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Topical application of L-Menthol – Physiological and genetic considerations to assist in developing female athlete research: A narrative review

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ABSTRACT

L-menthol is a cyclic monoterpene derived from aromatic plants, which gives a cooling sensation upon application. With this in mind, L-menthol is beginning to be considered as a potential ergogenic aid for exercise and sporting competitions, particularly in hot environments, however female-specific research is lacking. The aim of this narrative review is to summarize available literature relating to topical application of L-menthol and provide commentary on avenues of consideration relating to future research developments of topical L-menthol in female athletes. From available studies in male participants, L-menthol topical application results in no endurance exercise performance improvements, however decreases in thermal sensation are observed. Mixed results are observed within strength performance parameters. Several genetic variations and single nucleotide polymorphisms have been identified in relation to sweat production, fluid loss and body mass changes – factors which may influence topical application of L-menthol. More specifically to female athletes, genetic variations relating to sweat responses and skin thickness, phases of the menstrual cycle, and body composition indices may affect the ergogenic effects of L-menthol topical application, via alterations in thermogenic responses, along with differing tissue distribution compared to their male counterparts. This narrative review concludes that further development of female athlete research and protocols for topical application of L-menthol is warranted due to physiological and genetic variations. Such developments would benefit research and practitioners alike with further personalized sport science strategies around phases of the menstrual cycle and body composition indices, with a view to optimize ergogenic effects of L-menthol.

1. Introduction

L-menthol is a cyclic monoterpene with a molecular formula $C_{10}H_{20}O$ derived from aromatic plants and responsible for giving a cooling minty taste to *Mentha species* plants (GPP et al., 2013). This natural compound has three asymmetric carbon atoms, with four pairs of optical isomers and is the principal form found in nature which has been shown to demonstrate cooling properties (GPP et al., 2013; Schä et al., 1986). L-menthol has been used in many fields including pharmaceuticals, cosmetics, food industry and tobacco, however more recently L-menthol has been proposed as an ergogenic aid to potentially benefit exercise performance due to the sensations and the cooling effect it elicits (Barwood et al., 2019, 2020; Flood, 2018; Jeffries and Waldron, 2019; McCubbin et al., 2020; Stevens et al., 2017b) (see Fig. 1).

It is proposed that L-menthol effects are triggered through stimulation of Transient Receptor Potential Melastatin 8 (TRPM8) (Barwood et al., 2020). These receptors are characterized by being voltage sensitive; and are activated by changes in membrane potential. TRPM8 can be stimulated by cold temperatures 8 - 28 °C (McKemy et al., 2007; Patel et al., 2007; Peier et al., 2002) with an activation threshold of ~23 °C (Peier et al., 2002). TRPM8 are abundant in trigeminal nerves, and are capable of sensing both cold and other compounds such as Icilin (AG3-5), and Hydroxycitronellal in addition to L-menthol (McKemy et al., 2007). L-menthol acts by interacting with calcium channels in the receptor, causing a rapid increase in intracellular calcium (Bharate and Bharate, 2012; Farco and Grundmann, 2012) and acting as a mediator for glutamate release in the somatosensory synapses; this potentiates sensory transmissions, with such cooling responses differing among body surfaces (Farco and Grundmann, 2012). In this sense, TRPM8 is regarded is a universal cold receptor in the thermoregulation system

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which could affect several cold-defense responses; cold-avoidance behaviors, skin vasoconstriction, and non-shivering thermogenesis in brown adipose tissue (Almeida et al., 2012; Kim and Lee, 2018).

Popular methods of L-menthol delivery are via topical application (e.g. gels, creams, sprays) and ingestion (e.g. beverages), meaning areas such as the skin, tongue and buccal region can be targeted by L-menthol (Barwood et al., 2020; Stevens et al., 2017b). Not only does the delivery method potentially determine sensitivity (Farco and Grundmann, 2012; Hermand et al., 2020; Hue et al., 2019; McKemy et al., 2007; Patel et al., 2007; Stevens et al., 2017b) with topical application of L-menthol inhibiting initiation of sweating at submaximal exercise intensities (Barwood et al., 2015). Additionally, psychological factors such as thermal comfort (TC), rate of perceived exertion (RPE) (Nybo et al., 2014), and motivation and expectance effects, can all be mediated by L-menthol application and are factors that may influence exercise performance (Stevens et al., 2017a), particularly in hot environments (Barwood et al., 2019; Flood, 2018; Flood et al., 2017; Hermand et al., 2020; Hue et al., 2019; Stevens et al., 2016). Additionally, research has shown that heat stress increases RPE and L-menthol may offer unique opportunities as a cooling strategy during exercise (Barwood et al., 2019, 2020; Flood, 2018; Stevens et al., 2017b).

Sport science practices for female athletes, including (but not limited to) strength & conditioning, injury management, recovery, and nutrition are often underpinned by research conducted in their male counterparts (Emmonds et al., 2019). Given the documented anatomical, physiological and endocrinological differences between cis-males and cis-females (McNulty et al., 2020; Sheel, 2016), female athletes will benefit from sex-specific research factoring in potential influences of female physiology on performance (Elliott-Sale et al., 2021; McNulty et al., 2020; Janse de et al., 2019). Currently, L-menthol topical application studies utilizing female athletes are scarce, therefore, the aim of this narrative review is to summarize available literature relating to L-menthol topical application in both endurance and strength-based exercise modalities and provide commentary for avenues of consideration relating to future research developments of L-menthol topical application in female athletes.

2. Materials and methods

2.1. Experimental approach to the problem

A computerized literature search was conducted using online databases: PubMed, Web of Science, and SPORTDiscus (via EBSCO) up to March 2023. The following search terms were used in all databases: ("L-Menthol OR Menthol [All Fields]) AND ("Topical Application" [All Fields]) AND ("Exercise AND Performance" [All Fields]). The search was conducted by the lead researcher independently and any disagreements were resolved through discussion with the research team. Criteria for inclusion were a) studies published in English language, with full-text availability, b) research undertaken between 1991 and March 2023, c) Intervention or Randomized Controlled Trials (RCTs) involving the topical application of L-menthol in exercise performance and d) studies conducted in human participants only.

Upon retrieval of eligible articles, citation lists were reviewed for any further eligible studies by the lead and senior author, that may not have been yielded within the initial literature search. Selected articles were read and relevant data were extracted into a custom Microsoft Excel document. Data extracted from each study included the research design, sample size and characteristics, details relating to L-menthol protocols, exercise protocols, and key results (including (but not limited to) exercise performance measures, RPE, thermal sensation; TS and TC).

3. Results

3.1. L-menthol and endurance exercise performance

Studies included within this narrative review regarding endurance exercise are described in Table 1, with several studies reporting the use of L-menthol topical application via spray or solution, with a concentration ranging from 0.05% to 0.2% (Barwood et al., 2012, 2014, 2015, 2019; Gillis et al., 2010; Hermand et al., 2020; Rinaldi et al., 2018) and an 8% L-menthol gel to the face via a dose of ~0.5g per 100 cm^2 of skin (Schlader et al., 2011). In relation to performance, when time trial (TT) protocols were adopted, no significant differences between conditions were observed (Barwood et al., 2012, 2014, 2015), however when time to exhaustion (TTE) protocols were adopted to assess exercise performance (Barwood et al., 2019) significant differences between conditions (Control: 2.4 ± 1.55 min vs. L-menthol: 4.6 ± 1.74 min, $p = 0.004$) were observed. Studies evaluating power output (PO) and RPE (Barwood et al., 2012; Gillis et al., 2010; Rinaldi et al., 2018) indicate disparity between these variables across studies, with variation in adopted methodologies meaning comparisons are difficult. For example, Gillis et al. (2010) adopted a fixed PO of 45% with a fixed exercise time protocol, whilst Rinaldi et al. (2018) had fixed TT where PO showed an increase of 15.6%. RPE findings varied between studies, with values significantly lower in L-menthol conditions in some studies (Barwood et al., 2015; Rinaldi et al., 2018), with others reporting no significant differences in RPE (Barwood et al., 2012, 2014; Gillis et al., 2010). One study which adopted a fixed-RPE protocol, reported that a higher total work load was completed in the L-menthol condition compared to control (Schlader et al., 2011). Studies involving L-menthol topical application also reported significantly lower TS within their respective L-menthol conditions (all: $p < 0.05$) while TC findings varied between studies (Barwood et al., 2014, 2015; Gillis et al., 2010; Rinaldi et al., 2018). Some studies have reported that rectal temperature significantly increases as a result of L-menthol topical application compared to control conditions (Gillis et al., 2010; Rinaldi et al., 2018) whereas other studies report no significant differences between groups (Barwood et al., 2015). Interestingly, no significant differences in skin temperature (T_{skin}) between conditions (i.e. control vs L-menthol) have been reported in studies assessing this variable (Barwood et al., 2014, 2015; Rinaldi et al., 2018).

A meta-analysis by Jeffries & Waldron (Jeffries and Waldron, 2019) showed a moderate-to-large effect (Hedges' $g = -0.71$, 95% CI −0.88, −0.54, p=<0.001) and a small effect (Hedges' $g = -0.30$, 95% CI −0.50, −0.10, $p = 0.004$) on exercise performance from L-menthol topical and oral application respectively. From the findings within this review, topical application improves TS while not affecting TC (Barwood et al., 2014, 2015; Gillis et al., 2010; Rinaldi et al., 2018), with the exception of Barwood et al. (2012), where L-menthol spray subsequently improved TC. When considering TS and TC it is important to understand that TS is usually attributed to air and skin temperature, governed by the sensory mechanism while TC may be subjective within a given thermal environment (Flouris and Schlader, 2015) and is influenced by blood flow and sweating response (Stevens et al., 2018) which is closely related to core temperature (T_{core}) and T_{skin} under normothermic conditions. For example, Kounalakis et al. (2010), used a concentration of 4.6% L-menthol sediment, which resulted in a larger measurable effect of skin vasoconstriction and increase in rectal temperature (T_{rec}) in male swimmers (Control: 2.99 ± 0.73°C•min^{-1} vs. Swimmers: 3.95 ± 1.23°C•min^{-1}). Such effects were attributed to a peripheral vasoconstriction and impaired sweating response in the athletes (Kounalakis et al., 2010). Moreover, Peel et al. (2023) found enhanced sensation of cooling, lower RPE, decreased pain response and reduce TS when L-Menthol application was administered, further supporting the effects of TC and TS in response to L-Menthol. Accordingly, both responses should be treated separately as they do not always necessarily act in unison. It is known that during exercising or hyperthermic states, TC is

Table 1
Summary of studies investigating L-menthol via topical application on endurance exercise performance.

Study	Characteristics	Total Participants (n =)	Methods	Main Results
Hermand et al. (Hermand et al., 2020)	M, moderately to well-trained runner, age: 21 ± 4 years, stature: 176 ± 6 cm, BM: 70 ± 9 kg, maximal aerobic speed: 16.2 ± 1.3 km h^{-1}	13	Participants completed four outdoor 10-km runs (T = 29.0 ± 1.3 °C, relative humidity 59.0 ± 13.6 %) wearing a t-shirt soaked every 2-km either in a CLD (~6 °C) or warm/ambient (~28 °C) solution, consisting in water or in a 4% menthol solution (CON, MEN-ambient, CLD and MEN-CLD).	*↑ Run performances from 4.8 to 6.1 % in CLD (51.4 ± 5.5 min), MEN-Amb (52.2 ± 5.9 min) and MEN-CLD (51.4 ± 5.1 min) conditions (vs. CON: 55.4 ± 8.4 min, $p < 0.05$), with ↔between these three conditions. *↓ TS after running in MEN-CLD (vs. CON: $p < 0.01$), and ↑ thermal acceptability in CLD and MEN-Amb (vs. CON, $p < 0.05$). ↔ in TC, feeling scale or RPE
Barwood et al. (Barwood et al., 2019)	M, 8 trained cyclists, age: 22 ± 2 years, stature: 184 ± 1 cm, body surface area: 2.05 ± 0.1 m^2, W_{max}: 363 ± 35.4 W	8	Participants completed 2 separate conditions of fixed-intensity cycling (50% maximal power output) for 45 min before a test to exhaustion (TTE; 70% maximal power output) with 100 mL of menthol spray (0.20% menthol) or control spray applied to the torso after 20 and 40 min	MEN spray improved TS after first spraying ($p = 0.008$) but did not alter TC ($P = 0.173$). *↓ Sweat production ($p = 0.020$) and SR ($p = 0.048$). *↑ TTE ($p = 0.004$). MEN spray effects diminished despite repeated applications, indicating ↑ contribution of visceral thermoreceptors to thermal perception.
Rinaldi et al. (Rinaldi et al., 2018)	M, elite road cyclists, age: 24 ± 4 years, BM: 65.3 ± 5.2 kg, W_{max}: 321 ± 41 W	8	Participants performed two randomized 20 min cycling trials in outdoor, each consisting of a 20-min cycling trial (T1) followed by 10 min of immersion during recovery and then a second 20-min cycling trial (T2) in hot conditions (29.1 °C ± 1.5 °C, 62 ± 4% rH). Between trials participants were treated with either a CWI or CMWI intervention for 10 min. T_{rec} and T_{skin} were measured before and immediately after T1, immersion, and T2. TS and TC were measured immediately after T1 and T2	*↑ PO in T2 compared with T1 in the CMWI condition (+15.6%). ↔ in performance in the CWI condition. ↓ T_{rec} in CWI (−1.17 °C) compared to CMWI (−0.6 °C) following immersion. *↓ TS decreased following immersion in both conditions. *↑ RPE in CMWI in T1 (6.57 ± 0.9) compared to T2 (5.14 ± 1.25). ↔in TC.
Barwood et al. (Barwood et al., 2015)	M, age: 21 ± 2 years, stature: 1.81 ± 0.07 m, BM: 83.1 ± 11.1 kg	8	Within-participant, double-blind, repeated-measures design. Following familiarization, Participants completed two 16 km cycling TT (CON and MEN) treatments in hot conditions (33.5 °C, 33% rH). TS, TC, T_{rec}, T_{skin}, RPE, HR, PO and TT completion time were measured	MEN spray made participants feel cooler and resulted in ↓ RPE, despite ↔ in performance (TT completion: CON spray 32.4 ± 2.9 min, MEN spray 32.7 ± 3.0 min). ↑ in T_{rec} with ↔ between conditions (CON spray: 1.40 ± 0.60 °C/h, MEN spray: 1.45 ± 0.40 °C/h)
Gillis et al. (Gillis et al., 2010)	M, age: 22 ± 3 years, BM: 75.7 ± 8.7 kg, stature: 179.1 ± 6.6 cm	12	Participants completed one PO_{peak} followed by three counter-balanced, heated exercise bouts (30 °C, 70% rH). Participants were treated with 100 ml of either 0.05% or 0.2% MEN or a CON solution.	↔ in MST, Tbody SR, SBF, HR, TC or RPE between conditions. *↑ in T_{rec} (0.2 °C) in MEN spray compared to other conditions ($p < 0.05$). MEN spray caused significantly cooler sensation than CON spray ($p = 0.001$). 0.2% MEN spray induced significantly cooler sensations than 0.05% MEN spray ($p = 0.01$). MEN spray induced greater irritation than CON-spray ($p < 0.001$)
Barwood et al. (Barwood et al., 2014)	M, age: 21 ± 1 years, BM: 78.9 ± 6.9 kg, stature: 1.80 ± 0.7 m, with a 5 km running completion time of ≤25 min	6	Following familiarization, participants completed three trials in hot conditions (34 °C) where their clothing was sprayed (CON spray or MEN spray) or not sprayed (CON) after a fixed intensity exercise period (15 min), which induced thermal discomfort, before completing a 5 km treadmill TT. TS, TC), T_{au}, T_{skin}, RPE), HR, PO and TT completion time were measured	MEN spray induced improvements in TS (up to 3 km of TT) and TC (up to 1 km) with T_{au} showing a tendency to be higher than CON spray and CON (0.20 ± 0.29 °C and 0.30 ± 0.34 °C, respectively, both $p > 0.05$). ↔ in TT completion time between conditions: CON: 27.9 ± 1.6 min, CON spray: 28.1 ± 1.1 min, MEN spray: 27.53 ± 2.85 min.
Barwood et al. (Barwood et al., 2012)	M. age: 30 ± 8 years, BM: 76.0 ± 8.3 kg, stature: 1.78 ± 0.6 m, body surface area 1.93 ± 0.10 m^2; Σ4SF: 41.4 ± 13.1 mm, a 40 km cycling TT in <70 min in the past 6 months.	11	Participants completed three 40 km cycling TTs in standardized conditions (32 °C, 50% rH) with thermal perception altered prior to exercise by application of cold-receptor-activating MEN spray, in contrast to a separate CON spray and no spray control (CON).	MEN spray induced feelings of coolness and improved TC before and during exercise. T_{skin} profile at the start of exercise was similar between sprays (CON spray 33.3 ± 1.1 °C and MEN spray 33.4 ± 0.4 °C, but different to CON 34.5 ± 0.5 °C), with ↔ in the pacing strategy adopted. ↔ in performance using MEN spray; TT completion times of 71.58 ± 6.21, 70.94 ± 6.06 and 71.04 ± 5.47 min for CON, CON spray and MEN spray respectively.
Schlader et al. (Schlader et al., 2011)	M, age: 23 ± 1 years, BM: 84.0 ± 4.8 kg body surface area: 2.04 ± 0.07 m^2, body fat: 11.7 ± 1.5%.	12	Participants exercised at a constant subjective RPE (16,'hard–very hard') while their face was thermally and non-thermally cooled, heated, or left alone (con trial).	↑ Work output in thermal and non-thermal cooling trials, compared to thermal and non-thermal heating and control trials. ↔ thermal sensory and discomfort sensations between thermal and non-thermal heating/cooling trials. ↔ in initial and final exercise intensities between trials. ↔ HR, MST, T_{rec}, whole body SR or local (neck) SR between trials

↑: Increased, ↓: Decreased, ↔: No difference, *: significantly, Σ4SF: Sum of four-site skinfolds, BM: Body mass, cm: Centimeter, CLD: Cold CON: Control, CWI: Cold Water Immersion, CWMI: Cold Water Menthol Immersion, HR: Heart Rate, km: Kilometer, M: Male, m: Meters, MEN: Menthol, Min: Minute, MST: Mean Skin

Temperature, PO: Power output, PO_{peak}: Peak Power Output, rH: Relative Humidity, RPE: Rate of Perceived Exertion, SBF: Skin Blood Flow, SR: Sweat Rate, T_{au}: Aural Temperature, TC: Thermal Comfort, T_{rec}: Rectal temperature, TS: Thermal Sensation, T_{skin}: Skin Temperature, TT: Time Trial, TTE: Time to exhaustion, W_{max}: Maximal Aerobic Power Output.

affected primarily by T_{core} (Flouris and Schlader, 2015) which may explain why TC remained unchanged in the studies where rectal temperature (T_{rec}; a measure of T_{core}) showed significant increases in the L-menthol condition (Gillis et al., 2010; Rinaldi et al., 2018). However, neither of the other studies (Barwood et al., 2014, 2015) showed a relationship between these measures. Thermal sensation is dictated by T_{skin} independent of T_{core} so it would be expected that a decreased TS would result from a decreased T_{skin} (Flouris and Schlader, 2015), but this was not the case as T_{skin} was not significantly different between conditions. Nevertheless, it should be considered that perceptual values have a psychological component; sensations expressed in the scales (ASHRAE 9-point analogue, 17-point category ratio scale, modified Hodder and Parsons or Bredford 7 point) can be influenced by motivation to show dissatisfaction (or satisfaction) with the situation or mood (Eccles, 1994). Considering that any observed decreases in TS appear to be evident in L-menthol topical application, it is important to highlight that thermoreceptors in the skin are meant to detect thermoregulation (Eccles, 2000), while receptors in the oral cavity are meant to detect temperature of food and drink (Eccles, 2000; Haggard and de Boer, 2014) but their function, apart from sensing temperature has not yet been well documented (Rinaldi et al., 2018). Such observations have been made by Valente et al. (Valente et al., 2015) who investigated absorption and metabolism pharmacokinetics of a single L-menthol oral versus skin administration and the effects on human thermogenesis and metabolic rate, who concluded that a single topical L-Menthol skin administration increased thermogenesis and metabolic rate in humans, however minimal effects of these parameters were observed following L-Menthol oral administration (Valente et al., 2015), and may offer insight as to the physiological responses observed in TS.

Another consideration is the temperature at which L-menthol is administered, and there could be a possible synergistic effect; a "double activation" of cold receptors via temperature and L-menthol (Peier et al., 2002). This proposed synergistic effect was observed in a study by Rinaldi et al. (2018), where cyclists went through a cold water immersion (CWI) or a cold water L-menthol immersion (CWMI) with a water temperature of 10 °C; TS significantly decreased in both conditions, but was greater in the L-menthol group (CWI: 5.6 ± 0.9 to 4.4 ± 1.2 vs. CMWI: 5.9 ± 1.0 to 3.6 ± 0.5). It should also be noted that T_{skin} was not impacted by condition, however was impacted by trial; being significantly lower after each immersion; which may explain the decrease in TS. Moreover, Botonis et al. (Botonis et al., 2018) found that topical L-Menthol application before prolonged water immersion (cool; 24°C or cold; 14°C) reduces heat loss resulting and a lessened Trec decline following cycling at 60% of maximum heart rate in healthy male participants, with the authors speculating that both vasoconstrictive and heat storage effects of L-Menthol application may be attributed to the stimulation of peripheral cold receptors (Botonis et al., 2018). This is not the case in studies where ingestion of L-menthol has been administered. For example, Riera et al. (2014) found that regardless of beverage temperature (neutral: 23 ± 0.1 °C, cold: 3 ± 0.1 °C, or ice slush: 1 ± 0.1 °C) administration of L-menthol had a significant effect on TS. Such findings may imply that temperature has a greater impact when applied topically as opposed to ingestion.

3.2. *L-menthol and strength exercise performance*

Studies included within this narrative review regarding strength exercise are described in Table 2, with three studies reporting the use of L-menthol topical application via spray or solution (0.2% concentration) (Over et al., 2023), or topical gel between 3.5% and 5% concentration (Tokunaga et al., 2017; Topp et al., 2011). Two studies used surface electromyography to measure the rectus femoris, biceps femoris, and

Table 2
Summary of studies investigating L-menthol via topical application on strength exercise performance.

Study	Characteristics	Total Participants (n =)	Methods	Main Results
Over et al. (Over et al., 2023)	M, resistance trained, age: 24 ± 5 years, stature: 174 ± 10 cm, BM: 76 ± 9 kg, deadlift 5RM: 132.3 ± 28.5 kg	9	Before completing the DLT (75% 1RM) and IMLT, subjects were sprayed with (~125 ml; 0.2%) of MEN or CON spray. Performance, EMG (root mean squared) of RF, BF, and medial gastrocnemius), TS_{Legs} and TC_{legs}, RPE, readiness to train, HR, and T_{skin} were measured.	DLT performance ↔, *↑ IMLT force production in MEN spray (MEN: 148 ± 30 kgf vs CON: 140 ± 30 kgf) condition (p = 0.035, h2p p = 0.444) with *↑ root mean square EMG in MEN (BF: MEN 3.8 ± 1.46 vs. CON 2.9 ± 0.34 V; p = 0.049, h2, p = 0.403).TS_{Legs} was ↓after menthol spray before IMLT.
Tokunaga et al. (Tokunaga et al., 2017)	M; healthy subjects, age: 20–65 years,	42	Isometric knee extensions at 35% MVC in three groups (Adult Placebo, Adult MEN, Older Adult MEN. Application of 5% MEN gel. Surface EMG from the VL, VM, and RF was recorded	Root mean square EMG in VL and VM *↑ with MEN stimulation both in Adult and Older Adult, but ↔ was observed between Adult MEN and Older Adult MEN.
Topp et al. (Topp et al., 2011)	M & F healthy subjects, age: 24 ± 3 years, stature: 171 ± 9 cm, BF%: 19 ± 8	17 (9 male, 8 female)	Intervention protocol involved application of 1 of 3 treatments (MEN, ice, or CON) for 20 min; blood flow was assessed before treatment application and 5, 10, 15, and 20 min afterward. After the blood-flow measurement, muscle-strength tests on right forearm was assessed using a Biodex 1000 isokinetic dynamometer. Following familiarization, participants completed 30 repeated maximum flexions and extensions of the wrist at a rotation speed of 30°/s. 5 highest torque recordings were averaged to arrive at a maximum wrist-extension and -flexion strength measure.	5 min after application of MEN blood flow ↓ in the radial artery by ~40%. ↓ in blood flow was not sustained at 10, 15, or 20 min after MEN treatment. Both MEN and CON conditions exhibited *↑ in wrist-extension strength at the 25- and 30-min data-collection points compared with strength measures obtained in the respective treatment condition at 20 min after treatment application.

↑: Increased, ↓: Decreased, ↔: No difference, *: significantly, BF: Biceps femoris, BF%: Body fat percentage, BM: Body mass, cm: Centimeter, CON: Control, DLT: Dynamic weightlifting task; EMG: electromyography, HR: Heart Rate, IMLT; Isometric weightlifting task, kgf: kilograms of force, M: Male, m: Meters, MEN: Menthol, Min: Minute, MST: Mean Skin Temperature, MVC: Maximum voluntary contraction, RF: Rectus femoris, RM: Repetition maximum; RPE: Rate of Perceived Exertion, TC: Thermal Comfort, TC_{Legs}: Leg thermal comfort, TS: Thermal Sensation, TS_{Legs}: Leg thermal sensation, T_{skin}: Skin Temperature, VL: Vastus lateralis; VM: Vastus medialis.

medial gastrocnemius during dynamic and isometric weightlifting tasks (Over et al., 2023) and the vastus lateralis, vastus medialis and rectus femoris during a 35% maximum voluntary contraction of the quadriceps muscle (Tokunaga et al., 2017). Physiological and perceptual measures were collected in one study (Peier et al., 2002) (see Table 2). Similarly, one study examined blood flow ($mL \bullet min^{-1}$) using ultrasound methodologies, with muscle strength assessed via a Biodex isokinetic dynamometer (Topp et al., 2011).

In relation to performance, using a 0.2% L-menthol topical spray, improvements in isometric weightlifting task performance were observed, with corresponding changes in electromyography seen in the biceps femoris (Over et al., 2023). Similarly, Tokunaga et al. (2017) observed significant increases in root mean square electromyography in the vastus lateralis and vastus medialis stimulation both in adult and older adult cohorts via a 5% L-menthol gel, but no significant difference was observed between adult L-menthol and older adult L-menthol groups (Tokunaga et al., 2017). Topp et al. (2011), observed significant increases in mean maximum wrist flexion torque (~2%) with L-menthol topical gel application at 25 min post-application compared with strength measures obtained in the respective treatment condition at 20 min (20mins: 10.86 ± 0.96 vs 25mins: 11.11 ± 1.14, +2.27% change).

4. Female athlete considerations for l-menthol topical application

4.1. L-menthol, menstrual cycle and physiological considerations

The menstrual cycle (MC) represents an important biological rhythm in females that serves to prepare the uterus for gestation (Blagrove et al., 2020). Alongside their principal roles in reproductive function and control of sexual characteristics, the main female ovarian hormones, namely estrogen and progesterone, influence a multitude of different physiological systems (Blagrove et al., 2020). Fluctuations in these, and other sex hormones (e.g., testosterone), can explain variations in physical performance and physiological responses to exercise over the course of a menstrual cycle (Blagrove et al., 2020; McNulty et al., 2020). Estrogen is responsible for regulation of a number of important anabolic processes and may influence central nervous system function (Blagrove et al., 2020; McNulty et al., 2020). In contrast, progesterone is purported to exert an inhibitory effect on the nervous system (Blagrove et al., 2020), with the thermogenic action causing an increase in core body and skin temperature during MC phases (Blagrove et al., 2020; McNulty et al., 2020) which positively influences nerve conduction velocity and consequently may positively influence performance in explosive strength-related tasks (Blagrove et al., 2020; McNulty et al., 2020). In eumenorrheic women, a MC typically lasts ~28 days, but can vary considerably (Blagrove et al., 2020; Dawson and Reilly, 2009; McNulty et al., 2020). It is well-established that fluctuations in estrogen and progesterone across the MC create significantly different transient hormonal profiles in females, and these fluctuations are used to differentiate between MC phases (Janse de and Jonge, 2003; McNulty et al., 2020). As such, the MC is commonly divided into three phases; 1) the early follicular phase, characterized by low estrogen and progesterone, 2) the ovulatory phase, characterized by high estrogen and low progesterone, and 3) the mid-luteal phase, characterized by high estrogen and progesterone (Janse de and Jonge, 2003). Given the associated physiological and hormonal mechanisms of action involved during MC phases, coupled with the proposed physiological responses to L-menthol topical application within available studies, this may provide an opportunity for future research to observe whether such responses are altered during MC phases, and subsequently whether female-specific guidance of L-menthol topical application is needed. This may be particularly pertinent when considering how progesterone may influence thermogenic responses (e.g. increasing T_{skin}) in females, and topical application of L-menthol appears to improve TS in exercising conditions. Although limited literature exists in female cohorts, Kim & Lee (Kim and Lee, 2018) investigated L-menthol topical application and activation of cutaneous cold receptors in non-exercising female students. Their results showed that both maximum and average temperatures of the T_{skin} during water immersion were lower in the L-menthol application compared to control. Within their study design, MC was not considered as vasoconstrictor responses to local cooling are not influenced by reproductive hormone status (Charkoudian et al., 1999; Kim and Lee, 2018). Whether similar hormonal responses and vasoconstriction would be observed within exercising, female athletes and L-menthol topical application throughout MC phases requires further investigation.

4.2. L-menthol, menstrual cycle and body composition

In relation to female athlete participation in sport and exercise, it may be important to consider the potential role of the MC on body composition indices and subsequent use of L-Menthol application. In addition to their reproductive function, estrogen and progesterone are purported to influence additional physiological processes, such as sodium balance and body water distribution (Sims et al., 2008; Stachenfeld and Taylor, 2004; Thompson et al., 2021). Elevated estrogen concentrations have been shown to encourage retention of extracellular fluid in plasma, while elevated levels of both estrogen and progesterone may favor retention of fluid within the interstitial space (Stachenfeld and Taylor, 2004) and may alter fat deposition, skin elasticity and thickness, and hydration status (Farage et al., 2009; Ong et al., 2022). These putative changes in body tissues pose some interesting questions, and potential avenues of future research, as to the efficacy of L-menthol as an ergogenic aid for female endurance athletes.

It could be hypothesized that fluctuations in body tissues, estrogen, and progesterone may have acute effects on body composition indices (Cumberledge et al., 2018; Hicks et al., 2017) and subsequently, any potential ergogenic effects of L-menthol topical application throughout a female athlete's training and competition schedule. However, research examining effects of the MC on body composition measurements has provided conflicting results. Studies utilizing bioelectrical impedance (BIA), air displacement plethysmography (ADP), ultrasound and dual energy x-ray absorptiometry (DXA) to assess body composition indices indicate no differences in these measures during different phases of the MC (Cumberledge et al., 2018; Hicks et al., 2017; Ong et al., 2022; Thompson et al., 2021). Conversely, research adopting skinfold (SKF) methodologies, provides further inconsistent results, with some reporting differences in SKF measures (Stacho and ń, 2016) and skin thickness (Lebrun et al., 1995) across phases of the MC, whilst others show no change across MC phases (Eisenbeiss et al., 1998; Ellard et al., 1991). Given these inconsistent findings, it remains unclear whether fluctuations in female hormones during phases of the MC affect both field and laboratory measures of body composition and subsequently, whether ergogenic effects of L-menthol topical application would be influenced by these fluctuations in body tissues. Given the current mixed findings in this area, it could be hypothesized that current practices and L-menthol concentrations adopted within the literature could be utilized effectively in female endurance athlete cohorts. Similarly, use of both laboratory and field-based methods (i.e., DXA, BIA, SKF etc.) to indicate changes in tissues during MC phases and determining body composition as part of anthropometric measurements, as observed via SKF in topical L-menthol application studies such as those adopted by Barwood et al. (2012), may need some consideration amongst researchers and practitioners. Subsequently this may offer an avenue of research to determine whether topical application of L-menthol concentrations needs adjusting when factoring in potential changes in MC phases in female endurance athletes and their body composition indices.

4.3. L-menthol, menstrual cycle and exercise performance

There are a range of proposed physiological mechanisms by which fluctuations in estrogen and progesterone across the MC might affect

exercise performance and subsequent ergogenic benefits of topical L-menthol application. Specifically, it has been suggested that estrogen may have an anabolic effect on skeletal muscle and purported impact on substrate metabolism (Baltgalvis et al., 2010; Lowe et al., 2010). Currently, the reported effects of fluctuations in estrogen and progesterone across the MC on exercise performance are conflicting. Some studies have previously reported improved performance outcomes during the early follicular (Pallavi et al., 2017; Tenan et al., 2016), ovulatory (Bambaeichi et al., 2004) and mid-luteal (Ekenros et al., 2013; Oosthuyse et al., 2005) phases of the MC. Whereas, other studies have shown no changes in exercise performance between MC phases (Dasa et al., 2021; Elliott et al., 2003; McLay et al., 2007; Oosthuyse et al., 2005; Taipale-Mikkonen et al., 2021; Vaiksaar et al., 2011). Whether such responses are mediated differentially by topical L-menthol application during differing phases of the MC phases remains an area for future investigation. From the available literature relating to topical L-menthol application, effectiveness of L-menthol appears to be dependent on the protocol adopted (e.g. TT vs. TTE) and variables being considered (e.g. PO, RPE etc.). Whether these variables change in MC phases of female athletes, with or without L-menthol intervention, in itself, remains an area for future research.

Current evidence from two systematic reviews with meta-analysis indicates that exercise performance may be trivially reduced during the early follicular phase of the MC (McNulty et al., 2020) and that strength-related measures appear to be minimally altered by fluctuations in ovarian sex hormones (Blagrove et al., 2020). Interestingly, both reviews concluded that due to the trivial effect size of exercise performance observed, large between-study variations, and the proportion of poor-quality studies, that general guidelines on exercise performance across the MC cannot yet be formed (Blagrove et al., 2020; McNulty et al., 2020). Therefore, further investigation is warranted to investigate the specific effects of the MC on exercise performance and training adaptations in female athletes. Currently, there is limited research available examining the use of L-menthol in conjunction with strength-based protocols (Barwood et al., 2020). However, of the limited studies available, isometric weightlifting performance, maximum voluntary contraction and maximum wrist-flexion appear to be improved with the use of topical L-menthol (Over et al., 2023; Tokunaga et al., 2017; Topp et al., 2011). Similar to that of endurance-based exercise studies, methodology varies within type of strength protocol adopted, measurements recorded, and cohort characteristics. For example, a wide age range within Tokunaga et al. (2017) versus a smaller cohort size and the use of resistance trained males within Over et al. (2023), makes comparison of the efficacy of L-menthol challenging. Despite the inclusion of both males and females within their study, findings by Topp et al. (2011) were not analyzed by gender, and as such, caution must be taken when interpreting their findings as to the effectiveness of an ergogenic effect on strength parameters within female-only cohorts. Interestingly, topical application appears to contradict L-menthol ingestion studies involving strength markers, which found no benefit to peak and mean force, vertical jump or 6-s sprint times (Best et al., 2020). When considering the mechanistic effects of L-menthol, a proposed mechanism of action may be the benefits of skin-cooling inducing increases in strength parameters such as (but not limited to) muscle fiber recruitment, rate of force development and isometrically generated force (Over et al., 2023).

With the findings of L-menthol topical application and strength performance in mind, hypothesizing the systematic findings of Blagrove et al. (2020) in female athlete strength parameters and translating these findings to interventions involving topical L-menthol application, especially given the purported anabolic effects of estrogen (Baltgalvis et al., 2010; Lowe et al., 2010), may warrant consideration in future research.

4.4. Sweat physiology and genetic variations

It has been proposed that thermoregulatory factors such as sweat rate can be influenced by genetics and the MC, which have been shown to modify the onset and/or sensitivity of the sweating response (Baker, 2017). During the luteal phase of the MC, regional sweating rate is lower at a given body core temperature, but no differences in whole-body sweating rate across the menstrual cycle phases (Baker, 2019). Similarly, sweat gland density is generally higher in women than men and accordingly, lower sweating rates reported in women may be as a result of lower output per gland (Baker, 2019). Despite these factors, higher whole-body sweat rates observed in men than women may be attributed to higher body mass and metabolic heat production (higher absolute exercise intensities), rather than sex (Baker, 2019), which indicates that when factoring in genetic and MC factors, women may not be at a thermoregulatory disadvantage compared with men during physical activity (Baker, 2019).

Despite being a potential factor of sweat physiology, little is known about genetic variations and any potential differences between genders, and subsequently how L-menthol would respond to differing genetic variations. Albeit within mice models, Kamberov et al. (2015) identified a large region on Chromosome 1 that controls both hair and eccrine sweat gland densities, with allelic expression analysis of the genes demonstrated that the level of *Engrailed Homeobox 1 (En1)* activity directs the relative numbers of eccrine glands and hair follicles. With the authors concluding that *En1* is determinant of hair follicle and eccrine sweat gland density and identify a pathway that could have contributed to the evolution of the unique features of human skin. Similarly, Endo et al. (2018) identified associated variants in independent signals within the Chromosome 2 (*Phospholipase B1*; *PLB1* and *Protein Phosphatase 1 Catalytic Subunit Beta*; *PPP1CB*) and Chromosome 16 (*ATP Binding Cassette Subfamily C Member 11*; *ABCC11* and *Lon Peptidase 2, Peroxisomal*; *LONP2*) regions. *PLB1* codes for phospholipase B1 protein (PLB), whilst *PPP1CB* encodes the beta-subunit of the Serine/threonine-protein phosphatase *PP1*, and despite their respective roles within skin barrier function by breakdown of lipids into free fatty acids, there is a possibility that it could function to modulate secretory processes in other situations such as sweating (Endo et al., 2018). Within their analysis, the authors concluded that *PPP1CB* single nucleotide polymorphisms (SNPs) may effect sweat production via the regulation of the water-specific channel aquaporin-5 (AQP5) and other regulatory proteins responsible for sweat gland production, and that an SNP (rs17822931) on the *ABCC11* gene is also associated with hyperhidrosis (Endo et al., 2018).

Interestingly, a systematic review by Rivera et al. (Rivera and Fahey, 2019) investigating the *Aquaporin-1* (*AQP1*) gene and endurance exercise performance found mixed results in terms of total fluid loss and whole-body mass changes. Within their included studies, the SNP (rs1049305) C-allele on the *AQP1* gene had a greater adjusted body fluid loss than non-carriers (3.7 ± 0.9 kg vs. 1.5 ± 1.1 kg) in 10-km road race athletes, whilst genotype effect did not influence in Ironman athletes (Rivera and Fahey, 2019; Saunders et al., 2015). Within the review, the authors concluded that the *AQP1* gene facilitates transfer of water from blood into muscle via rapid transport mechanisms and serves as a conduit for water reabsorption and thermal control, with increased active *AQP1* channels in skeletal muscle and sweat glands, which may provide physiological advantages and promote cooling via increased convective heat transfer and sweat rate (Rivera and Fahey, 2019), findings which may be pertinent for the physiological responses of topical L-menthol application. Additionally, it has been proposed that athletes with the more active *AQP1* gene C-allele may be able to train harder and recover faster (Rivera and Fahey, 2019; Rivera et al., 2011).

Overall, these findings pose interesting questions as to the direction of future research regarding genetic variations and the potential efficacy of L-menthol topical application in female endurance athletes. Given research has moved towards the importance of nutrigenetics and how 'personalized nutrition' can potentially optimize health and

performance. Several genetic variations have been identified in relation to sweat physiology phenotypes. Genetic variations and responses to ergogenic aids such as caffeine, has been investigated (Grgic et al., 2021), and whilst studies relating to topical L-menthol application, genetic variation and exercise performance are lacking (in both genders) it could be proposed that when considering such phenotypes and female-specific physiology (e.g., MC phases), coupled with the mechanistic effects of L-menthol topical application, this may be a novel avenue of future research in optimizing the ergogenic effect of topical L-menthol in female endurance athletes.

5. Conclusions

The findings of this narrative literature review indicate that topical application of L-menthol appears to be a novel ergogenic aid to assist with aspects of exercise performance and associated physiological responses. Topical L-menthol may be considered if perceptual factors require manipulation; findings that are supported by observed decreases in TS when applied to skin. However, it should be noted that the timing of topical L-menthol application evaluated in the studies tended to be towards the middle or end of the exercise. Given the purported physiological responses with core temperature (Gillis et al., 2010; Rinaldi et al., 2018) this has to be taken with care, with end users adhering to precautionary statement codes, advice from practitioners and consensus statements (Barwood et al., 2020). Relevant studies relating to L-menthol topical application and exercise performance have been conducted primarily within male cohorts who are recreationally active or trained, making it difficult to derive conclusions or extrapolate to female athlete populations.

The aim of this narrative review was to summarize available literature relating to L-menthol topical application in both endurance and strength-based exercise modalities and provide commentary for avenues of consideration relating to future research developments of L-menthol topical application in female athletes. Despite previous meta-analysis being undertaken on effects of L-Menthol in both topical and oral application (Jeffries and Waldron, 2019), there is limited research in to effects of topical L-Menthol in exercising females. As such, to address the aims of this review, the authors adopted a narrative approach, allowing for a subjective examination and critique of available literature and exploration of topics that are under-researched, in addition to offering new insights or ways of thinking in what is otherwise a well-developed, robustly researched field (Sukhera, 2022).

It has been documented that a greater volume of research focusing on areas unique to female physiology is required to inform best practice guidelines for sport science and nutrition (Elliott-Sale et al., 2020, 2021; Emmonds et al., 2019; (Janse de et al., 2019). Research within female athletes and considerations relating to body composition indices, the menstrual cycle and how topical application of L-menthol may be influenced by these factors, is lacking. Methodological considerations for studies involving cis-female participants (Elliott-Sale et al., 2021), as well as the considerations highlighted within this review may need to be taken into account when designing studies involving topical application of L-menthol (see Fig. 1). For instance, it is thought that females are less effective at regulating body temperature in dry heat and have a significantly lower sweat rate compared with men (Smith and Havenith, 2012), which should be taken into account when considering outcomes in efficacy of topical L-menthol applications. Further research is required among female athletes of all training backgrounds, as there may be possible variations in outcomes due to variations in regional adiposity, MC phases, genetics related to sweat physiology, and other factors highlighted within this review.

5.1. Practical applications

Researchers and practitioners should aim to trial a personalized approach to L-menthol topical application, with individual effectiveness in representative conditions for training and competition scenarios within female athletes. L-menthol topical application should be examined alongside MC phases and alterations in body composition brought about by training adaptations, MC phases or hormonal contraception, and potential genetic variations in the preparation for competition in order to identify individual female athlete specific benefits.

CRediT author statement

Tatiana Villegas Serna: Conceptualization, Methodology, Formal

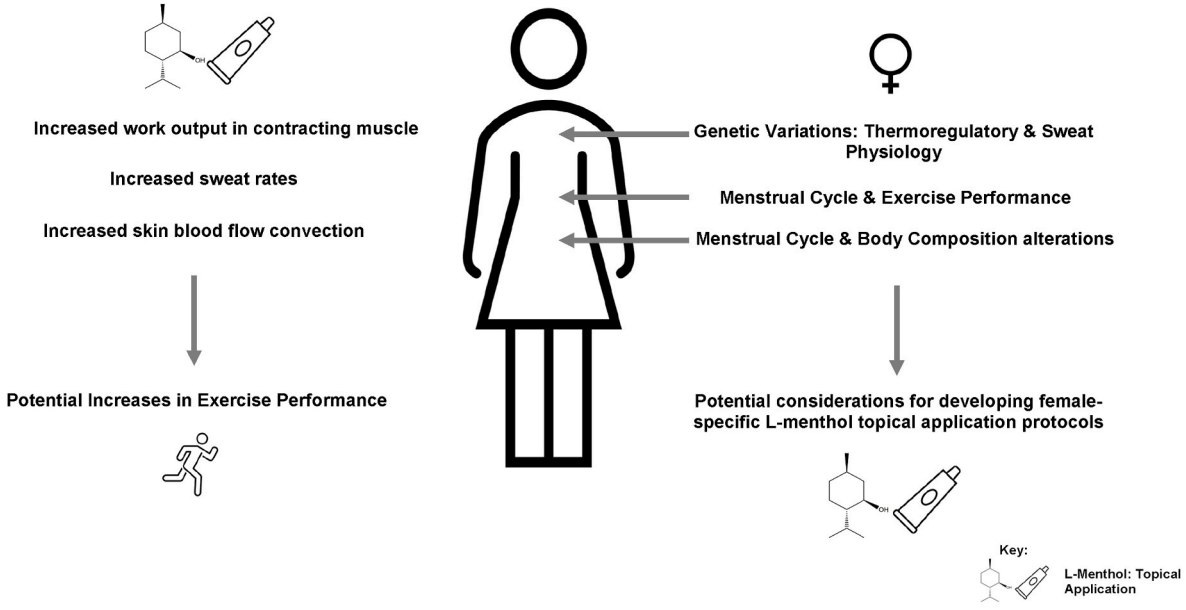

Fig. 1. Schematic overview of topical L-menthol application on temperature regulation factors. Topical L-menthol application may affect highlighted factors (left-hand side of diagram) and may cause an increase in exercise performance enhancement via these mechanisms. Female-specific factors (right-hand side of diagram) may affect efficacy of L-menthol topical application and requires further investigation. Adapted from Best (Best, 2019) and Gisolfi & Wenger (Gisolfi and Wenger, 1984).

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Declaration of competing interest

The authors have no conflicts of interest, financial or otherwise, to declare.

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