

NATURAL HEALTH PRODUCT

COUNTERIRRITANTS

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredients.

Definition of Counterirritant

An externally applied substance that causes irritation or mild inflammation of the skin for the purpose of relieving pain in muscles or joints by reducing inflammation in deeper adjacent structures (Medline 2012; MediLexicon 2012; US FDA 1983).

Notes

- ▶ Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant's discretion.
- ▶ The solidus (/) indicates that the terms and/or statements are synonymous. Either term or statement may be selected by the applicant.

Date

April 29, 2019

Proper name(s), Common name(s), Source material(s)

Table 1. Proper name(s), Common name(s), Source material(s) – Medicinal ingredients

Proper name(s)	Common name(s)	Source ingredient(s)	Source material(s) ¹	
		Common name(s)	Proper name(s)	Part(s)
<ul style="list-style-type: none"> ▶ 3-isothiocyanato-1-propene ▶ Allyl isothiocyanate ▶ Isothiocyanic acid allyl ester 	Allyl isothiocyanate	Allyl isothiocyanate	N/A	N/A
Ammonium hydroxide	<ul style="list-style-type: none"> ▶ Ammonia water ▶ Ammonium hydroxide 	Ammonium hydroxide	N/A	N/A
<ul style="list-style-type: none"> ▶ (1R, 4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one ▶ d-camphor 	<ul style="list-style-type: none"> ▶ (+)- Camphor ▶ Camphor ▶ d-camphor ▶ natural camphor 	d-camphor	N/A	N/A
<ul style="list-style-type: none"> ▶ (1RS, 4RS)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one ▶ dl-camphor 	<ul style="list-style-type: none"> ▶ (+-)- camphor ▶ dl-camphor ▶ Racemic camphor 	dl-camphor	N/A	N/A



<ul style="list-style-type: none"> ▶ (6E)-N-[(4-Hydroxy-3-methoxyphenyl)methyl]-8-methyl-6-nonenamide ▶ (E)-8-methyl-N-vanillyl-6-nonenamide 	Capsaicin	Capsaicin	N/A	N/A
<i>Eucalyptus globulus</i>	<ul style="list-style-type: none"> ▶ Eucalyptus essential oil ▶ Eucalyptus Globulus Leaf essential oil 	N/A	<i>Eucalyptus globulus</i>	Leaf
<ul style="list-style-type: none"> ▶ 1,3,3-Trimethyl-2-oxabicyclo(2.2.2)octane ▶ 1,8 Cineole ▶ 1,8-Epoxy-p-menthane 	<ul style="list-style-type: none"> ▶ Cineole ▶ Eucalyptol 	Eucalyptol	N/A	N/A
<ul style="list-style-type: none"> ▶ 1H-imidazole-4-ethanamine, dihydrochloride ▶ 2-imidazol-4-ylethylamine dihydrochloride ▶ 4-(2-aminoethyl)imidazole dihydrochloride 	Histamine dihydrochloride	Histamine dihydrochloride	N/A	N/A
<ul style="list-style-type: none"> ▶ (1R,2S,5R)-rel-5-methyl-2-(1-methylethyl)-cyclohexanol ▶ (1RS,2RS,5RS)-(±)-5-methyl-2-(1-methylethyl)cyclohexanol ▶ dl-Menthol 	<ul style="list-style-type: none"> ▶ dl-Menthol ▶ Racemic Menthol 	dl-menthol	N/A	N/A
<ul style="list-style-type: none"> ▶ (1R,2S,5R)-5-Methyl-2-(1-methylethyl)cyclohexane ▶ (1R,2S,5R)-5-methyl-2-(propan-2-yl)cyclohexan-1-ol ▶ l-Menthol 	<ul style="list-style-type: none"> ▶ l-menthol ▶ Menthol 	l-menthol	N/A	N/A

3-pyridinecarboxylic acid methyl ester	Methyl nicotinate	Methyl nicotinate	N/A	N/A
<ul style="list-style-type: none"> ▶ 2-(Methoxycarbonyl) phenol ▶ 2-Hydroxybenzoic acid methyl ester ▶ Methyl 2-hydroxybenzoate 	Methyl salicylate	Methyl salicylate	N/A	N/A
Turpentine essential oil	<ul style="list-style-type: none"> ▶ Turpentine essential oil ▶ Turpentine oil 	Turpentine essential oil	N/A	N/A

¹ All ingredients, except ammonium hydroxide, must be pharmacopoeial grade (see Table 6 in the specifications below).

References: Ph.Eur. 2013, BP 2012, Merck 2012, NLM 2012, USP 36, ChEBI 2011, CTFA 2008, Bruneton 1999.

Table 2. Proper name(s), Common name(s), Source material(s) – Complementary ingredients (safety only)

Proper name(s)	Common name(s)	Source ingredient(s)	Source material(s) ¹	
		Common name(s)	Proper name(s)	Part(s)
<i>Syzygium aromaticum</i>	Clove essential oil	N/A	<i>Syzygium aromaticum</i>	Flower bud
<ul style="list-style-type: none"> ▶ 1-methyl-3-hydroxy-4-isopropylbenzene ▶ 5-methyl-2-(propan-2-yl) phenol ▶ 5-methyl-2-(1-methylethyl)-phenol ▶ 5-methyl-2-isopropyl-1-phenol 	Thymol	Thymol	N/A	N/A

¹ All ingredients must be pharmacopoeial grade (see Table 6 in the specifications below).

References: Proper name: Ph.Eur. 2013, BP 2012, Merck 2012, NLM 2012, USP 36 2013, ChEBI 2011, Bruneton 1999.

Route of administration

Topical

Dosage form(s)

Acceptable dosage forms for the age category listed in this monograph and specified route of administration are indicated in the Compendium of Monographs Guidance Document.

Plaster, compress or patch

Menthol, methyl salicylate, eucalyptus oil and eucalyptol are the only medicinal ingredients allowed in these forms (Higashi et al. 2010).

Use(s) or Purpose(s)

Products containing an ingredient in Table 1

Temporarily relieves aches and pains of muscles and joints associated with one or more of the following: simple backache, lumbago, strains and sprains (involving muscles, tendons, and/or ligaments), and arthritis.

Dose(s)

Subpopulation(s)

Children 2 to 11 years, Adolescents 12 to 17 years and Adults 18 years and older

Quantity(ies)

Table 3. Medicinal Ingredient Doses

Medicinal Ingredients	Doses
Allyl isothiocyanate	0.5 – 5.0 %
Ammonium hydroxide	1.0 – 2.5 %
d-camphor	3 – 11 %
dl-camphor	3 – 11 %
Capsaicin	0.025 – 0.25 %
Eucalyptus essential oil	0.5 – 25.0 %
Eucalyptol	0.5 – 20.0 %
Histamine dihydrochloride	0.025 – 0.1 %
l-menthol	1.25 – 16 %
dl-menthol	1.25 – 16 %
Methyl nicotinate	0.25 – 1.0 %
Methyl salicylate	10 – 30 %
Turpentine essential oil	6 – 50 %

References: JC 2012, AU TGA 2007, Janjua et al. 2004, ESCOP 2003, APhA 2002, WHO 2002, Blumenthal et al. 2000, CPhA1996, Mathias et al. 1995, US FDA 1983, 1979.

Table 4. Complementary Ingredients Doses (Safety only)

Complementary Ingredients	Doses
Clove essential oil	0.1 – 2.0 %
Thymol	0.1 – 2.0 %

References: US FDA 1979.

Permitted combinations

- ▶ Clove essential oil and thymol must be used in combinations with other medicinal ingredients in Table 1, as they cannot support the efficacy of the product on their own (US FDA 1983; US FDA 1979).
- ▶ Except as noted above, any ingredient from Table 5 can be combined with other ingredients from the table provided that the combination contains only one ingredient from each group and that each ingredient is within the quantities given in Tables 3 and 4 (US FDA 1983).
- ▶ Group B1 ingredients may be used in combination with each other, and this may be combined with any ingredients from the table provided that combination contains only one ingredient from each of the other groups.

 Table 5. Permitted combinations¹

Groups ²	Ingredients
A	Allyl isothiocyanate, ammonium hydroxide, methyl salicylate, turpentine essential oil
B1	Camphor, menthol
B2	Eucalyptus essential oil, eucalyptol
C	Histamine dihydrochloride, methyl nicotinate
D	Capsaicin
E	Thymol, clove essential oil

¹ See Appendix 1 for grouping rationale.

² Permitted combinations for all groups are supported by US FDA 1979, except for Group E which is supported by Merck 2012, Martindale 2010, and Leung and Foster 2003.

Direction(s) for use

All products

- ▶ For external use only.
- ▶ Avoid contact with the eyes and mucous membranes (US FDA 1983).
- ▶ Do not apply to wounds or damaged skin (US FDA 1983).
- ▶ Do not tightly bandage (US FDA 1983).
- ▶ Do not apply with external heat, such as an electric heating pad, as this may result in excessive skin irritation or skin burn (Pray 2006; APhA 2002).

For children and adolescents 2-12 years

Application should be supervised by an adult (Ragucci et al. 2007; Love et al. 2004).

Products in liquid or semi-solid form

Apply thinly and evenly to affected area up to 3-4 times per day. Rub and/or massage into skin until solution vanishes (US FDA 1979).

Products in compress, plaster or patch form

Do not leave on skin for more than 8 hours (Higashi et al. 2010).

Products in pump spray form

Do not inhale (APhA 2002).

Duration(s) of use

Products containing capsaicin as a single medicinal ingredient

- ▶ May take 1-2 weeks to produce beneficial effects.
- ▶ Consult a health care practitioner/health care provider/health care professional/doctor/physician for use beyond 6 weeks (Martindale 2010; CPS 2008; APhA 2002; CPhA1996).

All other products (including multiple ingredient products containing capsaicin)

Consult a health care practitioner/health care provider/health care professional/doctor/physician for use beyond 7 days (US FDA 1983).

Risk information

Caution(s) and warning(s)

All products

- ▶ Keep out of the reach of children.
- ▶ Call a Poison Control Center immediately if overdose or accidental ingestion occurs (CPS 2008; HC 2006).
- ▶ Stop use and consult a health care practitioner/health care provider/health care professional/doctor/physician if symptoms worsen, or re-occur within a few days (CPhA1996; US FDA 1983).

Products containing camphor, menthol, and/or methyl salicylate

Consult a health care practitioner/health care provider/health care professional/ doctor/physician prior to use if you are pregnant or breastfeeding (Brinker 2001).



Products containing methyl salicylate and/or methyl nicotinate

Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are taking anticoagulant medications (Martindale 2010; APhA 2002).

Products containing methyl nicotinate

Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are taking medication or natural health products that cause dilation of blood vessels (APhA 2002).

Contraindication(s)

No statement required.

Known adverse reaction(s)

All products

Stop use if hypersensitivity/allergy, rashes and/or burning discomfort occur (Martindale 2010; Zhang et al. 2008; Hoffman 2003; APhA 2002; McCleane 2000).

Products containing capsaicin

Stop use if headache and/or redness occur (Zhang et al. 2008; APhA 2002; McCleane 2000).

Products containing menthol

Stop use and get medical help right away if you experience pain, swelling or blistering (HC 2017).

Non-medicinal ingredients

Must be chosen from the current Natural Health Products Ingredients Database (NHPID) and must meet the limitations outlined in the database.

Storage conditions

Store in airtight, light-resistant container at room temperature (Ph.Eur. 2013; BP 2012; USP 36).



Specifications

- ▶ The finished product specifications must be established in accordance with the requirements described in the Natural and Non-prescription Health Products Directorate (NNHPD) Quality of Natural Health Products Guide.
- ▶ The medicinal ingredient must comply with the requirements outlined in the NHPID.
- ▶ The medicinal ingredient must be of pharmacopoeial grade and may comply with the specifications outlined in the pharmacopoeial monographs listed in Table 6 below. Please note that other pharmacopoeias may also be acceptable.
- ▶ To mitigate the potential risk to the health of children, child-resistant packaging/containers should be used for (JC 2012 sections C.01.001(2) to (4)):
 - clove essential oil (Martindale 2010)
 - camphor (AU TGA 2008)
 - eucalyptol (AU TGA 2008)
 - eucalyptus essential oil (AU TGA 2008)
 - methyl salicylate (JC 2012 subsections C.01.031(1) (a) (i); APhA 2002).

Table 6. Monographs published in the British (BP), European (Ph.Eur.), and American (USP) Pharmacopoeias

Pharmacopoeia	Monographs
BP 2012	Natural Camphor Racemic Camphor Cineole Histamine Dihydrochloride Methyl Nicotinate Methyl Salicylate Thymol
Ph.Eur. 2013	D-Camphor Camphor, racemic Cineole Clove Oil Eucalyptus Oil Histamine dihydrochloride Menthol, Racemic Methyl Nicotinate Methyl Salicylate Thymol Turpentine Oil
USP 36 – NF 31	Allyl isothiocyanate Camphor Capsaicin Clove oil Eucalyptol Menthol Methyl Salicylate Thymol



References cited

APhA 2002: Berardi RR, DeSimone EM, Newton GGD, Oszko MA, Popovich NG, Rollins CJ, Shimp LA, Tietze KJ, editors. Handbook of Nonprescription Drugs: An interactive approach to self-care. 13th edition. Washington (DC): American Pharmaceutical Association; 2002.

AU TGA 2008: Australia Therapeutic Goods Administration, 2008. Therapeutic Goods Order No. 80 Schedule 1. Child-resistant packaging requirements for medicines (27/08/2008). Federal Register of Legislative Instruments (FRLI): Legislative Instrument - F2008L03428. [Accessed 2017 January 30]. Available from:

<http://www.comlaw.gov.au/Details/F2008L03428/Download>

AU TGA 2007: Australian Therapeutic Goods Administration. Substances that may be used in Listed medicines in Australia. 12 December 2007 [Internet]. [Accessed 2017 January 30]. Available from: <http://www.tga.gov.au/pdf/cm-listed-substances.pdf>

Blumenthal M, Goldberg A, Brinckmann J, editors. Herbal Medicine: Expanded Commission E Monographs. Boston (MA): Integrative Medicine Communications; 2000.

BP 2012: British Pharmacopoeia, 2012. London (GB): The Stationary Office on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA).

Brinker F. Herb Contraindications and Drug Interactions. 3rd edition. Sandy (OR): Eclectic Medical Publications; 2001.

Bruneton J. Pharmacognosy: Phytochemistry Medicinal Plants. 2nd edition. Paris (FR): Lavoisier Publishing; 1999.

ChEBI 2011: Chemical entities of biological interest: (-)-menthol (CHEBI:15409). Last modified 11 November 2015. [Internet]. Hinxton (GB): ChEBI is a database of the European Bioinformatics Institute. [Accessed 2017 January 30]. Available from: <http://www.ebi.ac.uk/chebi/searchId.do;D6D62EE6191A41FF796E0A250065D9DB?chebiId=CHEBI:15409>

CPhA 1996: Carruthers-Czyzewski P, editor. Non-Prescription Drug Reference for Health Professionals. First Edition. Ottawa (ON): Canadian Pharmaceutical Association; 1996.

CPS 2008: Repchinsky C, Welbanks L, Bhalla A, Fortin K, Jarvis B, Jovaisas B, Acharya S. Compendium of Pharmaceutical Specialties. Ottawa (ON): Canadian Pharmacists Association; 2008.

CSE 2006: Council of Science Editors, Style Manual Committee. Scientific Style and Format: The CSE Manual for Authors, Editors, and Publishers. Seventh edition. Reston (VA): The Council; 2006.

CTFA 2008: Gottschalck TE, Bailey JE, editors. International Cosmetic Ingredient Dictionary and Handbook. 12th edition. Washington (DC): The Cosmetic, Toiletry and Fragrance Association; 2008.

ESCOPE 2003: European Scientific Cooperative on Phytotherapy. The Scientific Foundation for Herbal Medicinal Products. 2nd edition. Exeter (GB): ESCOP 2003.

HC 2017: Health Canada. Recalls and safety alerts: Health Canada safety review finds risk of serious skin burns with over-the-counter topical pain relievers containing menthol.[Internet]. Ottawa (ON): Health Canada; February 2017. Available From: <http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/62178a-eng.php>

HC 2006: Health Canada. It's Your Health: Safe use of Health Products Containing Camphor and/or Eucalyptus Oils. [Internet]. Ottawa (ON): Health Canada; October 2004 [modified 2006 December 15; Accessed 2017 January 30]. Available from: <http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/life-vie/camphor-camphre-eng.php>

Higashi Y, Kiuchi T, Furuta K. Efficacy and safety profile of a topical methyl salicylate and menthol patch in adult patients with mild to moderate muscle strain: A randomized, double-blind, parallel-group, placebo-controlled, multicenter study. *Clinical Therapeutics* 2010;32(1):34-43.

Hoffman D. Medical Herbalism: The Science and Practice of Herbal Medicine. Rochester (VT): Healing Arts Press; 2003.

Janjua NR, Mogensen B, Andersson AM, Petersen JH, Henriksen M, Skakkebaek NE, Wulf HC. Systemic absorption of the sunscreens benzophenone-3, octyl-methoxycinnamate, and 3-(4-methyl-benzylidene) camphor after whole-body topical application and reproductive hormone levels in humans. *The Journal of Investigative Dermatology* 2004;123:57-61.

JC 2012: Justice Canada. *Food and Drug Regulations* (C.R.C., c. 870). Ottawa (ON): Justice Canada. [Accessed 2017 January 30]. Available from: http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870

Leung AY, Foster S. Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics. Second edition. Hoboken (NJ): John Wiley & Sons, Inc; 2003.

Love JN, Sammon M, Smereck J. Are one or two dangerous? Camphor exposure in toddlers. *The Journal of Emergency Medicine* 2004;27(1):49-54.

Martindale 2010: Sweetman SC, editor. Martindale: The Complete Drug Reference. [Internet] London (GB): Pharmaceutical Press; Copyright 1933-2010. [Accessed 2017 January 30]. Available from: <http://www.medicinescomplete.com>

Mathias BJ, Dillingham TR, Zeigler DN, Chang AS, Belandres PV. Topical capsaicin for chronic neck pain. *American Journal of Physical Medicine and Rehabilitation* 1995;74(1):40-44.
McCleane G. Topical application of doxepin hydrochloride, capsaicin and a combination of both

produces analgesia in chronic human neuropathic pain: a randomized, double-blind, placebo-controlled study. *British Journal of Clinical Pharmacology* 2000;49:574-579.

MediLexicon 2012: Medical Dictionary, Medical Terminology [Internet] Bexhill-on-Sea (GB). MediLexicon International Ltd; © 2004-2012. [Accessed 2017 January 30]. Available from: <http://www.medilexicon.com/medicaldictionary.php>

MedlinePlus 2012: Merriam-Webster Online Dictionary. Springfield (MA). Merriam-Webster, Incorporated; © 2012. [Accessed 2017 January 30]. Available from: <http://www.nlm.nih.gov/medlineplus/medlineplusdictionary.html>

Merck 2012: O'Neil MJ, Heckelman PE, Koch CB, Roman KJ, editors. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals* (14th Edition - Version 14.9). Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.; © 2006, 2012. [Accessed 2017 January 30]. Available from: <https://www.rsc.org/merck-index>

NLM 2012: National Institute of Medicine. ChemIDplus advanced [Internet]. Search terms: "allyl isothiocyanate," "Ammonia water," "Camphor," "Capsaicin," "Clove oil," "Eucalyptus oil," "Eucalyptol," "Histamine dihydrochloride," "Menthol," "Methyl salicylate," "Methyl nicotinate," "Thymol," "Turpentine oil." Bethesda (MD): Specialized Information Services, United States National Library of Medicine, National Institutes of Health, United States Department of Health & Human Services. [Accessed 2017 January 30]. Available from: <http://chem.sis.nlm.nih.gov/chemidplus/>

Ph.Eur. 2013: *European Pharmacopoeia 7th Edition*. 2013. European Directorate for the Quality of Medicines & HealthCare. Strasbourg (FR): Council of Europe.

Pray WS. *Non-Prescription Product Therapeutics*. 2nd edition. New York (NY): Lippincott Williams & Wilkins; 2006.

Ragucci KR, Trangmar PH, Bigby JG, Detar TD. Camphor ingestion in a 10-year-old male. *Southern Medical Journal* 2007;100(2):204-207.

US FDA 1983: United States Food and Drug Administration. *External Analgesics Drug Products for Over-the-Counter Human Use; Tentative Final Monograph* [Internet]. Federal Register, Volume 48, Number 27, February 8, 1983, Proposed Rules. Rockville (MD): United States Department of Health and Human Services, U.S. Food and Drug Administration. [Accessed 2017 January 30]. Available from: http://www.fda.gov/ohrms/DOCKETS/ac/05/briefing/2005-4099B1_03_FDA-Tab3.pdf

US FDA 1979: The USA Department of Health and Human Services: Food and Drug Administration. 21 CHR Part 348. *External analgesics drug products for over-the-counter human use: establishment of a monograph and notice of proposed rulemaking*, 1979. [Accessed 2017 January 30]. Available from: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2005_register&docid=05-3055.pdf



USP 36: United States Pharmacopeia and the National Formulary (USP 36 - NF 31). Rockville (MD): The United States Pharmacopeial Convention; 2013.

WHO 2002: WHO Monographs on Selected Medicinal Plants - Volume 2. Geneva (CH): WHO Library Cataloguing-in-Publication Data; © World Health Organization 2002. [Accessed 2017 January 30] Available from: <http://apps.who.int/medicinedocs/en/d/Js4927e/>

Zhang W, Moskowitz, RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence--based, expert consensus guidelines. *Osteoarthritis and Cartilage* 2008;16:137-162.

References reviewed

Altman RD. Practical considerations for the pharmacologic management of osteoarthritis. *The American Journal of Managed Care* 2009;15(8):S236-S244.

American College of Rheumatology. Recommendations for the medical management of osteoarthritis of the hip and knee. *Arthritis and Rheumatism* 2000;43(9):1905-1915.

Arendt-Nielsen L, Svensson P, Sessle BJ, Cairn BE, Wang K. Interactions between glutamate and capsaicin in inducing muscle pain and sensitization in humans. *European Journal of Pain* 2008;12(5):661-670.

Benfeldt E, Serup J, Menne T. Effect of barrier perturbation on cutaneous salicylic acid penetration in human skin: in vivo pharmacokinetics using microdialysis and non-invasive quantification of barrier function. *British Journal of Dermatology* 1999;140:739-748.

Bernstein JE, Bickers DR, Dahl MV, Roshal JY. Treatment of chronic postherpetic neuralgia with topical capsaicin. *Journal of the American Academy of Dermatology* 1987;17:93-96.

Bernstein JE, Korman NJ, Bickers DR, Dahl MV, Millikan LE. Topical capsaicin treatment of chronic postherpetic neuralgia. *Journal of the American Academy of Dermatology* 1987;21:265- 270.

Brinker 2016: Brinker F. Final updates and additions for Herb Contraindications and Drug Interactions, 4th edition, including extensive Appendices addressing common problematic conditions, medications and nutritional supplements, and influences on Phase I, II & III metabolism with new appendix on botanicals as complementary adjuncts with drugs. [Internet]. Sandy (OR): Eclectic Medical Publications. [Updated December 6, 2016; Accessed 2017 January 30]. Available from: <https://static1.squarespace.com/static/53a5065ee4b0cd7da76b4209/t/584715a66b8f5bb337eada45/1481053610871/HCDI4+UPDATES+AND+ADDITIONS+Dec%27+16.pdf>



Cal K. Skin penetration of terpenes from essential oils and topical vehicles. *Planta Medica* 2006;72:311-316.

Cavanaugh EJ, Simkin D, Kim D. Activation of transient receptor potential A1 channels by mustard oil, tetrahydrocannabinol and Ca^{+2} reveals different functional channel states. *Neuroscience* 2008;154:1467-1476.

Chad DA, Aronin N, Lundstrom R, McKeon P, Ross D, Molitch M, Schipper HM, Stall G, Dyess E, Tarsy D. Does capsaicin relieve the pain of diabetic neuropathy? *Pain* 1990;42:387-388.

Chan TYK. Life-threatening retroperitoneal bleeding due to warfarin–drug interactions. *Pharmacoepidemiology and Drug Safety* 2009;18:420-422.

Cohen M, Wolfe R, Mai T, Lewis D. A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate chondroitin sulfate, and camphor for osteoarthritis of the knee. *The Journal of Rheumatology* 2003;30(3):523-528.

Committee on Drugs. Camphor: Who needs it? *Pediatrics* 1978;62(3):404-406.

Committee on Drugs. Camphor revisited: Focus on toxicity. *Pediatrics* 1994;94(1):127-128.

Cross SE, Anderson C, Roberts MS. Topical penetration of commercial salicylate esters and salts using human isolated skin and clinical microdialysis studies. *British Journal of Clinical Pharmacology* 1998;46:49-35.

Deal CL, Schnitzer TJ, Lipstein E, Seibold JR, Stevens RM, Levy MD, Albert D, Renold F. Treatment of arthritis with topical capsaicin: a double-blind trial. *Clinical Therapeutics* 1991;13(3):383-395.

Davis JE. Are one or two dangerous? Methyl salicylate exposure in toddlers. *The Journal of Emergency Medicine* 2007;32(1):63-69.

Elad S, Ackerstein A, Bitan M, Shapira MY, Resnick I, Gesundheit B, Cohen Y, Diss O, Barak D, Dray L, Or R. A prospective, double-blind phase II study evaluating the safety and efficacy of a topical histamine gel for the prophylaxis of oral mucositis in patients post hematopoietic stem cell transplantation. *Bone Marrow Transplantation* 2006;37:757-762.

Gibson DE, Moore GP, Pfaff JA. Camphor ingestion. *American Journal of Emergency Medicine* 1989;7(1):41-43.

Gonzalez N, Sumano H. Design of two liquid ibuprofen-poloxamer-limonene or Menthol preparations for dermal administration. *Drug Delivery* 2007;14:287-293.

Goldin E. Topical capsaicin—a novel and effective treatment for idiopathic intractable pruritus ani: a randomised, placebo controlled, crossover study. *Gut: An International Journal of Gastroenterology and Hepatology* 2003;52:1323-1326.



Gottrup H, Hansen PO, Arendt-Nielsen L, Jensen TS. Differential effects of systemically administered katmine and lidocaine on dynamic and static hyperalgesia induced by intradermal capsaicin in humans. *British Journal of Anaesthesia* 2000;84(2):155-162.

Green BG. Sensory characteristics of camphor. *The Journal of Investigative Dermatology* 1990;94(5):662-666.

Grieve M. *A Modern Herbal, Volume 1*. New York (NY): Dover Publications; 1971 [Reprint of 1931 Harcourt, Brace & Company publication].

Grieve M. *A Modern Herbal, Volume 2*. New York (NY): Dover Publications; 1971 [Reprint of 1931 Harcourt, Brace & Company publication].

Guilbert J, Flamant C, Hallalel F, Doummar D, Frata A, Renolleau S. Anti-flatulence treatment and status epilepticus: a case of camphor intoxication. *Emergency Medical Journal* 2007;24:859- 860.

Guppy L, Lowes NR, Walker MJA. Effect of a proprietary rubefacient "Tiger Balm" on rabbit skin. *Food and Chemical Toxicology* 1982;20:89-93.

Guy RH, Tur E, Bjerke S, Maibach HI. Are there age and racial differences to methyl nicotinate-induced vasodilatation in human skin? *Journal of American Academic Dermatology* 1985;12:1001-1006.

Hautkappe M, Roizen MF, Toledano A, Roth S, Jeffries JA, Osterme AM. Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *The Clinical Journal of Pain* 1998;14(2):97-106.

Hagedorn-Leweke U, Bernhard CL. Absorption of sunscreens and other compounds through human skin *in vivo*: Derivation of a method to predict maximum fluxes 1995;12(9):1354-1360.

Hatem S, Attal N, Willer JC, Bouhassira D. Psychophysical study of the effects of topical application of menthol in healthy volunteers. *Pain* 2006;122:190-196.

Health Canada. Consumer Products Safety. List of Prohibited and Restricted Cosmetic Ingredients (The Cosmetic Ingredient Hotlist). [Accessed 2017 January 30]. Available from: <http://www.hc-sc.gc.ca/cps-spc/cosmet-person/hot-list-critique/index-eng.php>

Health Canada. Natural Health Products Ingredients Database. Ingredient Search: [Internet]. Ottawa (ON): Natural and Non-Prescription Health Products Directorate, Health Canada. [Accessed 2017 January 30]. Available from: <http://webprod.hc-sc.gc.ca/nhpid-bdipsn/search-rechercheReq.do>

Ichiyama RM, Ragan BG, Bell GW, Iawmoto GA. Effects of topical analgesics on the pressor response evoked by muscle afferents. *Medicine & Science in Sports & Exercise* 2002;34(9):1440-1445.



Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JWW, Dieppe P, Gunther K, Hauselmann H, Herrero-Beaumont G, Kaklamanis P, Lohmander S, Leeb B, Lequesne M, Mazieres B, Martin-Mola E, Pavelka K, Pendleton A, Punzi L, Serni U, Swoboda B, Verbruggen G, Zimmerman-Gorska I, Dougados M. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a task force of the standing committee for international clinical studies including therapeutic trials (ESCISIT). *Annals of the Rheumatic Diseases: The EULAR Journal* 2003;62(12):1145-1155.

Jordt SE, Bautista DM, Chuang HH, McKenney DD, Zygmunt PM, Hogestatt ED, Meng ID, Julius D. Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. *Nature* 2004;427:260-265.

Koppert W, Zeck S, Blunk JA, Schmelz M, Likar R, Sittl R. The effects of intradermal fentanyl and ketamine on capsaicin-induced secondary hyperalgesia and flare reaction. *Anesthesia & Analgesia* 1999;89:1521-1527.

Lee KKC, Chan TYK, Lee CW. Improvements are needed in the existing packaging of medicated oils containing methyl salicylate. *Journal of Clinical Pharmacy and Therapeutics* 1997;22:279-281.

Liebelt EL, Shannon MW. Small doses, big problems: A selected review of highly toxic common medications. *Pediatric Emergency Care* 1993;9(5):292-297.

Lutgendorf S, Logan H, Kirchner L, Rothrock N, Svengalis S, Iverson K, Lubaroff D. Effects of relaxation and stress on the capsaicin-induced local inflammatory response. *Psychosomatic Medicine* 2000;62:524-534.

Lysy J, Sistiery-Ittah M, Israelit Y, Shmueli A, Strauss-Liviatan N, Mindrul V, Keret D, Martin D, Valdez J, Borne J, Mayersohn M. Dermal absorption of camphor, menthol, and methyl salicylate in humans. *The Journal of Clinical Pharmacology* 2004;44:1151-1157.

Mascie-Taylor BH, Widdop B, Davison AM. Camphor intoxication treated by charcoal haemoperfusion. *Postgraduate Medical Journal* 1981;57:725-726.

McCarthy GM, McCarthy DJ. Effect of topical capsaicin in the therapy of painful osteoarthritis of the hands. *Journal of Rheumatology* 1992;19(4):604-607.

McCleverty D, Lyons R, Henry B. Microdialysis sampling and the clinical determination of topical dermal bioequivalence. *International Journal of Pharmaceutics* 2006;308:1-7.

McGuffin M, Hobbs C, Upton R, Goldberg A, editors. *American Herbal Products Association's Botanical Safety Handbook*. Boca Raton (FL): CRC Press; 1997.

McGuffin M, Kartesz JT, Leung AY, Tucker AO, editors. *Herbs of Commerce*. 2nd edition. Silver Spring (MD): American Herbal Products Association; 2000.



Morteza- Semnani K, Saeedi M, Hamidian M. Anti-inflammatory and analgesic activity of the topical preparation of *Glaucium grandiflorum*. *Fitoterapia* 2003;75:123-129.

Nortier YLM, Van de Haven JA, Koks CHW, Beijnen JH. Preparation and stability testing of a hydrogel for topical analgesia. *Pharmacy World and Science* 1995;17(6):214-217.

Prashar A, Locke IC, Evans CS. Cytotoxicity of clove (*Syzygium aromaticum*) oil and its major components to human skin cells. *Cell Proliferation* 2006;39:241-248.

Pharmacopée française. X^e édition. Huile essentielle de térébenthine (type Portugal). St-Denis (FR): Agence française de sécurité sanitaire des produits de santé; 2003.

Serra J, Campero M, Ochoa J. Flare and hyperalgesia after intradermal capsaicin injection in human skin. *Journal of Neurophysiology* 1998;80:2801-2810.

Scheffler NM, Sheitel PL, Lipton MN. Treatment of painful diabetic neuropathy with capsaicin 0.075%. *Journal of the American Podiatric Medical Association* 1991;81(6):288-293.

Schenone S, Bruno O, Ranise A, Bondavalli F, Filippelli W, Falcone G, Rinaldi B. *O*-[2-Hydroxy-3-(dialkylamino)propyl]ethers of (–)-1,7,7-trimethyl bicyclo[2.2.1]heptan-2-one oxime (camphor oxime) with analgesic and antiarrhythmic activities. *Il Farmaco* 2000;55:495-498.

Soeborg T, Basse LH, Halling-Sorenson B. Risk assessment of topically applied products. *Toxicology* 2007;23:140-148.

Tandan R, Lewis GA, Krusinski PB, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy. *Diabetes Care* 1992;15(1):8-14.

Theosadakis J, Grove ML. A randomized, double blind, placebo controlled trial of a topical cream containing Glucosamine Sulfate, Chondroitin Sulfate, and Camphor for osteoarthritis of the knee. *The Journal of Rheumatology* 2004;31(4):826-827.

United States Department of Agriculture, Agricultural Research Service, National Genetic Resources Program. Germplasm Resources Information Network (GRIN) [Online database]. *Syzygium aromaticum*; *Eucalyptus globulus* Labill; *Cinnamomum camphora*; *Syncarpia glomulifera*. Beltsville (MD): National Germplasm Resources Laboratory. [Accessed 2017 January 30]. Available from: http://www.ars-grin.gov/cgi-bin/npgs/html/tax_search.pl

United States Food and Drug Administration. New Drugs: Camphorated Oil Drug Products for Human Use. Federal Register, Volume 47, Number 183, September 21, 1982, Rules and Regulations. Rockville (MD): United States Department of Health. [Accessed 2017 January 30]. Available from: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemaking/ucm107353.pdf>

United States Food and Drug Administration. Clean-up of Ineffective Ingredients in OTC Drug Products. [Accessed 2017 January 30]. Available from: <http://pinch.com/skin/docs/fda/FDA-OTC-ingredients-ban>

United States Food and Drug Administration. Use Caution with Over-the-Counter Creams, Ointments. Consumer Updates. [Accessed 2017 January 30]. Available from: <http://www.fda.gov/forconsumers/consumerupdates/ucm049367.htm>

United States Food and Drug Administration. Salonpas Pain Relief Patch (10% methyl salicylate & 3% 1-menthol). [Accessed 2017 January 30]. Available from: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm169963.htm>

Weiss J, Catalano P. Camphorated oil intoxication during pregnancy. *Pediatrics* 1973;52:713-714.

Williamson EM. *Potter's Herbal Cyclopaedia: The Authoritative Reference work on Plants with a Known Medical Use.* Saffron Walden (GB): The C.W. Daniel Company Limited; 2003.

Wolowich WR, Hadley CM, Kelley MT, Walsom PD, Casavant MJ. Plasma salicylate from methyl salicylate cream compared to oil of wintergreen. *Journal of Toxicology* 2003;41(4):355-358.

Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. *European Journal of Clinical Pharmacology* 1994;46:517-522.

Appendix 1

Table 7. Groupings based on effects/modes of action (US FDA 1983; US FDA 1979)

Groups	Ingredients	Effects/Modes of action ¹
A	Allyl isothiocyanate, ammonium hydroxide, methyl salicylate, turpentine essential oil	Redness, irritation; relatively more potent than other commonly used counterirritants
B1	Camphor, menthol	Cooling/warmth/tingling sensation, organoleptic properties
B2	Eucalyptus essential oil, eucalyptol	Cooling/warmth/tingling sensation, organoleptic properties
C	Histamine dihydrochloride, methyl nicotinate	Vasodilation, vasoactive properties
D	Capsaicin	Irritation without rubefaction, although about equal in potency to Group A do not produce redness

¹These are not uses or purposes.