute +40% relative	3 breathing cycles short-term intervention
Schneider, 2017b (Study 1)[d]	Field	Women with menstrual pain	Onset of pain relief	0.6 0.1 < *d* < 1.1	−17 min	During menses for 1 hr
			Pain duration	0.6 0.1 < *d* < 1.1	−88 min	
Schneider, 2017b (Study 2)[d]	Field	Chronic back pain individuals	Pain intensity at relief onset	2.6 1.6 < *d* < 3.6	From strong to low	On pain days for 1 hr
			Pain intensity after 3 hrs	3.7 2.4 < *d* < 5.0	From strong to very low	
Schneider, in press	Field	Individuals suffering from Seasonal Rhinitis	Overall nasal symptom relief	2.0 1.2 < *d* < 2.8	From moderate to little	14 days a minimum of eight times daily
			Individual nasal symptom relief	2.8 1.9 < *d* < 3.7	From very much to moderate	

[a]Effect sizes/confidence intervals (rounded values).

[b]Differences were calculated in comparison with baseline measures or controls depending of the type of study.

[c]These studies explored different inhalers and different stress reduction interventions which are not reported here.

[d]Aromatherapy given as adjuvant (add-on).

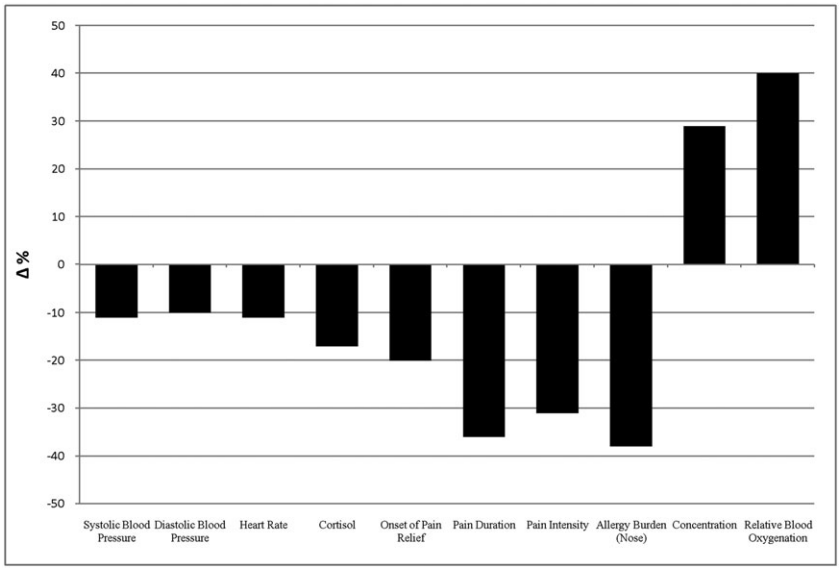

FIGURE 1 Overview of some of the physiological changes caused by different AromaStick® inhalers; improvements are depicted for the main effects reported in Table 1. Cardiovascular parameters (blood pressure and heart rate) were averaged for Studies 1–4 in Schneider (2016a)

the odor inhaler was nonetheless able to not only reduce pain intensity but also to greatly improve time pain dynamics like pain duration.

Another observation was that the AromaStick® improved symptom burden even in persons who had been suffering from the respective medical condition for many years and who had been resorting to conventional treatment for quite some time with moderate to little success. In fact, most of them had come to terms with the fact they would live in pain, have to be on medication to treat their blood pressure, continue to suffer from seasonal rhinitis if not treated with antihistamines, or have a hard time to find stress relief. As with every new treatment, one cannot rule out that the effects observed may have been due to its novelty character. However, many participants had rather low expectancies that the inhaler would bring them relief. Hence, psychological factors did not play that much of a role (Schneider, 2012; Schneider & Kuhl, 2012) and, in fact, could be totally discarded when accounted for (Schneider, 2017a, 2017b; Schneider, in press).

Together, these findings support the notion that, for aromatherapy to be clinically effective, the act of smelling as such is as important as the quality and specificity of the odor molecules absorbed. As mentioned above, regular breathing only results in 5–10% of the inhaled air reaching the olfactory epithelium in the nose. A special mode of sniffing is required to direct airflow to the olfactory receptors at rates over and above that rate if physiologically significant effects are to be caused by essential oils. With the AromaStick® the primary focus for olfactory processing is enhanced. As a consequence, the potentially beneficial effects of essential oil components are potentiated causing distinct physiological changes.

There are a number of important inferences that can be drawn from these findings.

1. The effects of the inhalers are specific and not due to unspecific factors like expectation or pleasantness of the odors.
2. They target different physiological systems (blood oxygenation, cardiovascular parameters, adrenal parameters, pain perception, respiratory function, and brain faculties).
3. These effects are only produced when delivered directly to the nose and not when diffused in the ambient air (which is the case for almost all ordinary inhalation interventions). They are fast-acting and observable after only a few inhalations.
4. The inhalers outperform other interventions intended to alter physiological processes (such as passive resting, progressive muscle relaxation, placebo, or Bach flowers), enhance normal bodily and cognitive functions (e.g., breathing and concentration), and increase effective measures as adjuvant (e.g., pain).
5. They have very little to no side effects and are tolerated by nearly all users.
6. The AromaStick® is suitable for self-treatment, portable, and therefore can be used anywhere and anytime.
7. Depending on the condition treated, users may vary in the degree to which they respond to the inhalers. Obviously, as with any pharmacologic agents, there are degrees of responsiveness due to both the pharmacokinetics of odors (i.e., what the body does to them) and their pharmacodynamics (i.e., what they do to the body). Consequently, effects may be the highest in responders, which was the case, for example, in Study 5 of Schneider (2016a) and in the study by Schneider (in press).

6 | LIMITATIONS

Despite the findings of this new delivery method, there are a number of unanswered questions that will be described briefly.

1. Due to the nature of the intervention, the exact dose of the inhaled air cannot be standardized. This, however, applies to all inhalation aromatherapies even when air diffusion is standardized. Designed primarily for individual or personal application, users may need to find the mode that delivers the best results. On the other hand, a small person with a smaller lung volume will absorb fewer molecules in one sniff than a larger person. Unlike for standardized drugs (e.g., pain killers), the very act of sniffing is very idiosyncratic and therefore physiologically adaptive.

2. The reported studies mainly investigated whether the inhalers produce relevant specific effects. They did not investigate underlying mechanisms of how the effects were determined (e.g., neurobiologically and biochemically). Nonetheless, the effects were noticeable for most users in those instances when there was a relief of burden (e.g., stress or pain relief), and in that regard, subjective experience is at least as important as objective changes in medical parameters.
3. Some of the studies investigated symptomatology over an extended period, but the jury is out as to how long the observed effects actually last. In some medical conditions, the use of the device may be prolonged as long as the burden exists (e.g., allergy or hypertension). In some, it may be discontinued after the burden has abated to a tolerable level (e.g., stress or pain).
4. Closely related to this point is the issue that therapy success can only be achieved by applying the inhaler regularly and, in some cases, many times a day. This is due to the fact that technically only a limited amount of volatile scent molecules can be applied per administration. In some field studies, participants decided themselves to use the inhaler more often than required by the study protocol. In turn, this also means that therapy success is dependent on the user's discipline. Unlike drugs to be taken once or twice a day and thus not requiring much diligence, the administration of the inhaler may be too cumbersome a treatment for some patients.
5. The degree to which the AromaStick® inhaler may lend itself as an adjuvant should be addressed in more detail in future studies. AromaStick® inhalers may not outperform pharmacologic agents (e.g., pain killers), but they may assist in complementing them such that the overall treatment effect is enhanced. This could potentially even reduce the amount of pharmacologic intake, thus reducing their side effects.
6. Likewise, there might be differences with regard to acute and chronic ailments. It would be desirable to test the odor inhaler against additional forms of active treatment in clinical settings with different boundary conditions.
7. The findings were not derived from a clinical setting or a medical context, and therefore, the results may be biased. However, the fact that the effects were large and replicable across a broad class of conditions shows that the inhalers work.

7 | SUMMARY AND DISCUSSION

The herein reported findings across a wide range of physiological systems show that the inhalation of volatile compounds from essential oils yields almost immediate, large, and clinically relevant effects as long as the scents are delivered highly concentrated from an appropriate device. When sniffed in this manner, the volatile compounds of essential oils have true aromatherapeutic capacities in the sense of specific agents. Also, this form of application is noninvasive and less likely to be corrupted by sensory habituation. The changes caused in the body seem side effect-free and can be sustained when inhalation is repeated. Although unspecific effects like odor pleasantness may contribute to the inhalers' overall effect, in the sense that they enhance adherence, they are of only secondary importance. The AromaStick® is potentially suited as a stand-alone measure to address everyday challenges or as an adjunct to medical treatments. The presented studies call for replication and further studies.

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All authors have contributed substantially to this work. R. S. designed and conducted the original AromaStick® studies and wrote the manuscript. N. S. and T. S. studied the essential oils and the olfactory system, developed the AromaStick® idea, composed the odor mixtures, and helped outline the manuscript with arguments beyond the actual research.

CONFLICT OF INTEREST

The studies reported were funded by the company manufacturing the inhaler (AromaStick®), and therefore, in principal, the principal investigator R. S. could have been biased with regard to the outcomes. To make sure that this was not the case, R. S. did not interfere with the actual treatments and had no contact with the participants. Instead, independent and, depending on the type of study, blinded experimenters ran the studies. Also, all collected data were initially blinded as to the group allocations and only unblinded after the analyses were performed. Last, the study was run under the recorded stipulation that they be published independent of the outcome.

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