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REVIEW ARTICLE

A Review of the Digestive, Respiratory and Nocioceptive Benefits, Associated Performance Outcomes and Clinical Considerations following Mint and Menthol application

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ABSTRACT
Mint and to a lesser extent menthol have been used since antiquity for medicinal purposes. Key components of mint and menthol use such as composition and intake, safety and traditional uses are discussed prior to a review of clinical and human performance outcomes in the areas of digestive and respiratory health; antibacterial and anti-fungal properties, nocioception, migraine and headache and emerging evidence regarding COVID 19. Evidence suggests benefit for patients with irritable bowel syndrome and related digestive issues, with analgesic and respiratory effects also noted. Perceptual characteristics relating to thermal comfort and sensation, taste sensitivity and alertness are also considered; these effects are predominantly driven by stimulation of transient receptor potential melastatin 8 (TRPM8) activity resulting in sensations of cooling and freshness, with lesser influence on thirst. Finally, sport performance is considered as a domain that may further elucidate some of the aforementioned underpinning outcomes due to its systemic and dynamic nature, especially when performed in hot environmental conditions.

Keywords: Mint; Menthol; Digestion; Respiration; COVID-19; Sport; Pain

Introduction

Peppermint is a naturally occurring hybrid of water mint and spearmint. Peppermint use is evident across a wide range of ancient cultures, spanning from Iceland to China, via ancient Egypt[1], mainly for culinary and medicinal purposes. Peppermint has traditionally been used to alleviate gastro-intestinal (GI) symptoms, the proposed mechanisms for which are discussed later in this review. Other traditional uses of peppermint include but are not limited to: calmative, anti-tussive, anti-bacterial/fungal, pain reduction, and treatments for headache, migraine or menstrual symptoms[1,2]. Menthol is a derivative of peppermint and is either extracted as an oil, then frozen and filtered to produce crystals, or synthesised. Of the eight isomers of menthol, the one that occurs naturally and is most commonly consumed is (-)-Menthol. Other arrangements present with lower or no perceptible intensity of freshness[3]. Academic literature dating to 1890 espouses the benefits of menthol for respiratory infections[4] and cooling via stimulation of thermoreceptors was first noted in 1896[5]. These subjective abilities to impart sensations of cooling and alleviate nasal congestion are excellently reviewed by Ronald Eccles, who summarises menthol's cooling characteristics and associated psychophysiological responses[6,7,8].

Both peppermint and menthol stimulate transient receptor potential melastatin 8 (TRPM8) receptors. These are voltage gated ion channels embedded within cell membranes and are especially prevalent in the dorsal and trigeminal ganglia[9,10]; but are also found in the upper gut, vascular smooth musculature, bladder and male genitalia[11]. Upon stimulation, through either a fall in temperature to < 26 °C or application of menthol or eucalyptol, there is a depolarisation and the electric potential of the membrane is altered due to a flux in Ca^{2+} and Na^{+} ions, and subsequent generation of an action potential[12,13]. If a menthol containing stimulus is applied at a sufficient concentration/intensity, either orally or topically, behavioural, physiological and sensation modifications may occur. Bautista and colleagues[11] elegantly demonstrated that in TRPM8 knock-out mice there is a loss of cold and menthol sensitivity down to a temperature of 10°C[11] and in doing so elucidated TRMP8's role as the primary detector of environmental cold. It is also noteworthy that menthol stimulates in a manner that is inversely proportional to the thickness of the stratum corneum in the area to which it is applied[14]. This explains the use of the tongue as a tissue of interest in most animal research concerning the absorption and resultant excitation of nerve fibres following menthol application, and the less potent effects observed when menthol is applied topically, especially at low-moderate concentrations.

The form of menthol and peppermint administration warrants practicable and pharmacological consideration too. Liquids are likely the most easily administered and transported, but the potential for menthol to attenuate thirst[7,15,16] suggests this may not always be the best option. Ice slurries or blocks present an appealing combination of physical and perceptual coolants. A hydrogel or gum allows for a small dose of carbohydrate to be mentholated and easily consumed, with greater control over the dose and concentration of menthol compared to other forms and thus has been used as a mode of drug administration[17]; although it should be noted that menthol itself may enhance transdermal drug delivery due to its penetrating effects[18]. Modes of administration alter pharmaco-kinetic effects, both with respect to plasma and salivary concentration and urinary excretion rates[20,17]. Encapsulated menthol elicits approximately nine-fold higher plasma concentrations and eight-fold greater urinary excretion rates than peppermint candy or tea[20], when areas under the curve (AUC) and excretion (mg) are expressed as ratios. Importantly, peppermint containing products also demonstrate a greater coefficient of variation in plasma elimination and AUC, compared to menthol capsules, indicating that if we are to consider therapeutic applications of these substances, whilst perhaps being viewed as more natural by patients, whole peppermint products may elicit less consistent and thus potentially non-therapeutic responses compared to menthol application/ingestion.

Despite being ubiquitously consumed and available in an array of applications, peppermint/menthol can impart systemic toxic effects. This has been demonstrated in animal models and in humans, either when consuming menthol or in its preparation. The first documented case of menthol poisoning noted a cooling sensation from the blood[21,22]. Further case studies reveal coma inducement when ingested as peppermint oil[23] and excessive consumption of cough lozenges[24]. Similarly, acute lung injury and oedema can occur when peppermint oil is administered intravenously[25]. The mechanisms underpinning toxicity appear to be hepatotoxicity[26] or nephrotoxicity[27]. Toxicity may still prove fatal when exposure is indirect and of a limited duration i.e. inhalation of peppermint fumes for ~60 min[28]. It should be noted that serious or fatal cases used doses beyond the recognised upper tolerable limit and in environments that may have also facilitated

a negative outcome e.g. poorly ventilated. Safe doses are related to the form of administration; liquids containing doses of 0.1 – 0.5 $g.L^{-1}$, sprays of 0.8% and topical gels of 8% have been safely administered [29,30,31]. Importantly, menthol may confer heat storage responses when applied topically in high concentrations due to vasoconstrictive effects; likewise menthol or peppermint applications are not intended to replace physiological cooling where exposure to high environmental temperatures or presence of high core body temperature are apparent[32].

In the following sub-sections, the effects of oral or topical application of menthol or peppermint are reviewed as they relate to the digestive, respiratory and nocioceptive systems. Potential implications for targeted use of mint/menthol following COVID-1 infection are also discussed, given its importance and relevance to the present clinical zeitgeist. Wider applications stemming from the outlined underpinning mechanisms are also presented, for those clinicians interested in application beyond clinical settings.

Potential Health Benefits

Digestive health

Peppermint is commonly used to treat gastrointestinal symptoms, and has been shown to be particularly effective in the alleviation of irritable bowel syndrome (IBS) symptoms[33,34,35]. IBS symptoms may improve within two weeks; children reported feeling 'better' or 'much better' (71% of population) and remaining participants reporting no difference[35] when compared to placebo. Similarly, in their meta-analysis Ford *et al.,*[34] report a pooled relative risk of IBS symptoms of 0.43 (95% CI: 0.32 to 0.59) compared to placebo interventions. Importantly, this review notes only five adverse reactions from 174 participants who received peppermint oil. A more recent review by Alanmar *et al.,*[33] also notes minimal adverse events, that adverse events are typically mild and transitory, and that evidence is generally considered of high quality indicating that we can apply these findings with clinical confidence.

To a lesser extent supplementation has also been shown to reduce nausea[36,37], colonic tension[38], and flatulence[35]. Peppermint may also improve the rate of gastric emptying[39]. These findings suggest that the administration of peppermint oil, or its derivative menthol, may have potential therapeutic benefits for those that suffer with gastrointestinal issues[40]. The mechanism of action is a relaxation of smooth musculature within the GI tract, brought about by antagonism of Ca^{2+} channels following peppermint exposure, which induces a transient blockade, alleviating symptomology.

Respiratory health

Similar to the digestive tract mentioned above, menthol and peppermint also act as smooth muscle relaxants when applied to the respiratory system. Within the upper respiratory tract, application via aspiration, inhalation or ingestion results in sensations of increased nasal patency but this has not been shown to be objectively altered[41,42,43]. A related sensation is the decrease in the drive to breathe (i.e. 'air hunger') following menthol application to the upper respiratory tract[7,44]. This mirrors effects seen with the application of cold-air to target nasal cold receptors, indicating a use in those suffering with clinical conditions associated with dyspnoea[45,46]. Effective doses are as low as 11mg of menthol, administered via a lozenge[42,47]. The lozenge targets multiple mechanisms and sites of action. Initially, by stimulating the major palatine nerve, which is hypothesised to have an independent role in nasal sensation of airflow[48]; then as a vapour, acting upon cold receptors within the nasal cavity that are served via the trigeminal nerve[44,49], and finally providing localised relief due to smooth muscle relaxation.

By the same mechanism, menthol vapour application may exert antitussive effects in the lower respiratory tract[50,51]. Whilst these effects modulate the cough response lower down the respiratory tract, the mechanism of action appears to be related to TRPM8 containing trigeminal ganglia, as opposed to localised tissues[51,52]. Relatedly, these effects are not seen with either +(–) menthol (inactive isomer) or by icilin, which also targets TRPM8 and TRPA1 receptors[53,54,55]. TRPA1 channels are susceptible to causing airway irritation if higher concentrations of menthol are administered[50]. A further potentially adverse effect of menthol is that it increases mucus production, but also minimises mucus clearance due to ciliary movement reductions[50]. In clinical populations suffering from conditions that are associated with coughing e.g. COPD[56,57,58], this may be problematic as menthol may provide respiratory relief, but further impair mucus clearance[50]. Due to the mechanisms listed above, menthol and peppermint application also increase ventilation ($\dot{V}E$; $L{\cdot}min^{-1}$) during exercise[59] and have the potential to confer further beneficial effects during physical activity, too. These are discussed subsequently in sub-sections pertaining to thermal comfort and sensation, and sports performance.

Nociception, Migraine and Headache

Pain is considered the interpretation of a nocioceptive stimulus that has the potential to cause actual or perceived tissue damage, or the perception thereof[60]. Given the likelihood of temperature extremes to inflict tissue damage (cold: frost-bite; heat: burns) and the tendency of evolutionary pressure to produce economical outcomes, pathways associated with pain are also involved in temperature detection and may propagate appropriate behavioural outcomes[61,60]. More specifically, noxious temperature stimuli are detected by lamina 1 neurons which in turn stimulate the parabrachial nucleus. From here, signals are diverted via the hypothalamus to efferent pathways or continue for further processing to one or more of the anterior cingulate, anterior insula and interoceptive cortices[62]. The interoceptive cortex appears to be unique to primates, and is stimulated in a graded manner by noxious, temperature, exercise and respiratory stimuli, as well as hunger and thirst[63,62]. Due to the shared higher-level pathways of these homeostatic stimuli, an afferent to one pathway may confer wider systemic effects e.g. peppermint or menthol.

Topically applied menthol or peppermint have noted analgesic effects, especially when applied following purposefully induced tissue damage e.g. resistance exercise[64,65,66] or in clinical scenarios such as arthritis or neuropathy related pain[67,68]. Menthol application (4% cream) may improve muscular recovery (quantified via vertical jump performance; +1-5cm in comparison to placebo or control cream) when applied post-muscle-damage[64]. In this context is unclear whether menthol facilitates enhanced tissue capabilities, motivational factors, motor unit recruitment, or factors not otherwise stated[64]. The combination of chemical and mechanical stimuli, such as that outlined above, may induce afferent signalling via indirect neuronal pathways, as keratinocytes have been shown to affect local nerve endings either by calcium or adenonsine triphosphate release and subsequent signalling[69,10,52]. Further beneficial mechanisms associated with a reduction in pain may be decreases in arterial blood flow and vasoconstriction of peripherical blood vessels[65,66]; the latter may lead to a reduction in local skin temperature dependent upon the measurement approach used and the concentration applied, but this is not a true reduction in temperature per se, more an alteration in local blood flow that happens to alter local temperature acutely[70].

It is important to note that the effects of peppermint and menthol are not proportional to their concentration for the purposes of pain relief or underpinning mechanisms. The optimal concentration of topical applicants for pain reduction appears to be circa 4%, with higher concentrations capable of inducing pain and a localised heat storage response [70,64,30,65,66]. These factors are particularly important when considering potential application to migraine. Migraine is thought to have a genetic component that may be expressed in part via TRPM8 receptors[71]. These receptors are densely distributed throughout the trigeminal region, so there is an opportunity for menthol/peppermint application to this region to either combat or induce migraine dependent upon the concentration and frequency of application[37]. Another noxious effect is the onset of trigeminal-palatine ganglioneuralgia, otherwise known as 'brainfreeze', upon consumption of considerable volumes of cold substances (with or without peppermint/menthol[73,72]. Given the importance of the trigeminal network in detecting a range of stimuli, menthol and peppermint's abilities to exert effects upon it and the susceptibility of cranial nerves to impairment as a result of COVID-19 infection[74], investigation into the effects of menthol and peppermint administration in COVID-19 affected individuals warrants consideration, and would be a natural extension upon much of the work mentioned above.

Implications for mint and menthol administration relating to COVID-19

Coronavirus 2019 (COVID-19) has been consistently demonstrated to adversely affect a range of systems, beyond the obvious severe respiratory involvement, potentially for a prolonged period of time exceeding that of acute infection [75,76,77]. This continuation of symptoms or impairment relative to normal function is deemed long-COVID. The neural system, and the cranial nerves in particular appear to have consistent involvement in symptoms related to COVID-19[74]. Most pertinent to this review are an impairment of individuals' senses of taste and or smell [78,79,80] and loss of sensitivity to TRP channel agonists such as menthol (TRPM-8) and capsaicin (TRP-V1), which may occur in both hyposmic and anosmic individuals [81,82]. This is primarily facilitated by infection of the olfactory epithelia support cells and subsequent damage to olfactory neurons [74,83,80]. Preliminary. evidence has also suggested that the alpha variant may lead to loss of brain mass (0.2% - 2%) in areas associated with olfaction relative to non-infected controls[84]. Likewise, a case study reported the only symptom of COVID-19 being trigeminal neuralgia[85]. The above indicate a mechanistic impairment to olfaction, facilitated by infection of

neural structures, as a result of COVID-19. The time course of recovery is unclear. However, the location and severity of infection suggest there is a potential role to use mint and or menthol as targeted recovery tools, through smell training or similar rehabilitation processes, to assess and accelerate recovery of olfaction following infection with COVID-19, provided they are administered safely.

Similar effects are also seen acutely following upper respiratory tract infection[44], and may be important in chronicling recovery following COVID-19 infection, by using return of taste and TRP afferent sensitivity post-infection[86]. The implications regarding long COVID are currently unclear, but some participants in related trials have reported prolonged impairment of olfactory sensitivity. Polymorphisms in bitter taste receptors have also been considered with respect to COVID mortality, due to their extra-oral links with mucosal immunity[87]. However, these suggestions have not been investigated sufficiently and one research group has used this mechanism to suggest vaccine scepticism[87]. Whilst menthol or peppermint sensitivity may be indicative of infection and subsequent recovery in those with low to mild degrees of infection, this system is also affected/impaired by age[88,89] and may show genetic differences[74,90] as per thermal perception; thus, clinicians are encouraged to consider taste and related chemosensory sensitivity of secondary importance in those with moderate to severe COVID-19 infection.

By way of completeness, it is important to acknowledge that there appears to be differing effects of COVID-19 in those with spinal cord injury[91]. Individuals with spinal cord injuries display non-normal thermoregulatory presentation, typically experiencing poikilothermia (resting core temperature ~35.7 °C) and impairment to other thermoregulatory mechanisms[91], proportional to the level of injury. These reasons when combined with mint and menthol's ability to impact thermoregulatory responses via stimulation of TRPM-8 and wider neurological effects suggest application of (topical) menthol in COVID-19 symptomatic individuals with spinal cord injury may interfere with desirable health outcomes.

Downstream Performance Outcomes

The following sub-sections outline the potential downstream performance outcomes of peppermint or menthol administration. These effects may be considered by clinicians as global manifestations of menthol/peppermint induced alterations in one or more of the above reviewed physiological systems.

Alertness

There is a small body of literature assessing peppermint and menthol's ability to affect alertness. Delivery modes have varied from vapour (as previously outlined under Respiratory health) to chewing gum[3,5,99,115,129]. Both peppermint and menthol odours affects upon reaction time and cognitive tasks have been researched [5,58,91,99,107,138], but these effects appear to diminish under repeated trials as does the perceived qualitative characteristics of these odours. This indicates a potentially rapid habituation to menthol containing stimuli, or that a sufficient interval is required to observe repeatable effects[16]. Similarly, chewing peppermint/menthol gum improves alertness in healthy participants and upper respiratory tract infection patients (URTI[129]), but again there is an habituation to the hedonic component of this exposure. Nasal symptoms are also reduced as a result of chewing gum, suggesting that either menthol (at the dose in chewing gum) or chewing, or the combination thereof, sufficiently stimulates the trigeminal nerve, which is impaired by URTI [44,129]. When menthol has been administered as a mouth rinse in military personnel performing cognitive tasks in the heat[3] increases in brain metabolism, expressed as alterations in oxygenated ($p = 0.024$) and deoxygenated ($p = 0.17$) haemoglobin, were observed. Despite these alterations in brain metabolism, cognitive decline did not accompany participants' elevated core temperature, thus the practical implications from these findings remain unclear[3].

Thermal comfort and sensation modification

Menthol has been adopted as a perceptual cooling strategy to attenuate symptoms associated with exercising and task performance in the heat, as assessed by thermal comfort and sensation[32,92]. As per the other beneficial effects, the degree of perceptual change is driven by the concentration of the product applied and the thermo-sensitivity of the location(s) to which it is applied[14,31]. Larger effects are typically seen at sites with the highest density of receptors (e.g. face[30]) and are inversely proportional to stratum corneum thickness[14,31]. There is documented genetic variation in the allele that codes for the TRPM-8 receptor[47,90,93]; the extent of which is sufficient to be described by latitude and local temperature, with 88% of Finnish population thought to possess the upstream single nucleotide polymorphism, rs10166942[93]. Clinicians should be aware of this not just for the purposes of thermal perception, but because a related allele may be protective to migraine [47,90,93], further highlighting

the potential systemic therapeutic application of menthol/peppermint.

Of further interest to clinicians are the decreased sensitivity of TRPM-8 receptors across the lifespan and potential sex differences in response to stimuli. Menthol and peppermint containing compounds will likely display less efficacy in geriatric populations[94,95]. This has been documented by Waldock and colleagues[95], who demonstrated no perceptual differences compared to control when menthol was applied during daily living tasks at temperatures representative of British Summer (35°C, 50% humidity). This population was responsive to physiological cooling, but may not always feel sufficient perceptual thermal change to apply such strategies. These findings are of concern as the elderly are considered a vulnerable population with regard to global warming induced heat illness[96,97,98] due to a combination of health conditions, impaired sweat responses and medication use impairing heat resilience [96,98]. With respect to sex differences, Parton et al.,[99] noted that thermal sensation was lowered in male and female participants but this reduction only lasted 40% of the trial duration in females, during self-paced exercise; this had behavioural effects with respect to exercise pacing too. Gavel and colleagues[100] similarly found that females may experience non-perceptually mediated enhancements in performance during a cycling time trial.

Habituation of thermal sensation has been observed when a moderate menthol concentration of 0.2% was applied topically over the course of a week[101]. This habituation response was attributed to a pathway specific to thermal sensation, as it occurred independent of other physiological or perceptual responses[101]. Similarly, habituation to sweet stimuli have been reported[102], and was attributed to gustative habituation to sweet taste, as opposed to a reduction in pleasure derived from exposure to sweet stimuli, although this response is yet to be observed in oral menthol or peppermint application. This response is absent in an acute menthol stimulus, but given habituation to topical application, it is reasonable to suggest that oral cold receptors can also become habituated to menthol or peppermint stimuli, at appropriate concentrations through a similarly mediated or trigeminal pathway.

Clinicians may be reluctant to employ menthol as an adjunct treatment when symptoms such as dehydration or elevated core temperature are also observed[32,103]. In severe cases of heat illness, menthol or peppermint application is not recommended. However, in mild cases of heat stress or heat exertion, combining menthol with physiological cooling strategies that directly reduce core temperature and or improve hydration status e.g. ice slurry ingestion, may attenuate thermal sensation and encourage consistent cooling behaviours due to menthol/peppermint's hedonic qualities.

In occupational settings, menthol has been shown to positively influence thermal perception during simulated firefighting, but may lead to earlier increases in core temperature elevation[29], and unfavourable increases in oxygen consumption[104]. Similar to firefighters and military personnel and of relevance to current and future pandemic protocols, access to cooling strategies reduces heat strain symptoms in healthcare workers, when wearing appropriate personal protective equipment[105,106,107]. To date menthol has not been considered in these settings but may be an appropriate adjunct strategy, provided the task duration does not confer a significant hyperthermic risk in and of itself. In this instance improved thermal comfort and reduced sensation may lead to better task outcomes, which may prove critical. The importance of alterations in thermal perception for sports performance are discussed below.

Exercise performance

As per the above subsections, menthol can be applied before, during or post-sport or exercise performance as either a topical (gel, spray) or oral (mouth-rinse) agent. The timing and mode of administration likely depend upon the activity in question, this also allows clinicians and sport and exercise scientists to better understand the potential health benefits listed above, as exercise/ sport amplifies many of the metabolic constraints or effects that may be clinically relevant. This is particularly true for respiration, nociception and thermal perception.

Before or during endurance exercise, topical application of menthol has consistently been shown to improve subjective thermal sensations[101,108-111] with accompanying increases in sweat rate, skin blood flow and potentially heat storage[110]. This may or may not (positively) influence exercise performance, with effects likely proportional to the strength (i.e. concentration or area to which menthol is applied) or frequency of the menthol application 'signal'. Barwood and colleagues[111] showed that a repeated application of a 0.20% menthol spray, delivered at 20 and 40 min of an exercise bout consisting of 45min fixed work and a time to exhaustion effort (TTE; 70% maximum power), improved TTE. This had previously not been shown following single application by the same research

group[108–110]. This suggests a relatively quick decay of menthol's effects that may be mediated by exercise intensity and the rate of evaporative cooling within the exercise environment e.g. wind-speed[15]; these effects are also known to be exaggerated if a topical application contains alcohol[112].

Oral menthol supplementation exerts temperature dependent effect upon cycling[113] and triathlon[114] training performance when athletes are concomitantly physiological cooled. These enhancements were statistically *moderate*[19] when administered before and during exercise. The same research group subsequently challenged these findings[115] as when completing a 30km cycling time trial, the combination of pre and percooling with a cold beverage and menthol ice slurry respectively, evoked *trivially* slower performances (3815 ± 455 s) relative to percooling with menthol ice slurry only (3737 ± 522 s). This may be indicative of a trigeminal sensory threshold, whereby the cold stimuli are perceived as too intense when simultaneously targeting physiological and perceptual mechanisms, thus detracting from performance enhancement.

Oral application of menthol as a mouth swill or co-ingested with physiological cooling strategies has been consistently shown to lower thermal sensation[116-119],improve thermal comfort[54] and increase VE[117,120]. These effects may improve endurance performance either by improving TTE[116-118] or time trial performance[120,121]. However, when paired with carbohydrate during endurance exercise, carbohydrate sensing may outweigh any perceptual benefit caused by menthol[16]. These effects have not been observed when oral menthol administration takes place during intermittent or high intensity exercise[123-125]. There are no known negative side-effects reported following menthol swilling or ingestion, nor has oral menthol administration been shown worsen performance. The effects of oral application of menthol are thought to last ~10 min[16,122]. These findings may be of interest in pre or post-operative care where menthol has been administered as ice popsicles to attenuate thirst[124].

A single paper had shown improvements across a range of physiological markers during exercise following chronic peppermint oil supplementation[92], however, the magnitude of reported effects warranted scepticism and a replication study debunked these effects[124]. In light of the perceptual similarity and common pharmaceutical pairing with both peppermint and menthol, researchers are advised to consider potential effects of eucalyptol or eucalyptus essential oil use circa-exercise as a model of better understanding potential clinical applications of both agents.

Clinical considerations

The degree to which peppermint or menthol containing treatments are employed may also depend upon cultural preferences and physiological tolerance to either substance. Physiological variation is partly explained by a host of factors, ranging from genetic to systemic. Specifically, genetic factors relating to the expression of TRPM8 receptors[55], the sensitivity of the trigeminal nerve[52,81,95] and one's ability to differentiate between trigeminal stimuli[29,48] as well as the thickness of the stratum corneum in the area under menthol exposure[14]. Cultural preferences may influence menthol concentration within products, and in doing so expose an individual to higher or lower concentrations of menthol acutely, or chronically if one is a habitual consumer, which in itself can alter one's sensitivity to menthol[22,32,125,126]. The role and time course of individual habituation to menthol has practical implications for those aiming to assess the effects of peppermint and menthol in health and associated settings. This may mean purposefully withholding menthol containing stimuli from research participants' diets, or withholding menthol concentrations to deliberately alter physiological or subjective factors pertinent to conditions of interest.

Conclusion

1. Mint and menthol have been used to impart sensations of refreshing and cool for millennia, alongside other purported traditional medicinal effects
2. Mint and menthol are typically safe when consumed in recommended quantities, although there is variability in individuals' sensitivity, predominantly driven by variation in TRPM-8 receptors
3. Peppermint and menthol exert effects across digestive, nocioceptive and respiratory systems. There are potential considerations relating to COVID-19, especially in those with spinal cord injuries.
4. Sports performance may reveal further insights into the limits of mint and menthol consumption and application, and advance research into related health outcomes

Table 1: Key reviews pertaining to peppermint and menthol administration as it pertains to health effects and or other human benefit

Authors	Date	Title	Area(s) reviewed
Barwood *et al.*,[32]	2020	Menthol as an Ergogenic Aid for the Tokyo 2021 Olympic Games: An Expert-Led Consensus Statement Using the Modified Delphi Method	Oral and topical application and safety of menthol for sport and exercise performance
Best *et al.*,[16]	2021	Can Taste be ergogenic?	Effects of peppermint/ menthol and bitter, carbohydrate and capsaicin tastants upon physical performance
Eccles[6]	1994	Menthol and related cooling compounds	Overview of classical menthol literature
Eccles[7]	2000	Role of cold receptors and menthol in thirst, the drive to breathe and arousal	Effects of menthol on titular parameters
Eccles *et al.*,[8]	2013	Cold pleasure. Why we like ice drinks, ice-lollies and ice cream	Mechanisms underpinning oral preference for cool/cold
Ford *et al.*,[34]	2008	Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis	As per title
Jeffries & Waldron[92]	2018	The effects of menthol on exercise performance & thermal sensation: a meta-analysis	Exercise performance and thermal sensation
Saniasiaya, Islam and Abdullah B[80]	2020	Prevalence and Characteristics of Taste Disorders in Cases of COVID-19: A Meta-analysis of 29,349 Patients.	Ageusia and anosmia as a result of COVID 19
Stevens & Best[31]	2017	Menthol: a fresh ergogenic aid for athletic performance	Oral and topical application of menthol for sport and exercise performance

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