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Review Article

The Bioactivity and Health Benefits of Oil of Wintergreen

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Abstract

Oil of wintergreen is extracted from the evergreen plant *Gaultheria procumbens* and other evergreens in the same family. The principal constituent of natural and pure wintergreen oil is 95 - 98% methyl salicylate, but it also contains multiple terpenes, notably α-pinene, β-pinene, myrcene, 1,3-cineole (aka eucalyptol), δ-3-carene, limonene, linalool and ethyl salicylate. Synthetic wintergreen oil is commonly manufactured via the Kolbe-Schmitt chemical reaction and the reaction product, salicylic acid, is then methylated to form methyl salicylate. However, a side-product of the methylation process is dimethyl-4-hydroxyisophthalate, and detection of this compound in "wintergreen oil" is a positive indicator that the essential oil has been adulterated with synthetic methyl salicylate or is wholly the synthetic product.

Although topically-applied salicylates are useful in pain management because of their analgesic, antipyretic and anti-inflammatory effects. The indications are that the bioactivity of natural oil of wintergreen, notably the inhibition of pro-inflammatory enzymes and suppression of pro-inflammatory and pro-oxidant functions of human neutrophils, are ascribable to the minor terpene constituents. Since the latter are not present in synthetic wintergreen oils, the efficacy of these oils may be questionable and are likely to be inferior to those the natural essential oil.

Keywords: *Gaultheria procumbens; Wintergreen Oil; Natural Essential Oil; Analgesic; Antipyretic; Anti-Inflammatory Effects*

Introduction

Wintergreen essential oil is distilled from the evergreen plants *Gaultheria procumb*ens (native to North America), *Gaultheria yunnanensis*, (native to Asia), *Gaultheria fragrantissima* (native to Asia and India) and *Betula lenta* (sweet birch). *Gaultheria procumb*ens is known by several different names, as indicated in table 1.

Teaberry
Eastern teaberry
Checkerberry
Boxberry
American wintergreen

Table 1: *Alternative names for Gaultheria procumbens.*

Likewise, wintergreen oil also is commonly known by various names, notably Gaultheria oil, Gaultheria fragrantissima, betula oil and teaberry oil as well as by the chemical names of its principal components, salicylic acid methyl ester (methyl salicylate) and methyl 2-hydroxybenzoate.

Traditionally, wintergreen oil was distilled from the twigs of *Gaultheria procumb*ens, *Gaultheria fragrantissima* and *Betula lenta*. The alternative approach was to steep the evergreen leaves in warm water and allow them to ferment, thereby releasing enzymes from within the plant leaves. In this process, a compound called gaultherin [1] present in the leaves is enzymatically hydrolyzed to methyl salicylate, the latter giving wintergreen its signature minty aroma and which is the principal ingredient (90 - 98%) of wintergreen oil. Thereafter, wintergreen oil is extracted by steam distillation. Interestingly, the leaves of wintergreen plants are themselves odorless and tasteless until the enzymatic hydrolytic formation of methyl salicylate occurs.

Natural sourcing of wintergreen oil, however, has been declining in recent years and is being replaced by commercially available and synthetically produced methyl salicylate aka "wintergreen oil" or oil of wintergreen. One manufacturing process involved in synthetic wintergreen oil production is the Kolbe-Schmitt reaction[1].

Synthetic oil of wintergreen, i.e. methyl salicylate, is manufactured by methylating[2] the salicylic acid produced in the Kolbe-Schmitt reaction. However, during the latter process, excess methylating agent may add a second methoxy group to the methyl salicylate. This will produce various compounds but, commonly dimethyl-4-hydroxyisophthalate and, as recently been shown, detection of this compound is a very strong affirmation of essential oil adulteration with synthetic methyl salicylate [2].

In fact, synthetic methyl salicylate may be the principal and possibly the sole ingredient in most commercial "wintergreen" products that often are claimed to contain one of several types of oils, including wintergreen oil, gaultheria oil or teaberry oil. This "singularity of content" is immediately apparent from GCMS chromatogram of synthetic wintergreen oil (Figure 1a) compared to that of the natural oil (Figure 1b).

The analgesic action of the salicylates has been ascribed to the inhibition of prostaglandins.

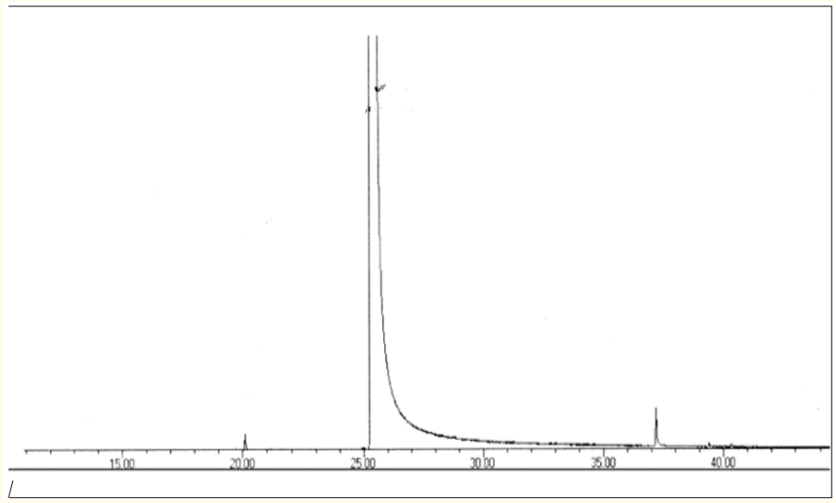

Figure 1a: *GCMS chromatogram of synthetic wintergreen oil.*

[1]The Kolbe-Schmitt chemical reaction or, simply, the Kolbe process, is a carboxylation process involving heating sodium phenoxide (the sodium salt of phenol) with CO_2 under pressure, usually 100 atm and 125°C, and then treating the reaction product with sulfuric acid. The end product is the aromatic hydroxy acid known as salicylic acid, the precursor to aspirin.

[2]In organic chemistry, the term methylation refers to the alkylation process in which a methyl (CH^3) group replaces a hydrogen atom in a compound. Common methylating agents include iodomethane, dimethyl sulfate, dimethyl carbonate and tetramethylammonium chloride.

It can be seen from figure 1a, the chromatogram for synthetic wintergreen oil, that this product is predominantly methyl salicylate with a fractionally small content of ethyl salicylate, detected as the very small peak at 37.2 m/z ratio.

In contrast, figure 1b, the chromatogram of natural wintergreen oil, shows a considerably greater number of peaks, the smaller peaks indicating the relatively large content of minor ingredients within the natural oil. As discussed below, these minor components make a significant contribution to the bioactivity of oil of wintergreen.

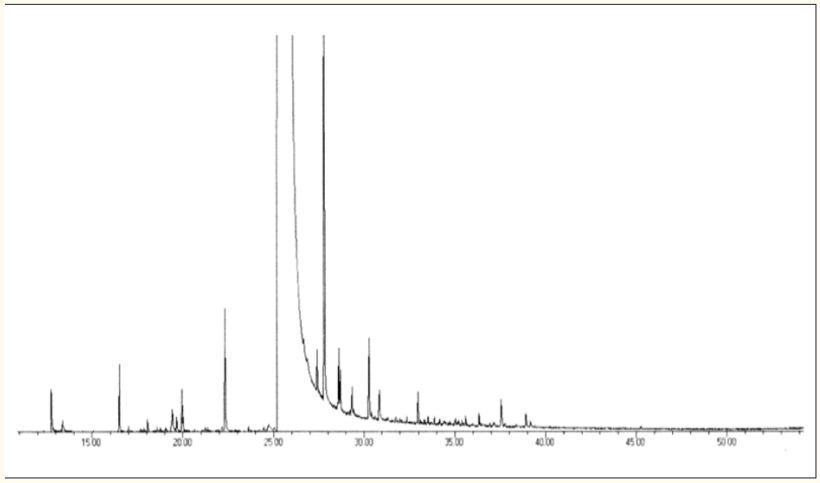

Figure 1b: *GCMS chromatogram of natural oil of wintergreen.*

Components of wintergreen oil

The principal constituent of natural wintergreen oil is 95 - 98% methyl salicylate, but it also contains multiple terpenes, notably α-pinene, β-pinene, 1,3-cineole (aka eucalyptol), limonene, linalool and ethyl salicylate. The "sister" natural product, betula oil (also known as oil of betula and birch oil but which is frequently called "oil of wintergreen"), is obtained from the bark and twigs of the sweet birch. Betula oil has a somewhat similar composition to wintergreen oil, with the main components being salicylic acid and methyl salicylate together with the triterpene betuline and the triterpenoid alcohol, betulenol.

Wintergreen oil has a natural sweet and fresh aroma, very similar to that of peppermint oil, and this taste and aroma is the basis for its addition to, and presence in, foods, teas, household products and in cosmetics as well as its use in aromatherapy. The high methyl salicylate content (95 - 98%) of wintergreen oil accounts for almost all the healing and health-promoting properties of this essential oil when applied topically. Likewise, these characteristics are the reason wintergreen oil is used as a flavorant in candy, tobacco products, mints and chewing gum as well as in various beauty products, dentifrices and household products.

The bioactivity of wintergreen oil

The localized pain relief capabilities of methyl salicylate are well-established, with numerous over-the-counter products being available for topical application although the effectiveness of the topically applied product depends on the release of the drug from the ointment [3,4]. Whereas methyl salicylate constitutes by far and large the major component of wintergreen oil, phytochemical research on

the genus *Gaultheria* indicates the presence of numerous other constituents, notably methyl salicylate derivatives, terpenes, terpenoids, flavonoids and many other compounds [5,6]. The presence of these minor components in natural wintergreen oil was previously mentioned (See figure 1b).

Salicylates are useful in pain management because of their analgesic, antipyretic (fever-reducing), and anti-inflammatory effects. Apparently, salicylates lower body temperature by dilating peripheral blood vessels such that as blood flows out to the extremities, it results in the dissipation of the heat caused by fever, which in turn cools the body.

The analgesic action of the salicylates has been ascribed to the inhibition of prostaglandins [6,7]. In particular, salicylic acid directly and irreversibly inhibits the activity of both types of cyclo-oxygenases (COX-1 and COX-2) to decrease the formation of precursors of prostaglandins[3] from cell membrane wall components such as arachidonic acid. In other words, it appears that salicylate may competitively inhibit prostaglandin formation by its specific antagonist effect on glycine receptors containing α1-subunits [8].

It should be mentioned here that most salicylates, including aspirin (acetyl salicylate), are converted (metabolized) to salicylic acid by enzymatic action in the body and the similarity in structure of methyl salicylate, acetyl salicylate and salicylic acid is very clear from figure 2. Thereafter, acid-base reactions within the body or on the skin convert the salicylic acid to salts (salicylates) which produce their biochemical effects.

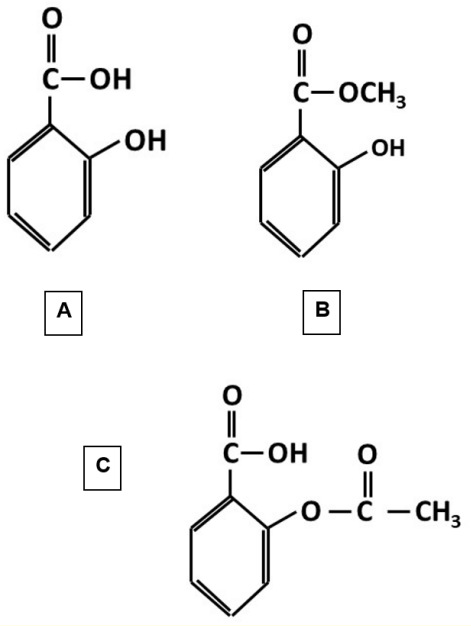

Figure 2A-2C: *Salicylic acid, B: methyl salicylate and C: acetyl salicylic acid (aspirin).*

[3]Prostaglandins are a group of unsaturated fatty acid mediators occurring in almost every tissue of the body and body fluids. They are generated within cell membranes and function as hormones and when released, prostaglandins increase the sensitivity of pain receptors in the tissue, making the patient more likely to feel pain.

As previously stated, wintergreen oil is often described as having a minty flavor and aroma but in mint plants, menthol is the sensory molecule (agonist) that is responsible for activating a transient receptor potential (TRP) in the body. In turn, this channel, known as RPM8, activates the cold response. In contrast, the methyl salicylate in wintergreen activates TRPA1, the sensor responsible for the burning cold response. In addition, methyl salicylate also activates TRPV1, the same channel activated by capsaicin, the principal component in hot peppers.

Activation of TRPV1 opens the channel, leading to an influx of sodium and calcium ions which in turn initiates a cascade of events (Figure 3). The agonists activating TRPV1 include but are not limited to capsaicin, hydrogen ions (from acids), heat and methyl salicylate. When activated, the TRPV1 channel opens, allowing sodium (Na^+) and calcium (Ca^{2+}) ions to transit the membrane. In turn, the sodium and calcium ions passing through the open channel stimulate sensory neurons in the spinal cord.

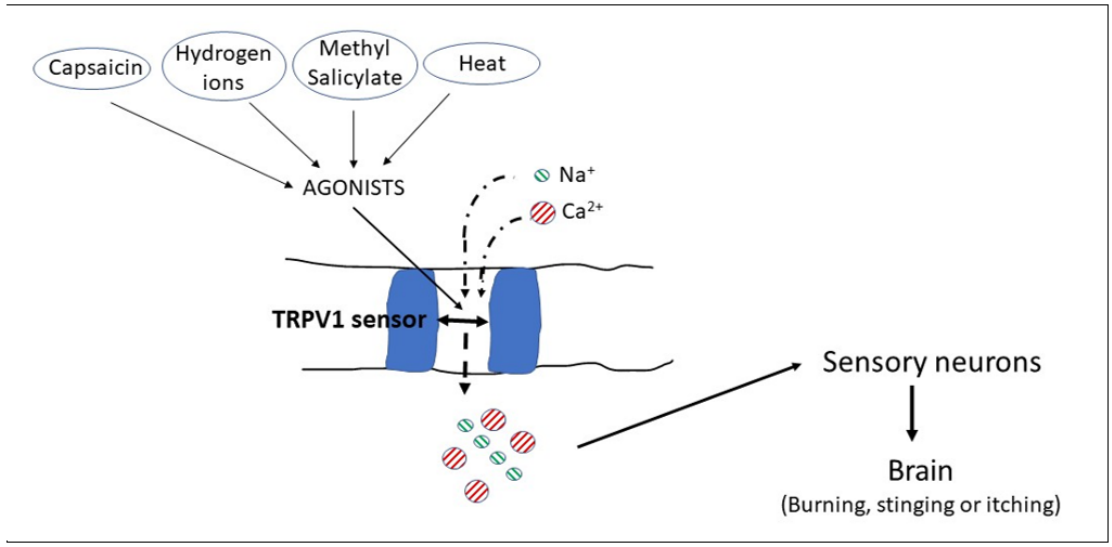

Figure 3: *Activation of the TRPV1 sensor to open the ion channel.*

The stimulated sensory neurons send signals to the brain via the central nervous system, leading to the perception of such sensations as burning, stinging or itching. Interestingly, the heat sensation felt from the initial administration of TRPV1 agonists such as capsaicin actually is pain because activation of TRPV1 initially causes hypothermia [9]. It has also been reported that another acute effect of TRPV1 agonists on people is an increase in oxygen consumption [10,11].

Medicinal uses of wintergreen oil

Medicinal applications of wintergreen oil have been widely known for centuries, particularly to the Native Americans. There are apocryphal reports that the latter used wintergreen leaves for treating respiratory tract infections and apparently chewed wintergreen leaves to increase endurance and respiratory capacity, helping them run long distances [12]. The latter use of wintergreen leaves might be in accord with the reported effect on oxygen consumption through activation of TRPV1 sensors mentioned above. It also appears that Co-

lonial troops during the American War of Independence used wintergreen leaves as a replacement for real tea leaves when "brewing up" the world's favorite beverage.

In fact, numerous medicinal uses are claimed for wintergreen oil, many of which are presumed to be based on its methyl salicylate content (Table 2). The properties of methyl salicylate have been studied extensively over a great many years and the general consensus is that it is useful to help relieve pain and inflammation, hence its popularity in topical pain-relieving products [3,4,7,13]. OTC topical ointments used to relieve muscle aches and joint pains include those based on methyl salicylate/menthol mixtures such as Cool Azul®, Bengay®, Icy Hot®, Mentholatum D® and Salonpas® to name just a few readily available products. The effectiveness of methyl salicylate/menthol applications in relieving pain has been confirmed in a randomized, double-blind, parallel-group, placebo-controlled, multicenter study [14]. It was found that a single 8-hour application of a patch containing methyl salicylate and L-menthol provided significant relief of pain associated with mild to moderate muscle strain in a group of adult patients compared with patients receiving a placebo patch. These findings are supported by recent work, cited above [5], on the inhibition of pro-inflammatory enzymes and suppression of pro-inflammatory and pro-oxidant functions of human neutrophils by wintergreen oil extracts.

Analgesic (pain relief)
Anti-arthritic
Anti-fungal (especially for plants)
Anti-inflammatory
Anti-oxidative
Anti-rheumatic
Antiseptic
Antispasmodic
Astringent
Carminative[1]
Diuretic
Emmenagogic[2]
Immune system enhancement
Relaxational and mood uplifting
Relief of sinus, lung and respiratory issues
Rubifacient[3]

Table 2: *Claimed medicinal properties of wintergreen oil.*

[1]A carminative is a drug or agent that relieves flatulence.

[2]An emmenagogue is a drug or agent that stimulates or increases menstrual flow.

[3]A rubefacient is a topically applied substance that produces redness of the skin by dilating the capillaries and increasing blood circulation. Rubefacients are sometimes used to relieve acute or chronic pain.

It has also been found that that wintergreen leaves contain antioxidants, which have high anti-inflammatory potential [15]. These anti-oxidant and anti-inflammatory properties were ascribed to the presence of relatively high levels of antioxidant polyphenols in the leaves of *G. procumbens* which appear to be readily extractable. In particular, among these phenolic constituents, low- and medium-molecular weight proanthocyanidins[4] and phenolic acids are the primary source of the antioxidant capacity, whereas flavonoids are the main determinants of the anti-inflammatory effects [16]. Other anti-oxidants found in wintergreen oil include α-pinene, myrcene, δ-3-carene, limonene, 3,7-guaiadiene, and δ-cadinene, as previously mentioned.

It follows from these findings that the minor constituents in natural wintergreen oil (See figure 1b above) may be the bioactive phytocompounds responsible for the potent bioactivity, notably its immune-enhancing action through lowering inflammation and pain reduction. These characteristics have great significance because of the important and deleterious role inflammation has in such diseases as diabetes, asthma, cardiovascular diseases and cancer.

It also follows that this recent research [1,2] suggests that synthetic wintergreen oils may be unable to achieve the same beneficial medicinal effects of the natural oil, primarily because they do not contain the antioxidants and bioactive phytocompounds present in natural wintergreen oil. This conclusion is a natural consequence of the fact that the scientific literature does not appear to support certain health claims for "wintergreen oil" and/or methyl salicylate. In particular, certain essential oils, notably wintergreen, lime, peppermint and spearmint, showed no antibacterial activity against *Streptococcus mutans*, the primary causative agent in dental caries (i.e. dental decay or cavities) [17]. Nevertheless, methyl salicylate, identical to the major ingredient in wintergreen oil, is present in Listerine® mouthwash, together with eucalyptol, menthol and thymol, which is recommended as an approach to reducing plaque, gingivitis and bad breath.

Likewise, there appears to be no scientific evidence supporting the use of wintergreen oil as a natural astringent and antiseptic in treating acne and seborrhea[5]. Although a traditional (i.e. common or folk remedy) is that a few drops of natural wintergreen oil added to regular shampoo relieves scalp itching and helps treat the condition.

Other workers have reported that a wide variety of flavonoids such as rutin and various phenolic compounds can be extracted from the leaves of *Gaultheria fragrantissima* collected from Nepal [18]. It was noted that these compounds exhibited antioxidant and antibacterial properties but surprisingly, when even a "crude" methanol extraction was performed, the extracted material showed higher antioxidant and antibacterial activity compared to the essential oil.

It should also be noted that anecdotal and traditional health approaches do support various medicinal uses of wintergreen oil. Further, there are numerous anecdotal/traditional dermatological claims that wintergreen oil can be very effective in toning and firming the skin, diminishing blemishes and other minor skin problems. It is often said to control acne and prevent the formation of pimples and blackheads caused by localized microbial infections.

Although various statements commonly are made for wintergreen oil being a digestive aid, such claims do not appear to be supported in the literature. However, because the taste and smell of mint often helps reduce food cravings and promote the feelings of satiety, many people find it comforting to chew mint-flavored gum after a meal or even between meals to stave off hunger pangs. Apparently, simply sniffing wintergreen oil or applying a few drops to the temples, chest or clothing appears to be helpful through its olfactory effects.

[4]Proanthocyanidins are polyphenols that give the fruit or flowers of many plants their red, blue or purple colors. Initially studied for their importance as plant pigments, they are now known to inhibit/retard oxidation reactions, counteracting oxidative damage in tissues and possibly prevent cancer.

[5]Seborrhea or seborrheic dermatitis is commonly known as dandruff but for infants, the condition is known as cradle cap.

Toxicity

Although diluted wintergreen oil is used extensively as an additive in food flavorings, cosmetic products, dentifrices, mouthwashes and even tobacco products, only relatively small amounts are present in these applications. This is because the pure (concentrated) essential oil can be very toxic[6] when ingested and the allowable daily intake for ADULTS is estimated to be 11 mg/kg [19].

Because of the severity of the symptoms of salicylate poisoning, there has been an ongoing research interest in the toxicology of wintergreen oil (and methyl salicylate) for several decades. Warnings over the risk of severe salicylate poisoning from ingesting topical medications containing wintergreen oil were issued as early as 1996 [20], if not before. A review of U.S. poison center data for 2004 indicated over 40,000 exposures to salicylate-containing products with infants and children being particularly susceptible to salicylate poisoning [21]. Ingestion of more than a lick or taste of oil of wintergreen (98% methyl salicylate) by children under 6 years of age and over 4 mL of oil of wintergreen by children ≥ 6 years of age can cause systemic salicylate toxicity and death [20,22].

The consensus regarding the toxicity of wintergreen oil is that when used aromatherapeutically, i.e. diffused via a vaporizer or added to a bowl of steaming hot water, there appear to be no health hazards. When diluted in a safe carrier oil such as coconut oil or olive oil and applied topically, there should be no toxicity problems provided that the treated area is not licked and that there is no contact of the prepared liniment with the eyes or mucosal tissues. Further, care should be taken to prevent transfer of the diluted wintergreen oil to infants, young children and even pets by the hands or fingers.

Ingestion of wintergreen oil, even when diluted, should always be avoided due to the risk of salicylate poisoning.

Conclusion

The bioactivity of wintergreen oil has been established for millennia in many aspects of Complementary and Alternative Medicine (CAM) or, simply, folk medicine. In particular, topical application of wintergreen oil to relieve pain and inflammation is commonplace throughout the world. Many other medicinal applications of wintergreen oil, particularly in aromatherapy and massage therapy, take advantage of the anti-oxidants found in natural wintergreen oil, notably α-pinene, myrcene, 1,3-cineole (aka eucalyptol), limonene, and linalool, which promote the immune-enhancing action of the oil by lowering inflammation and pain reduction. This effect occurs through activation of TRPV1 receptors by the terpene minor constituents of oil of wintergreen.

It should be noted, however, that ingestion of both natural and synthetic wintergreen oil can elicit toxic effects due to the high content of methyl salicylate and caution must be exercised with proposed or intended internal use of wintergreen oil.

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[6]Typical symptoms of salicylate toxicity include hematemesis (vomiting of blood), tachypnea (abnormally rapid breathing), hyperpnea (increased depth of breathing), dyspnea (labored breathing), tinnitus (ringing in the ears), deafness, lethargy, seizures, unexplained lethargy and confusion.

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