The Effects of Frankincense Essential Oil on Stress in Rats

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Abstract: Frankincense essential oil, obtained from Boswellia carteri, is a popular essential oil, which is widely used in many parts of the world. While some of its properties are known, its effects on stress and sleep have not been studied. The effects of frankincense essential oil and its major components, limonene and α-pinene, on plasma corticosterone and glutathione (GSH) levels, as well as on sleep and wakefulness behaviour, were studied in sleep-deprived rats. The substances were applied topically after dilution in jojoba oil (vehicle). As compared to vehicle, frankincense essential oil at a dilution of 1/1000 (1:10^3) significantly reduced corticosterone levels (p < 0.05). In contrast, its major constituents (α-pinene and limonene), elevated levels of this stress hormone. Frankincense, limonene, and α-pinene, all led to significant reductions in plasma GSH levels. Although frankincense dose-dependently reduced plasma concentrations of antioxidant ions albeit to levels insufficient to neutralize oxidative stress; levels of products of oxidative metabolism metabolites were decreased by the frankincense. In sleep-deprived rats, frankincense 1:10^3 respectively increased and decreased the amount of wakefulness and non-rapid eye movement sleep. Frankincense essential oil can counter the effects of stress by effectively relieving sleep debt and maintaining antioxidant capacity without increasing oxidative stress, and, therefore, may be beneficial in the management of stress.

Key words: corticosterone, frankincense essential oil, glutathione (GSH), oxidant stress, sleep

1 Introduction

Essential oils have been shown to alleviate many medical and dental symptoms in the fields of pain, cancer, neuro-psychiatry, otolaryngology, dermatology, nephrology, urology and oral hygiene as well as disorders of the circulatory, digestive, endocrine and immune systems1–3. Among the various essential oils, that derived from frankincense has been used since ancient times. Its effects have been ascribed to its antioxidant, anti-inflammatory, antimicrobial, and antitumor potency in treating asthma, arthritis, cerebral edema, chronic pain syndrome, chronic bowel diseases, and cancer. Interestingly, it has been claimed that frankincense essential oils in cosmetic and other applications may improve learning and enhance memory4–12. Although many of the above-mentioned ailments are associated with stress and poor sleep, and stress and disturbed sleep can disrupt cognitive functions, there are no detailed studies that examine how stress and sleep may be influenced by frankincense essential oil or the other two major components of frankincense essential oil, α-pinene and limonene; the chemical composition of frankincense essential oil is depicted in Fig. 113.

The present study focused on the stress-relieving properties of frankincense essential oil, α-pinene, and limonene in sleep-deprived rats; the oils were applied topically at

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Accepted June 16, 2019 (received for review April 26, 2019)
Journal of Oleo Science ISSN 1345-8957 print / ISSN 1347-3352 online
http://www.jstage.jst.go.jp/browse/jos/  http://mc.manuscriptcentral.com/jjocs

Fig. 1 Percentage of each component of frankincense essential oil.
2 Experimental Procedures

2.1 Animals and treatments

Adult male Sprague-Dawley rats, held under standard laboratory conditions on a 12:12 light-dark cycle (lights on at 09:00), were used in all experiments. A total of 134 rats were used in this study; rats were housed singly per cage and had ad libitum access to water and a standard lab diet. Animals were deprived of the ability to sleep by gently touching them with a cotton bud stick during the first 6 hours of light on the day of experiment, during which treatments were applied.

Seven days before the testing of substances, diurnal blood samples were collected for the determination of corticosterone and GSH levels (see below) under basal conditions; blood was collected by tail venepuncture, a minimally invasive procedure to which rats easily habituate.

Frankincense essential oil (Young Living Essential Oil, Utah, USA), α-pinene and limonene (both from Kanto Chemicals, Ibaraki, Japan) were diluted (1:10^2-1:10^3) in odorless vehicle (jojoba oil, from Koei Perfumery, Tokyo, Japan). Vehicle, frankincense essential oil, α-pinene, or limonene were applied topically at hourly intervals from 10:00 until 15:00 (6 applications of 50 μL each onto the fur on the nape of neck) (Fig. 2). Substances were applied using a pipette to avoid potentially stressful physical handling.

2.2 Determination of plasma corticosterone levels

Tail vein blood was withdrawn at two points in the diurnal cycle (9:00 and 15:00, corresponding to the first and last application of the test substances). Blood plasma was assayed for corticosterone using commercial enzyme-linked immunosorbent assay (ELISA) kits (Arbor Assays, Michigan, USA), the lower limit of detection being 16.9 pg / mL.

2.3 Assay of GSH levels in CSF

Two samples (50 μL) of CSF were collected from lightly-anesthetized (halothane) rats (vehicle n = 9, frankincense n = 8, α-pinene n = 8, limonene n = 7) just before (09:00) and after the last (15:00) application of vehicle and test oils. CSF was gently withdrawn by inserting 21 G needle to the basilar part of the occipital bone; after addition of 1 mL of a 2% of ascorbic acid, samples were stored at −180°C freezer until analyses. In the assay, samples were run through C-18 (SC-50DS; Eicom, Kyoto, Japan) separation columns before assaying GSH levels by high performance liquid chromatography (HPLC)-electrochemical detection (ECD; 1250 mV, Diamond electrode vs. AgCl reference; ECD system DTA-300 from Eicom, Kyoto, Japan). The mobile phase in the HPLC consisted of 93% 100 mM phosphate buffer (pH 2.5) and 7% methanol, containing 150 mg / L octansulphonic acid (Nacalai Tesque, Japan). The lower and upper detection limits of the assay were 0.1 ng / μL, and 1.0 pg / μL, respectively.

2.4 Analysis of antioxidant capacity and oxidative stress levels

Plasma from blood samples from the tail vein, collected after the last application of vehicle and oils was used to estimate antioxidant capacity and oxidative stress levels using the biological antioxidant potential (BAP) and derivatives of reactive oxygen metabolites (d-ROM) tests.

The BAP which measures the antioxidant capacity of molecules in the blood that can donate electrons to reactive oxygen species (free radicals) is coulometry-based. It specifically assesses the potential for neutralization of ferric (Fe3+) ions; to maintain health, antioxidant ions, as measured by the BAP test should be > 2,200 μmol / L.

Assaying derivatives of reactive oxygen metabolites (d-ROM) provides an index of the ratio between oxidative and antioxidant reactions and potential oxidative damage to cells and tissues; the d-ROM test used here is based on measurements of the products of oxidative stress, namely organic hydroperoxides (ROOH) for; for this, we used a Free Radical Analytical System device (FRAS4, Wismerll, Tokyo, Japan). The principle of the colorimetric assay used is based on the ability of transition metals to catalyse the formation of free radicals (in the presence of peroxides), that are subsequently trapped by an alchiamine. Results are expressed in arbitrary units (Carratelli units, CARR U; 1 CARR U ~0.08 mg / 100 mL of H2O2; normal range: 200-300, borderline levels: 301-320; levels > 321 indicate oxida-
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tive stress).

2.5 Recordings of sleep and wakefulness

Sleep and wakefulness, as well as muscular tension/relaxation, was monitored in sleep-deprived rats, immediately after the last application of vehicle or frankincense essential oil (and components), between 15:00 and 21:00 (last 6 hours of daily light cycle) (Fig. 2). Recordings were made via for electroencephalogram (EEG) and electromyogram (EMG) electrodes that had been surgically-implanted at least 1 week prior to the oil treatments. The polygraphic recordings were analysed to reveal time spent in wakefulness, and rapid eye movement (REM) and non-rapid eye movement (NREM) sleep.

Sleep latency i.e. latency to sleep onset, was also analysed for NREM and REM sleep.

2.6 Statistical analysis

Data are shown as mean ± standard error (SE). A p value < 0.05 was considered statistically significant. Multiple comparison tests were used as appropriate. Dunnnett’s multiple comparison test was used to compare oil-treated vs. vehicle-treated animals, when the variance from the whole set of data was considered as a pooled estimate, Tukey test was used if the population variances were not equal, Student’s t-test was used if the population variances (sample sizes) were the same in all groups. In contrast, the Tukey-Kramer test was applied when treatments (sample groups) had an unequal number of observations. Student’s t-test was used to estimate the variance between two groups.

All procedures used were in accordance with the standards of the institutional ethics committee of Tokyo Medical and Dental University.

3 Results

3.1 Influence of frankincense essential oil and its major components on plasma corticosterone levels

Plasma corticosterone levels showed a diurnal variation from 66.6 ± 27.2 ng/mL at 09:00 to 215.8 ± 71.6 ng/mL at 15:00 (n = 6, not shown). Application of jojoba oil (vehicle) to control animals increased plasma corticosterone levels to 265.7 ± 10.3 ng/mL at 15:00 (N.S. vs. unhandled controls at 15:00), suggesting that the application procedure was mildly stressful (Fig. 3).

Undiluted (1:1) frankincense essential oil further increased plasma levels of corticosterone (p < 0.05 vs. controls), but significantly reduced corticosterone levels when applied at 1:104 and 1:105 dilutions (vs. 1:1 frankincense essential oil), as shown in Fig. 3. In contrast, none of the tested doses (dilutions) of α-pinene and limonene were potentially able to counteract the effects of handling (oil application): corticosterone levels were not significantly different from those observed in rats receiving vehicle treatment.

3.2 Frankincense attenuates CSF levels of GSH

The GSH levels in the CSF showed a diurnal variation from 37.8 ± 1.0 pmol/L at 9:00 to 45.6 ± 2.0 pmol/L at 15:00 (n = 6, not shown).

As compared to vehicle (jojoba oil), undiluted frankincense, α-pinene and limonene, significantly reduced (p < 0.05) CSF levels of GSH (from 33.2 ± 2.3 pmol/L in vehicle-treated animals to 26.4 ± 1.8, 23.7 ± 1.8 and 21.7 ± 1.8 pmol/L, in frankincense-, α-pinene- and limonene-treated rats, respectively (Fig. 4). All measurements were made at 15:00, i.e. after the last topical application of the different oils.
3.3 Influence of frankincense essential oil on antioxidant capacity and oxidative stress levels

Frankincense essential oil, administered at dilutions of 1:10³ - 1:10⁴ produced slight, but statistically insignificant decreases in antioxidant ion concentrations in the blood (Fig. 5A). Consistently with this finding, blood concentrations of metabolic derivatives of the products of oxidative stress were also not increased by the frankincense essential oil regimens tested in this study (Fig. 5B).

3.4 Frankincense essential oil enhances wakefulness in sleep-deprived rats

As shown in Fig. 6, frankincense essential oil applied at a 1:10³ dose significantly increased the time of wakefulness from 64.5 ± 3.4 to 77.8 ± 2.5 min (p < 0.05). The essential oil also significantly decreased NREM sleep (from 258.7 ± 3.4 to 243.9 ± 4.6 min, p < 0.05).

A NREM sleep latency in jojoba oil-treated rats was 446.0 ± 33.0 sec and 224.0 ± 49.3 sec in frankincense oil-treated rats, respectively (N.S. n = 5, not shown). A REM sleep latency in jojoba oil-treated rats was 853.0 ± 83.9 sec and 824.0 ± 151.3 sec in frankincense oil-treated rats.

4 Discussion

The secretion of glucocorticoids (cortisol in humans, corticosterone in rodents) in response to stressors allows physiological and behavioural adaptation to alterations in the psychological and physical environment. However, their prolonged or excessive secretion can be maladaptive and even result in somatic and brain pathologies. Glucocorticoids are in fact essential for life and follow a circadian rhythm; in rodents and other nocturnal species, secretion is low at the onset of light (in this study at 09:00) and gradually rises to peak at the onset of darkness (in this study at 21:00) [23, 24]. This rhythmic pattern facilitates coordination of metabolic, physiological and behavioural functions and thus maintains health. As shown here, a mild stress, such as handling during the daily period of rest (15:00), can stimulate corticosterone secretion. Importantly, we observed that topical application of a 1:10³ dilution of frankincense essential oil could attenuate stress-induced elevations of corticosterone secretion at an inappropriate time of day (Fig. 3). In contrast, undiluted frankincense essential oil lacked this ability, possibly because of its strong novel and/or aversive aromatic properties; in addition, we
observed that diluted and undiluted preparations of α-pinene and limonene (principal components of frankincense) did not influence handling stress-related increases in corticosterone levels. This finding indicates that the stress-reducing effects of frankincense essential oil reflect interactions between its different constituents, rather than any one of its main components; this view is supported by evidence from traditional Chinese medicine in which mixtures of various plants, which are otherwise ineffective on their own, have medicinal properties.

External stressors can also cause cellular or oxidative stress, a phenomenon frequently associated with cancer. Organisms are endowed with physiological mechanisms to combat this form of stress, provided that the insult is not too great. GSH is one molecule that serves as endogenous antioxidant: by neutralizing reactive oxygen species (e.g., peroxide), it plays a detoxifying role and helps maintain homeostasis, reflected in improvements in sleep. Consistent with previous findings, we here observed circadian changes in brain levels of GSH (lower in the daily light / resting phase, higher during the dark / active phase). Although GSH levels are normally increased under stressful conditions, we here observed levels of GSH to be decreased when animals were exposed to undiluted frankincense essential oil (as well as α-pinene and limonene). This interesting finding suggests that frankincense essential oil and its major components themselves may have sufficient detoxification capacity, eliminating the need for endogenous GSH. This interpretation is supported by a previous report of the antioxidant properties of frankincense essential oil as well as our observation that diluted frankincense essential oil caused a decrease in metabolite generation (relative to control, jojoba oil-treated animals).

However, it is important to note that treatment with frankincense essential oil did not completely eliminate reactive oxygen species, indicating that dosage might still require optimization. On the other hand, it is also important to note that, as shown in Fig. 5B, frankincense essential oil maintained active oxygen metabolites within a normal (healthy) range.

Monitoring of sleep and wakefulness in sleep-deprived rats revealed that frankincense essential oil at a dilution 1:10³ (the same as that found to attenuate the stress response) could effectively relieve "sleep debt" (urge to sleep); specifically, the oil increased the time of wakefulness while decreasing the amount of time spent in NREM sleep. Frankincense oil-treated rats fell into sleep more quickly and spent less time asleep compared to the jojoba oil-treated rats. This sleep profile is indicative of improved sleep quality (high delta power and shortened recovery sleep).

Since sleep deprivation in the frankincense essential oil-treated animals was not accompanied by higher blood levels of the stress hormone corticosterone, this result suggests that the sleep-improving effects of the oil were independent of its stress-reducing properties. At first glance, the sleep data obtained here appear inconsistent with results of a previous study which showed that exogenous administered GSH increases the amount of NREM sleep, and that oxidized GSH (GSSG) induces sleep. In fact, as shown in Fig. 6, while the sleep recording between 15:00 and 21:00 would be sufficiently long to induce rebound of sleep, application of frankincense essential oil prevented the accumulation of GSH in the brain and thus, reduced NREM sleep.

5 Conclusion

This work shows that frankincense essential oil has stress-reducing properties, antioxidant and detoxifying effects, and can compensate for sleep loss. The data presented here suggest that these multiple actions cannot be attributed to a single component of this essential oil. A challenge for future studies will be to dissect the molecular pathways and mechanisms that mediate the above-described anti-stress and psychotropic actions of frankincense essential oil.

Acknowledgment

We thank Prof. Moses Akanmu and Dr. Osborne Almeida for helpful discussions and critical reading of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1) Sharifi-Rad, J.; Sureda, A.; Tenore, G.C.; Daglia, M.; Sharifi-Rad, M.; Valussi, M.; Tundis, R.; Sharifi-Rad, M.; Loizzo, M.R.; Ademiluyi, A.O.; Sharifi-Rad, R.; Ayatollahi, S.A.; Iriti, M. Biological activities of essential oils: From plant chemoecology to traditional healing systems. Molecules 22, pii:E70 (2017).
2) Elshafie, H.S.; Camele, I. An overview of the biological effects of some mediterranean essential oils on human health. Biomed. Res. Int. 2017: 9268468 (2017).
3) Dagli, N.; Dagli, R.; Mahmoud, R.S.; Baroudi, K. Essential oils, their therapeutic properties, and implication in dentistry: A review. J. Int. Soc. Prev. Community Dent. 5, 335-340 (2015).
Bertocchi, M.; Isani, G.; Medici, F.; Andreani, G.; Usca, I.T.; Roncada, P.; Forni, M.; Bernardini, C. Anti-inflammatory activity of Boswellia serrata extracts: An in vitro study on porcine aortic endothelial cells. *Oxid. Med. Cell. Longev.* 2018:2504305 (2018).

5) Beghelli, D.; Isani, G.; Roncada, P.; Andreani, G.; Bostumo, O.; Bertocchi, M.; Lupádi, G.; Alumo, A. Antioxidant and ex vivo immune system regulatory properties of Boswellia serrata extracts. *Oxid. Med. Cell. Longev.* 2017:7468064 (2017).

6) Hamidpour, R.; Hamidpour, S.; Hamidpour, M.; Shahlari, M. Frankincense (Boswellia species): From the selection of traditional applications to the novel phytotherapy for the prevention and treatment of serious diseases. *J. Tradit. Complement. Med.* 3, 221-226 (2013).

7) Andreani, G.; Ferlizza, E.; Macri, E.; Beghelli, D.; Isani, G. Effect of Boswellia serrata supplementation in addition to insulin on glycemic control in a diabetic dog. *Slov. Vet. Res.* 54, 173-179 (2017).

8) Al-Yasiry, A.R.M.; Kiczorowska, B. Frankincense - therapeutic properties. *Postepy Higieny i Medycyny Doswiadczalnej* 70, 380-391 (2016).

9) Chen, y.; Ahou, C.; Ge, Z.; Liu, Y.; Liu, Y.; Feng, W.; Li, S.; Chen, G.; Wei, T. Composition and potential anticancer activities of essential oils obtained from myrrh and frankincense. *Oncol. Lett.* 6, 1104-1146 (2013).

10) Ni, X.; Suhail, M.M.; Yang, Q.; Cao, A.; Fung, K.M.; Postier, R.G.; Woolley, C.; Young, G.; Ahang, J.; Lin, H.K. Frankincense essential oil prepared from hydrodistillation on Boswellia sacra gum resins induces human pancreatic cancer cell death in cultures and in a xenograft murine model. *BMC Complement. Altern. Med.* 12:253 (2012).

11) Suhail, M.M.; Wu, W.; Cao, A.; Mondalek, F.G.; Fung, K.M.; Shih, P.T.; Fang, Y.T.; Woolley, C.; Young, G.; Lin, H.K. *Boswellia sacra* essential oil induces tumor cell-specific apoptosis and suppresses tumor aggressiveness in cultured human breast cancer cells. *BMC Complement. Altern. Med.* 11:129 (2011).

12) Van Vuuren, S.F.; Kamatou, G.P.P.; Viljoen, A.M. Volatile composition and antimicrobial activity of twenty commercial frankincense essential oil samples. *S. Afr. J. Bot.* 76, 686-691 (2010).

13) Young Living Essential Oils. Analysis of Component, Frankincense Lot: 14945. *Flora Research Certificate of Analysis* (2014).

14) Aquilano, K.; Baldelli, S.; Ciriolo, M.R. Glutathione: new roles in redox signalling for an old antioxidant. *Front. Pharmacol.* 5:196 (2014).

15) Lu, S.C. Glutathione synthesis. *Biochim. Biophys. Acta* 1830, 3143-3153 (2013).

16) Gawryluk, J.W.; Wang, J.F.; Andreazza, A.C.; Shao, L.; Young, L.T. Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. *Int. J. Neuropharmacol.* 14, 123-130 (2011).

17) Circu, M.L.; Aw, T.Y. Reactive oxygen species, cellular redox systems and apoptosis. *Free Radic. Biol. Med.* 48, 749-762 (2010).

18) Ballatori, N.; Krance, S.M.; Notenboom, S.; Shi, S.; Tieu, K.; Hammond, C.L. Glutathione dysregulation and the etiology and progression of human diseases. *Biol. Chem.* 390, 191-214 (2009).

19) Murias, M.; Luczak, M.W.; Niepsuj, A.; Kuzniak, V.K.; Przyjemksa, M.Z.; Jagodzinski, P.P.; Jager, W. Szekeres, T.; Liebert, J.J. Cytotoxic activity of 3, 3’, 4, 4’, 5’, 5’-hexahydroxystilbene against breast cancer cells is mediated by induction of p53 and downregulation of mitochondrial superoxide dismutase. *Toxicol. In Vitro* 22, 1361-1370 (2008).

20) Klarod, K.; Gatterer, H.; Frontull, V.; Philippe, M.; Burtscher, M. Effects of short-term antioxidant supplementation on oxidative stress and exercise performance in the heat and the cold. *Int. J. Physiol. Pathophysiol. Pharmacol.* 7, 98-104 (2015).

21) Knez, W.L.; Pieriard, J.P. The impact of match-play tennis in a hot environment on indirect markers of oxidative stress and antioxidant status. *Br. J. Sports Med.* 48, i59-63 (2014).

22) Kimura, M.; Kodama, T.; Aguila, M.C.; Zhang, S.Q.; Inoue, S. Granulocyte-macrophage colony-stimulating factor modulates rapid eye movement (REM) sleep and non-REM sleep in rats. *J. Neurosci.* 20, 5544-5551 (2000).

23) Sundar, I.K.; Yao, H.; Huang, Y.; Lyda, E.; Sime, P.J.; Sellix, M.Y.; Rahman, I. Serotonin and corticosterone rhythms in mice exposed to cigarette smoke and in patients with COPD: Implication for COPD-associated neuropathogenesis. *Plos One* 9(2), e87999 (2014).

24) Egawa, M.; Inoue, S.; Sato, S.; Takamura, Y.; Takahashi, K. The effect of ventromedial hypothalamic lesions on circadian corticosterone rhythm. *Prog. Med.* 6, 842-844 (1986).

25) Chen, D.; Bobko, A.A.; Gross, A.C.; Evans, R.; Marsh, C.B.; Khramtsov, V.V.; Eubank, T.D.; Friedman, A. Involvement of tumor macrophage HIPs in chemotherapeutic effectiveness: Mathematical modelling of oxigen, pH, and glutathione. *Plos One* 9(10), e107511 (2014).

26) Pompella, A.; Visvikis, A.; Paolicchi, A.D.; Tata, V.; Casisi, A.F. The changing faces of glutathione, a cellular protagonist. *Biochem. Pharmacol.* 66, 1499-1503 (2003).

27) Inoue, S. Advances in sleep research. *Japanese J. Geriatric Psychiatry* 12, 1329-1335 (2001).

28) Meister, M.; Anderson, M.E. Glutathione. *Ann. Rev. Biochem.* 52, 711-760 (1983).

29) Cao, H.; Qin, F.; Liu, X.; Wang, J.; Cao, Y.; Tong, J.;
Zhao, H. Circadian rhythmicity of antioxidant markers in rats exposed to 1.8 GHz radiofrequency fields. *Int. J. Environ. Res. Public Health* **12**, 2071-2087 (2015).

30) Miura, N.; Yanagiba, Y.; Ohtani, K.; Miia, M.; Togawa, M.; Hasegawa, T. Diurnal variation of cadmium-induced mortality in mice. *J. Toxicol. Sci.* **37**, 191-196 (2012).

31) Ponce, I.T.; Rezza, I.G.; Delgado, S.M.; Navigatore, L.S.; Bonomi, M.R.; Golini, R.L.; Gimenez, M.S.; Anzulovich, A.C. Daily oscillation of glutathione redox cycle is dampened in the nutritional vitamin A deficiency. *Biol. Rhythm. Res.* **43**, 351-372 (2012).

32) Shiomi, H. Sleep induction mechanism and pain control mechanism. in *Mechanism of Sleep*. Asakura Publishing, Tokyo, pp. 74-102 (1997).