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## REVIEW OF OVER-THE-COUNTER TOPICAL ANALGESIC PRODUCTS AVAILABLE IN AUSTRALIA

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**ABSTRACT:** Over-the-counter (OTC) topical analgesics are widely available in Australia and can be purchased without a prescription. These products are typically marketed as treatments for arthritic pain or muscle soreness. There is currently no literature examining the active compounds/botanical extracts usually incorporated in these products, especially relating to products which have not been independently assessed for efficacy by the Australian Therapeutic Goods Administration (TGA). This review aims to highlight the active ingredients commonly incorporated in OTC pain products available for purchase in Australia and assess the literature relating to their efficacy and mechanisms of action. Most of the active ingredients in these analgesic formulations are natural products or plant extracts/essential oils. The most cited active ingredient is *Arnica montana* despite the lack of conclusive evidence that this plant is efficacious in treating pain when administered topically. The mechanisms for pain relief in the products are mainly transient receptor potential channel agonism, or rubefacient/counterirritant effects, with other products exhibiting cyclooxygenase antagonism. The most common ingredients in TGA registered products are the natural products menthol, methyl salicylate, *Eucalyptus* oil and camphor.

**INTRODUCTION:** Pain is an important evolutionary trait developed to protect organisms from damage or harm. The unpleasant sensation of pain is necessary to learn from and respond to stimuli that otherwise could cause cellular damage or death. Pain is also one of the most common symptoms resulting in individuals seeking medical treatment as it is an obvious marker for physiological dysfunction. For tens of thousands of years, people have been trying to find ways to cure pain, with some of the earliest medicines for the treatment of pain being topical formulations of various medicinal herbs<sup>1</sup>.

Many of those herbs, or at least the mechanism they exerted to treat pain, are still in use today. Some of these medicines have been improved upon (i.e. modern non-steroidal anti-inflammatory drugs are an improvement of COX-inhibitors found in willow bark extract) while others are relatively unchanged (i.e. menthol was used by ancient Egyptians)<sup>1</sup>.

Today the overwhelming majority of Australians use multiple over-the counter (OTC) pain relievers every year according to a December 2013 survey by the Macquarie University Centre for Health Economy<sup>2</sup>. This survey found that a large majority of Australians (70.4%, N=1146) had used an OTC analgesic/pain reliever in the previous month, the next most used products were medicated skin products (28.0%), and muscle and pain rubs (27.5%). Over 95% of participants had ever used analgesics/pain relievers and almost 92% of participants had ever used a muscle or pain rub.

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Despite this high rate of use of muscle and pain rubs, there is an absence of information in the literature relating to the kinds of topical analgesic products used by Australians. This is particularly true where it relates to the use of complementary medicines that may not be registered with the Therapeutic Goods Administration (TGA).

The overall use of complementary medicine products in Australia is high, with 50.3% (N=2019) of individuals surveyed in 2017 indicating that they had used a complementary medicine in the preceding 12 months<sup>3</sup>. Among those 1016 individuals who had used a complementary product in the past year, 18.7% had used herbal medicines. This survey did not investigate the medical complaint which lead participants to use these complementary medicines, what active ingredients these products contained, or how they were administered. A literature review of 204 studies determined that between 60-80% of individuals who visit complementary medicine practitioners (osteopaths, Chinese medicine practitioners, or chiropractors) in Australia are seeking pain relief, which may suggest that a large proportion of complementary medicine users in Australia are using analgesic products<sup>4</sup>. Yet only two of the studies included in this review investigated herbal medicine interventions with most articles relating to the use of chiropractic or acupuncture therapies.

A review of current OTC topical analgesics is deemed necessary to gather information on the types of products available to consumers. Having access to this information highlights natural products that are in use as topical analgesics so that their efficacy may be assessed, active compounds characterised, and mechanisms of action solved. What's more, these natural products could form the basis of novel chemical entities that could be marketed as topical analgesic drugs in the future<sup>5-8</sup>.

The study aims to categorise and analyse 108 topical analgesic products available in Australia, investigating the prevalence of natural ingredients, their regulatory status, and potential for innovation in pain management. This review demonstrates the significant role of natural products in the topical analgesic market, with more than 90% of products containing at least one natural product. The review underscores the potential of these natural products

to serve as the foundation for novel chemical entities, contributing to the ongoing evolution of topical analgesics. As we unravel the complexities of traditional remedies and modern innovations, this review serves as a valuable resource for shaping the future of pain management and drug development in this critical therapeutic domain.

Of the 108 total products less than 25% are registered with the TGA, meaning that most topical analgesics available for purchase in Australia have not been independently assessed for efficacy. The most common ingredients in these topical analgesics are reviewed here for the benefit of consumers and researchers to better understand the mechanisms of analgesia and the market for natural compounds in topical pain relief products.

**MATERIALS AND METHODS:** The online pharmacy Healthy Life (<https://www.healthylife.com.au>) was searched under the category "topical pain relief" on 11 December 2023, resulting in 96 products being identified. Heat pack or patch products (n=19) were excluded as they are not traditional topically formulated products.

The remaining 77 products from 30 different brands were then searched in the Australian Register of Therapeutic Goods (ARTG) between the 11-15 of December 2023. The ARTG provides information on the active ingredients in each product as well as the sponsor and date of registration with the ARTG.

Each sponsor identified from the Register was then also searched on the ARTG and any other topical analgesics they have sponsored on the Register for sale in Australia were also examined, leading to the addition of a further 31 products.

The ARTG also provides information on if the product has been listed or registered with the TGA. Some products were not on the ARTG as they are neither listed nor registered, these products were included with active ingredient lists as indicated in the Healthy Life product description. The total number of products identified was 108 from 30 sponsors. **Fig. 1** outlines the process for identifying these products.

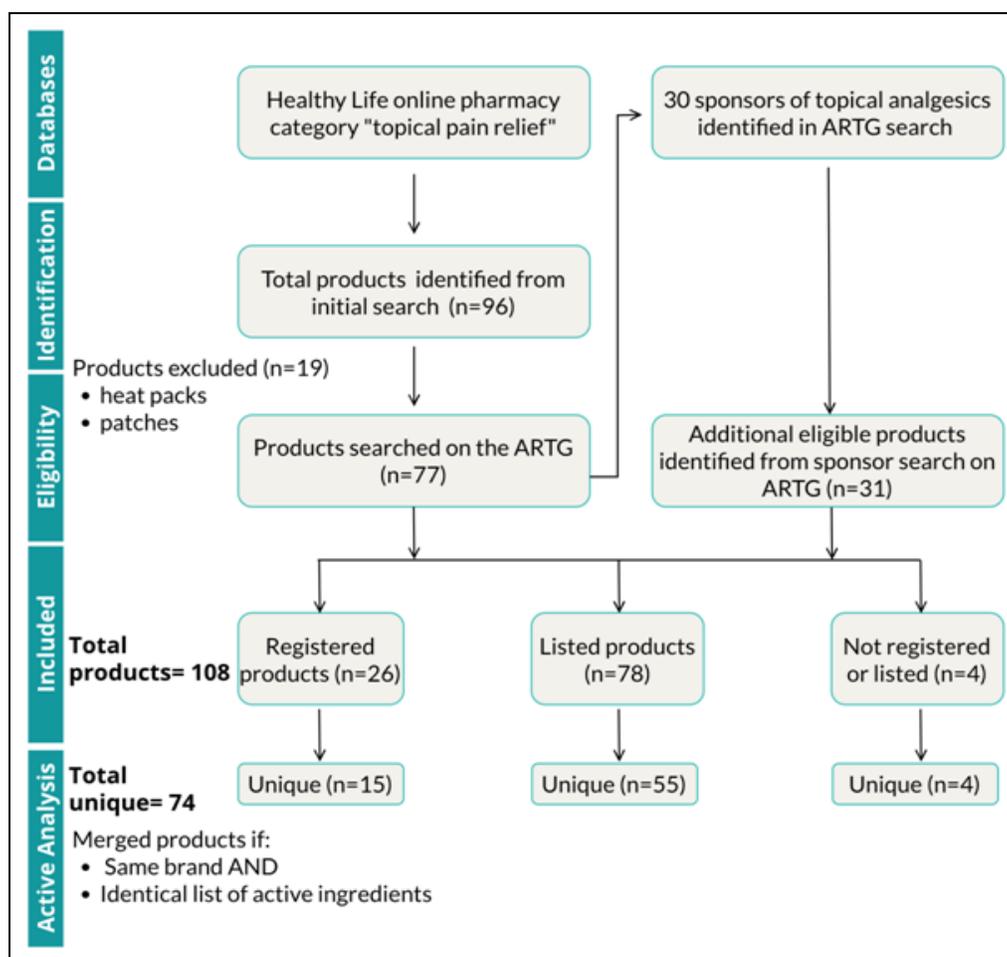


FIG. 1: THE SEARCH METHOD EMPLOYED TO IDENTIFY THE TOPICAL ANALGESIC PRODUCTS ANALYSED IN THIS REVIEW

## RESULTS AND DISCUSSION:

**Product Search Results:** Healthy Life was chosen as the primary search platform to identify topical analgesics as other online pharmacies such as ePharmacy, Chemist Direct, Super Pharmacy Plus, Chemist Warehouse, and Pharmacy Online do not have a category for topical analgesics. Rather, these sites categorise all analgesics together (including oral and topical formulations) or all topical treatments together (including analgesic and non-analgesic products). These methods of categorisation would have made the search for topical analgesic products much more difficult. Pharmacy Direct did have the ability to refine their analgesic products to find creams, gels, and sprays but this resulted in only 39 products and 24 brands while Healthy Life found 77 topical analgesics of interest from 30 brands. From the search of the Healthy Life and the ARTG, 108 total products were identified from 30 sponsors; 26 registered with the TGA, 78 listed with TGA, 4 not listed or registered **Fig. 2**.

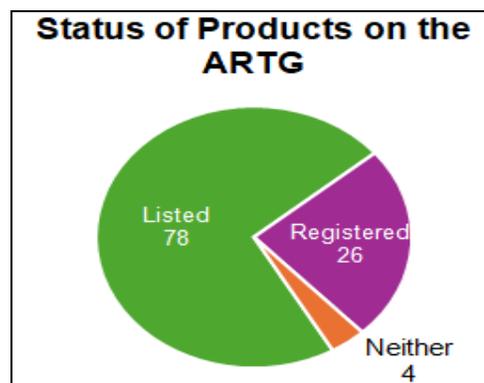
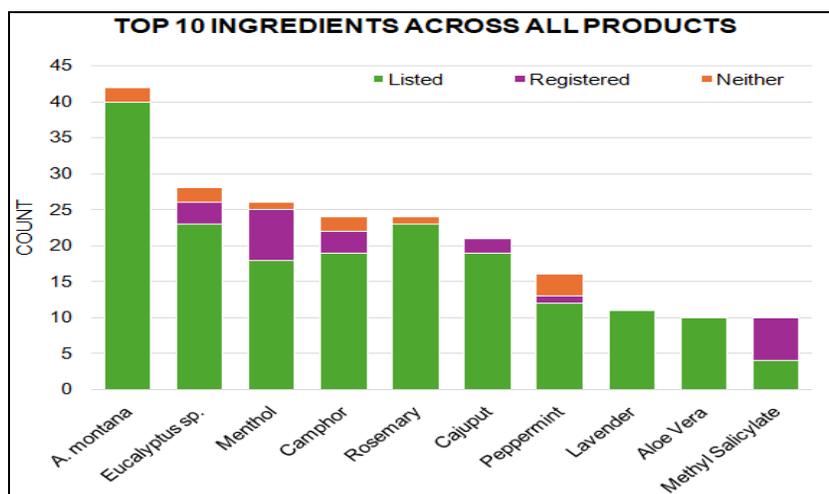


FIG. 2: THE PROPORTION OF TOPICAL ANALGESICS REGISTERED, LISTED, OR NOT PRESENT ON THE ARTG

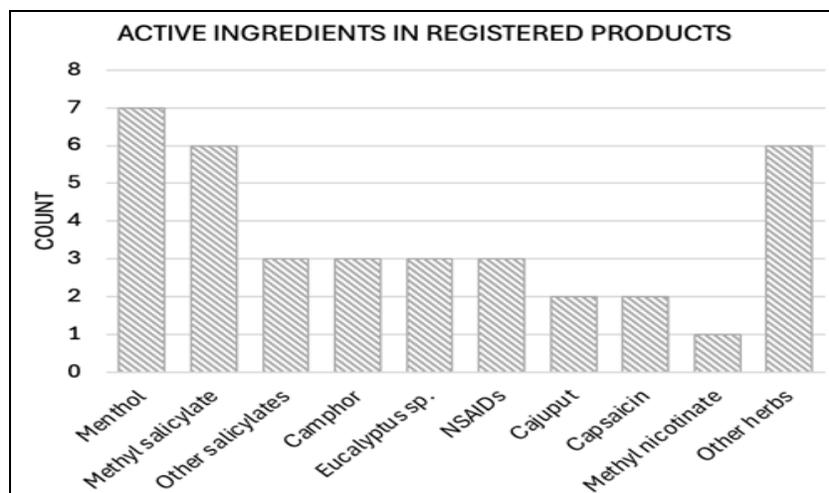
Registered products are independently assessed for efficacy and safety by the TGA, while listed products are generally made with pre-approved, safe ingredients but are not independently assessed for efficacy. Some products from the same brand have the same ingredient lists but different formulations (e.g. spray, gel, cream etc.) or concentrations (e.g. "extra strength" products).

Overall, there were 74 unique ingredient lists identified from the 108 total products. These are comprised of 89 total unique ingredients (after synonyms are accounted for), the most common

ingredients overall are outlined in **Fig. 3** while all active ingredients included in registered products are provided in **Fig. 4**.



**FIG. 3: THE 10 MOST COMMON ACTIVE INGREDIENTS OVERALL, ACROSS ALL UNIQUE TOPICAL ANALGESICS (N=74)**



**FIG. 4: ACTIVE INGREDIENTS LISTED IN TGA REGISTERED TOPICAL ANALGESICS AND HOW MANY OF THESE UNIQUE PRODUCTS THEY APPEARED IN (N= 15). MOST INGREDIENTS ARE RUBEFACIENTS AND/OR TRPV CHANNEL MEDIATORS, WHILE NSAIDS ARE COX INHIBITORS**

#### Top Ingredients in Topical Analgesics Overall:

The most common ingredients identified in this product search are outlined in **Fig. 3**. All these ingredients are plant derived. *Eucalyptus* (NO. 2), menthol (NO. 3), camphor (NO. 4), cajuput (NO. 6), peppermint oil (NO. 7), and methyl salicylate (NO. 10) are in the top 10 ingredients across all products. These ingredients were also incorporated in many of the registered products. *Arnica montana* (NO. 1), rosemary (NO. 5), lavender (NO. 8), and *Aloe vera* oils or extracts (NO. 9) were not found in any registered analgesic products but were present in many of the listed and unlisted/unregistered products. Unlike registered products, the TGA does

not independently assess the efficacy of listed medicines before they enter the market, although sponsors of listed medicines must certify that they hold evidence that the medicine will do as it claims. As a result, listed medicines are limited in their ability to make health claims. Listed medicines typically contain pre-approved low-risk ingredients which are considered safe. Overall, there are many essential oils incorporated in the topical analgesics, including listed and registered products. Essential oils have a high volatile content mainly comprising of monoterpenes, as well as sesquiterpenes and phenylpropanoids, and occasionally diterpenes<sup>9</sup>. Many essential oil components have been analysed

for analgesic activity. Monoterpenes including 1,8-cineol, R-(+)-limonene, (-)-linalool, linalyl acetate, (-)-menthol, (+)-menthone,  $\alpha$ -pinene, and others demonstrate analgesic properties<sup>9</sup>.

***Arnica montana*:** The most common ingredient identified in this search is *A. montana* extract which is traditionally taken orally or topically to treat bruising, swelling, and pain. However, there are conflicting reports in the literature relating to the efficacy of *Arnica* as a topical analgesic<sup>10</sup> and it is not present in any of the registered products. There is evidence that *Arnica* can reduce swelling and inflammation in pre-clinical experiments, reducing inflammatory markers and reactive oxygen species production<sup>11, 12</sup>. However, many preparations of *Arnica* are at homeopathic doses which may be below the therapeutic threshold. One recent review of 11 randomised control trials (RCT)<sup>13</sup> concluded that *Arnica* is not efficacious in the treatment of pain, swelling, and bruises at concentrations of up to 10% w/w. *A. montana* may be efficacious as a topical analgesic at higher concentrations. A review of 42 papers<sup>10</sup>, indicated that although some studies report negative outcomes, a relevant number of evidences support the use of *Arnica* formulations for the treatment of pain, bruises, and swelling that occur after traumatic injuries related to sport and surgical interventions as well as with arthritis and other inflammatory conditions. These positive results refer to *Arnica* as both a single remedy and as a combination with other active principles and remedies<sup>10</sup>.

The phytochemistry of *Arnica* is complex, with the flowers containing flavonoids, sesquiterpenes, acetylenes, hydroxy coumarins, phenols and more<sup>14</sup>. It is broadly accepted that the bioactive components of *Arnica* are the sesquiterpene lactones including helenalin **Fig. 5** and derivatives, which have demonstrated anti-inflammatory and cytotoxic effects and are also found in the flowers<sup>15</sup>. Small phenolic compounds such as 2,5-dimethoxy-p-cymene **Fig. 5** are also found in *Arnica* in good concentrations<sup>16</sup>. An investigation of the skin permeability of *Arnica* compounds found that while many of the compounds can be absorbed into the skin barrier, these sesquiterpene lactones irreversibly bound to skin proteins, which may be beneficial for localised treatment but would

limit systemic absorption<sup>17</sup>. Many of the *Arnica* containing products identified in this search also contain other herbs or analgesic compounds that may produce a synergistic effect in treating pain. This is true for all herbal mixtures in these products. There is an unfortunate lack of information in the literature relating to the use of *Arnica* in combinations with other herbs, making it difficult to comment on the efficacy of these combination products in the treatment of pain.

**Rosemary:** It can be difficult to untangle the effects of inhalation of volatile compounds in essential oils from that of compounds which are absorbed topically. Many studies on rosemary and lavender oil investigate the effect aromatherapy/massage treatment where it cannot be determined if the pain relief is due to the topical administration or the beneficial anti-anxiety or relaxation effects from inhaling volatile components of the oils<sup>18-20</sup>. Rosemary essential oil is mainly constituted of camphor (5-21%), 1,8-cineole (15-55%),  $\alpha$ -pinene and other monoterpenes while the aqueous extracts are high in rosmarinic acid, camphor, caffeic acid, ursolic acid, betulinic acid and other triterpenes<sup>21-23</sup>. The triterpenes carnosic acid, carnosol, betulinic acid, and ursolic acid have all demonstrated promising results in studies of analgesic and anti-inflammatory activity<sup>24, 25</sup>. Structures of these compounds which are present in rosemary oil are presented in **Fig. 5**. Topical application of rosemary oil has been found to alleviate severity of osteoarthritis pain in elderly patients<sup>26</sup>. A systematic review by Oltean *et al.* (2014) on the use of essential oils for lower back pain also found that rosemary oil may be more effective than placebo in treating pain, but the randomised control trial (RCT) studies examined were deemed to be of low to moderate quality limiting the confidence of this finding.

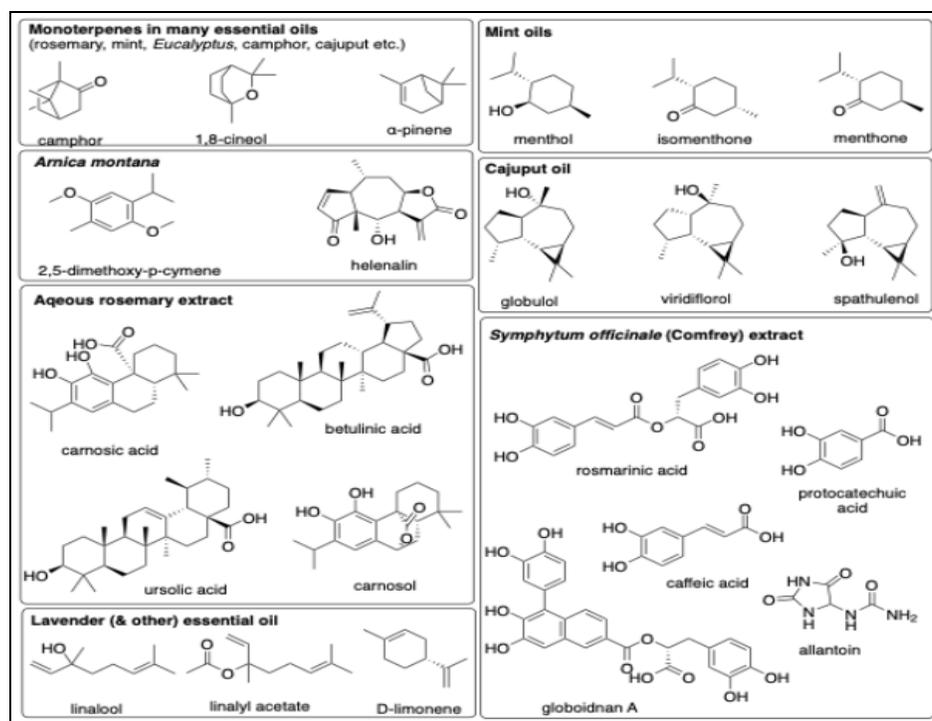
**Lavender Oil:** Oltean *et al.* (2014) also determined that lavender oil may alleviate lower back pain to a greater degree than placebo, but these studies were similarly affected by poor study design and high risk of bias<sup>27</sup>. Lavender oil comprising of linalool (35%), linalyl acetate (22%), D-limonene (7%) and other monoterpenes **Fig. 5** was found to have similar efficacy to the non-steroidal anti-inflammatory drug (NSAID) tramadol in a formalin

assay when given orally<sup>28</sup>. Topical application of the same oil was found to reduce inflammation, while inhalation exposure to 0.1% lavender essential oil induced analgesic and anti-inflammatory effects<sup>20</sup>. A lavender extract high in rosmarinic acid, rather than volatile terpenes, was found to have anti-inflammatory and antioxidant activities in a cell model<sup>29</sup>.

**Aloe vera:** *A. vera* contains 99-99.5% w/w water with the remaining 0.5-1% w/w containing hundreds of potentially bioactive molecules including phenolic compounds, anthraquinones, chromones, lipids, amino acids, sugars, and vitamins<sup>30</sup>. *A. vera* is a traditional treatment for burns and has been found to be an effective therapy in treating first- and second- degree burns, leading to faster healing times, reduced wound itch and less pain compared to controls<sup>31, 32</sup>. Several clinical studies on *A. vera*'s effectiveness in treating burns and other types of pain topically have been completed<sup>32-34</sup>. This includes a clinical trial that found significant reduction in pressure ulcer pain<sup>33</sup> and a meta-analysis finding that *A. vera* application for lactating women reduced nipple pain and irritation<sup>34</sup>. Aqueous extract of *A. vera* (oral administration) has also been shown to alleviate pain and inflammation at the high dose of 250 mg/kg<sup>35</sup>.

The current literature relating to the efficacy of topical application of the herbal extracts or essential oils mentioned above in clinical trials is overall mixed, with instances of poor study design and bias. Further, much of the evidence surrounding the analgesic effects of these plants are based on animal models or where the route of administration is not topical. The mode of preparation of these plant extracts or essential oils will affect the final chemical composition of the product which may contribute to the variation in clinical outcomes in the literature. Information about the preparation methods for the plants used in the topical analgesics is not available on the ARTG beyond simple descriptors such as "oil" or "extract" in some products.

**Ingredients in TGA Registered Topical Analgesics:** This search identified 26 registered products with 15 unique active ingredient lists, of these all but three ingredients are derived from natural products **Fig. 4**. These three non-natural products are all NSAIDs. This over-representation of natural products highlights the significant role of traditional medicines in the topical analgesic market. **Fig. 5** highlights major components of botanical extracts while **Fig. 6** presents the structures of compounds which are present in these topical medicines as listed active ingredients.



**FIG. 5: STRUCTURES OF SOME OF THE MAJOR COMPOUNDS FOUND IN ESSENTIAL OILS OR EXTRACTS OF PLANTS DISCUSSED IN THIS REVIEW**

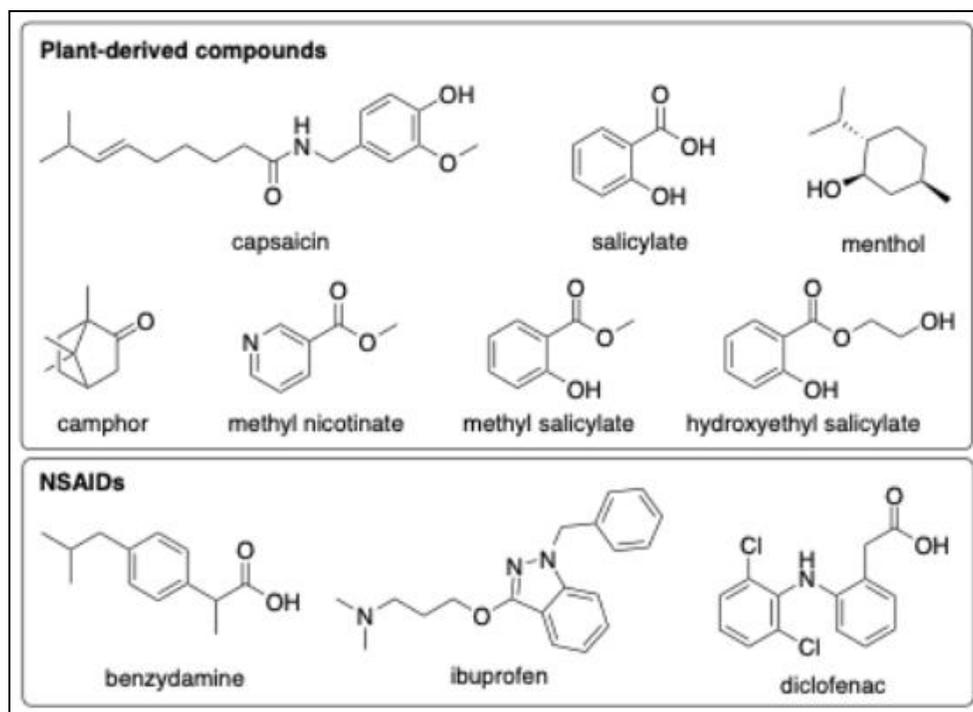


FIG. 6: STRUCTURES OF COMPOUNDS INCORPORATED IN REGISTERED PRODUCTS AS PURIFIED COMPOUNDS

**Menthol, Methyl Salicylate and Mint Oils:** The most common ingredients in registered topical analgesic are the naturally occurring compounds menthol and methyl salicylate. There is evidence that menthol<sup>36</sup> and methyl Salicylate<sup>37</sup> mediate transient receptor potential vanilloid 1 (TRPV1) channels, which could contribute to their analgesic effects. Methyl salicylate and menthol also agonise transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential melastatin 8 (TRPM8), respectively<sup>36, 38</sup>. These additional TRP channels are both implicated in pain pathways. The effect of methyl salicylate on other membrane proteins including  $\gamma$ -amino butyric acid type A receptors, N-methyl-D-aspartate receptors, and type-2 voltage-gated sodium channels demonstrated concentration dependent partial inhibition of all three proteins<sup>39</sup>. Moreover, these compounds are also rubefacients, (causing redness and a warming sensation upon topical application) and are common in heat rubs or creams marketed towards sportspeople to relieve muscle aches or soreness. Half of the registered products containing menthol and/or methyl salicylate, also contain at least one herbal oil that may add to the warming effect (e.g. peppermint oil, cajuput, clove bud oil, and turpentine oil). Peppermint oil is mainly comprised of menthol, menthone and derivatives thereof as

well as other monoterpenes<sup>40</sup>. As has previously been mentioned these compounds display analgesic properties by activation of TRP channels and counterirritant effects. Dementholised mint oil present in Tiger Balm™ products is a by-product of a crystallisation process which removes ~60% of the menthol content from the oil<sup>41</sup>. The major component of dementholised mint oil is still menthol, although the proportion of other compounds such as menthone, isomenthone, limonene and other monoterpenes, which may also exhibit analgesic properties, is increased<sup>41</sup>. Other essential oils including clove bud oil and turpentine oil similarly contain monoterpenes and other chemical entities which may exhibit rubefacient or analgesic effects.

Rubefacient compounds and herbs work to reduce pain by acting as counterirritants, producing a mild sensation of irritation in one part of the body to relieve irritation or pain at another site. The literature is limited by poor study models and small samples sizes regarding the efficacy of rubefacients in acute and chronic pain treatment leading to some disagreement among researchers about the relative efficacy of these compounds compared to topical non-steroidal anti-inflammatory drugs (NSAIDs)<sup>42, 43</sup>.

Matthews *et al.* (2009) reviewed rubefacients in acute and chronic pain, concluding that while salicylates are well tolerated in the short-term and may provide some pain relief, there is no evidence for the use of other topical rubefacients<sup>42</sup>.

***Eucalyptus* Oil and Camphor/*Cinnamomum camphora*:** The next most common ingredients after menthol and methyl salicylate are *Eucalyptus* oil and camphor/*C. camphora*. Camphor is the major component of *C. camphora* and is traditionally used to treat sprains, swelling and inflammation among other uses. Camphor produces a rubefacient sensation when applied topically and is known to interact with several transient receptor potential channels; TRPV1, TRPV3, TRPA1 and TRPM8<sup>36</sup>. Essential oils of three *Eucalyptus* species were found to significantly inhibit analgesia and inflammation when administered interperitoneally<sup>44</sup>. When co-administered with the NSAID flurbiprofen, the anti-inflammatory, anti-pyretic and analgesic effects were greater than the NSAID or oil alone<sup>44</sup>. Many *Eucalyptus* oil formulations contain high amounts of 1,8-cineol,  $\alpha$ -pinene, and other monoterpenes<sup>45</sup>. 1,8-Cineol is known to mediate neuropathic pain, likely through interactions with the P2X3 purinergic receptor protein<sup>46</sup> and TRP channels<sup>47</sup>. While even more targets have been proposed for treating other disease targets including diabetes via Sirt1<sup>48</sup> and dysregulated platelet aggregation *via* adenosine A(2A) receptor activation<sup>49</sup>. This compound is readily absorbed through the skin, making topical application logical. The other major compound in many *Eucalyptus* oils is  $\alpha$ -pinene, which inhibits analgesia through suppressing inflammatory signalling and COX-2 expression<sup>50</sup>.

**Cajuput (*Melaleuca cajuputi*) Oil:** Cajuput (*M. cajuputi*) oil also contains 1,8-cineole in moderate to high concentrations, while sesquiterpenes such as globulol, viridiflorol, and spathulenol are secondary components, and traces of other monoterpenes are present<sup>51</sup>. Cajuput leaves have traditionally been used to treat cold and flu as well as itching from insect bites, it is also used as a fragrance in many cosmetic products<sup>51</sup>.

***Capsicum annuum*:** Capsaicin is a natural product found in *C. annuum* (chilli pepper). Capsaicin is responsible for the painful burning sensation

associated with hot chillies caused by selective agonism of TRPV1 channels<sup>52</sup>. Paradoxically, topical acute high-dose or chronic low-dose application of capsaicin is known to produce analgesia by defunctionalisation of nociceptors<sup>52</sup>. The primary mode of action of capsaicin is nociceptor defunctionalisation, but this compound is also considered a rubefacient. Both ZO-rub™ □ and Goanna™ □ Heat Cream products include *Capsicum annuum* extract or purified capsaicin.

***Symphytum officinale*:** This search revealed only one registered product which comprises of a single herbal ingredient and that is Martin and Pleasance™ □ Comfrey Cream. Comfrey (*S. officinale*) root extract is accepted as a traditional treatment for pain and inflammation; however, the active phytochemicals and resulting mechanisms of action are ill-defined. Major constituents of Comfrey include allantoin, protocatechuic acid, caffeic acid, rosmarinic acid, and globoidnanA<sup>53</sup>. While the precise mechanism of action in treating pain is uncertain, the ethanolic extract of comfrey root has been shown to inhibit the NF- $\kappa$ B pathway *via* signalling cascade<sup>53</sup>.

**NSAIDs:** Difflam™ □, Nurofen™ □, and Voltaren™ □ products are topical NSAIDs containing Benzydamine, Ibuprofen, and Diclofenac, respectively. These analgesics are reversible cyclooxygenase (COX) inhibitors that work by reducing the production of prostaglandins involved in pain and inflammation pathways. Another NSAID, salicylic acid (aspirin), is present in the form of salicylate salts in Dencorub™ □ and Goanna™ □ arthritis creams. Salicylic acid irreversibly binds to COX receptors<sup>54</sup> to reduce inflammation and pain, although the literature suggests that there may be more to the clinical effectiveness of salicylic acid than this mechanism alone<sup>55,56</sup>.

Generally, the ingredients incorporated in registered topical analgesics target ion channels (predominately of the TRP class) or COX enzymes to exert their effects. Most of the registered products contain menthol and/or methyl salicylate, often in combination with one another or additional natural product extracts or oils. There is an abundance of topical products which contain essential oils from *Eucalyptus*, *Melaleuca*, mint,

clove, and pine species. These essential oils are high in monoterpenes which may produce analgesic effects. 1,8-Cineole appears in good concentrations in many of these oils. The only non-natural products appearing in the registered analgesics are the NSAIDs, Benzydamine, Ibuprofen, and Diclofenac. These NSAIDs are modern day COX-inhibitors, although this mechanism of pain relief has been exerted for thousands of years through the use salicylate containing plant extracts<sup>1</sup>.

**Adverse Effects Associated with the Identified Active Ingredients:** Typically, in the products identified in this review, the concentrations of essential oils are considered safe for topical application however (as with any medication) irritation, allergic reactions or other adverse events may still occur. Ingestion of even a small amount of some of the essential oils in these products (including *Eucalyptus*, wintergreen, and camphor) can cause serious side effects such as seizures or death<sup>57, 58</sup>. Over-administration of some essential oils can also lead to overdose, so it is important for consumers to follow the directions for use on any products containing essential oils. Further, as with any topical product, patch tests should be carried out before use to test for any irritation or allergic reactions that may be caused by some ingredients<sup>59</sup>. For example, cajuput and peppermint oil are known to cause rash or irritation in some individuals and some citrus oils can cause photosensitivity<sup>59-61</sup>.

NSAIDs are known to cause gastrointestinal irritation due to their nonspecific effects on the COX-1 receptor. Incidents of severe gastrointestinal side effects are reduced when NSAIDs are administered topically as compared to orally however, there is still potential for systemic adverse effects such as headache, gastrointestinal issues, or hepatotoxicity to occur<sup>62, 63</sup>. This risk is greater in older patients and with higher dose or longer duration of NSAID use. Topical NSAIDs may also cause adverse effects at the application site including dry skin, erythema, irritation, rash, or dermatitis.

**CONCLUSION:** This review of topical pain relief products in Australia indicates that natural products comprise a large proportion of the market with over 90% of topical products containing at least one

natural product. The significance of these findings indicates the influence of traditional medicines in the topical analgesic market. Most of these natural products exhibit rubefacient or counterirritant effects through the activation of TRP channels and/or inhibition of COX enzymes. While the precise composition of natural products extracts or essential oils in these formulations is dependent on the species used, season of harvest, location of growth, and the protocols used in the extraction or distillation processes; this review outlines the major compounds which may typically be found in the most common natural extracts. Many of these major compounds are known to exhibit analgesic effects and display good absorption through the skin for example, 1,8-cineol, menthol, and capsaicin. *A. montana*, rosemary, and lavender are incorporated in many of the listed products and have a history of use in pain relief, yet there is little evidence to support their use as topical pain relievers in the literature. Much of the literature which does support their use in this way exhibit potential bias and poor study design, indicating that higher quality studies of these plants are necessary, especially as these ingredients are so widely used.

Looking forward, this exploration offers valuable insights for future scientific research in the field of drug discovery. The observed reliance on natural products in registered formulations suggests a large space for investigating these compounds for their analgesic properties and potential to serve as a basis for novel chemical entities. Systematic and well-controlled studies, particularly focused on herbal combinations, are crucial to ascertain their efficacy and safety.

As with any medicine, there are possible side effects that need to be considered. To minimise the risk of side effects it is important for consumers to follow the directions for use, and spot-test the product before use in case of allergic reactions or irritation.

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