A Short Review of Wintergreen/Methyl Salicylate Toxicity

Gaultheria procumbens L. © Jason Hollinger/
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Methyl salicylate (MS - Cas. No.: 119-36-8) is, as its name implies, a salicylate; more precisely, it is an organic ester of salicylic acid (SA) with methanol, and it is naturally occurring as its glycosides in some aromatic plants; that is, those plants do not contain MS by itself but as linked to one or more sugar molecules.

The major sources of MS are species of the genus Gaultheria, from which we obtain the Wintergreen essential oils: *Gaultheria procumbens* L. (OE contains up to 99% MS), and *Gaultheria fragrantissima* Wall. (OE contains up to 99.5% MS), and other Gaultheria species, such as *Gaultheria hispidula* (L.) Muhl. ex Bigelow, or *Gaultheria leucocarpa* Blume.

It is also a major component of the volatiles of other species such as *Betula lenta* L. (90% MS), *Filipendula ulmaria* (L.) Maxim., *Filipendula rubra* (Hill) B.L.Rob. and of the roots of *Polygala paucifolia* Willd, and makes a significant contribution to the scents of Tuberose (*Polianthes tuberosa* – 8.4% MS), Ylang ylang (*Cananga aromatica* – 0–10% MS), Cassie (*Vachellia farnesiana* (L.) Wight & Arn. or *Acacia farnesiana* – <5% MS), *Mimusops elengi* L. (Bakul) – 2%), and *Monotropa hypopitys* L. It is present at low concentrations (from 10% to less than 1%) in *Dianthus caryophyllus* L. and *Acacia caven (Molina) Molina*.

Biosynthesis ad ecology of MS
Salicylates derive, in the plant, from the shikimic acid biosynthetic pathway, and can be recognized by the presence of a six-membered ring with either a one- or three-carbon substituent on position 1 and oxygenation in the third, and/or fourth, and/or fifth positions (Fig.1–3).
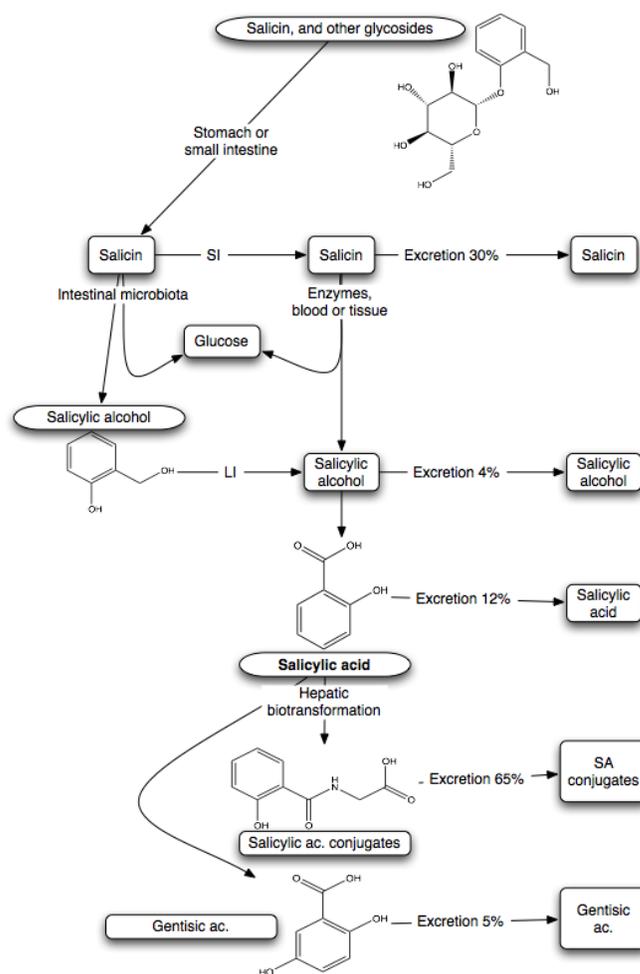

Figure 1. Metabolism of salicylates.

Shikimic acid is synthesized from phosphoenolpyruvate and erythrose-4 phosphate; its subsequent aromatization, without addition of the three additional carbon atoms from phosphoenolpyruvate, gives benzoic acid derivatives, and hydroxylation of benzoic acid leads to salicylic acid (o-hydroxybenzoic acid); from which esterification we obtain methyl salicylate (Fig. 1–3).
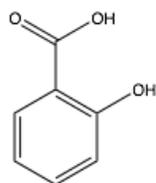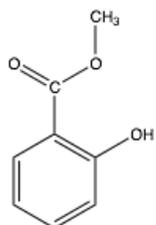
Figure 2. Salicylic acid.   Figure 3. Methyl salicylate.

Figure 4. Enzymatic hydrolisis

But why are plants producing salicylates? There are indications that plants increase the production of SA as a response (called hypersensitive reaction, henceforth HR) to the invasion of cells or tissues by a weak pathogen; this response includes also a process of programmed cell death, in order to contain the microbe and stop further replication. The pathogen-induced SA signal activates a molecular signal transduction pathway that eventually induces a systemic acquired resistance (SAR) that allows the plant to react faster and to a wider range of pathogens, via the production of pathogens-related proteins (PR).

SA can be converted to MS, which may act as a volatile SAR-inducing signal transmitted to distant parts of the plants and even to neighboring plants to produce PR proteins even in the absence of a direct pathogen attack on plant (Shulaev et al, 1997).

MS is also produced as an anti-herbivore defense, because it may function as an aid in the recruitment of beneficial insects to kill the herbivorous ones (James and Price, 2004).

Wintergreen EO
The MS-containing essential oils which we are most likely to encounter in the market, and which are the richest source of MS, are Wintergreen leaves and Birch bark oils. In both cases MS is not present in the plant in its free-form, but as a glycoside, that is, as a sugar-bound precursor, called gaultherin (2-[(6-O-β-d-Xylopyranosyl-β-d-glucopyranosyl)oxy] benzoic acid methyl ester), together with a specific enzyme, primeverosidase.

To free MS from the sugar it is necessary to cleave it enzymatically in the presence of water (enzymatic hydrolisis), and that is why prior to distillation Wintergreen leaves are macerated in warm water for 12 hours, allowing the enzyme primeverosidase to act on gaultherin and free MS from the sugar portion, primeverose (or glucoxylose) (Fig. 4).
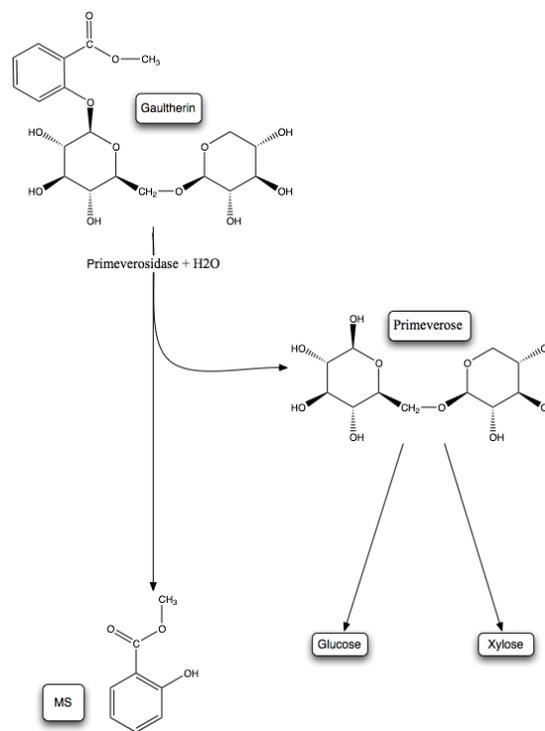
Once this is done, the material can be distilled, to obtain a colorless to pale yellow/pinkish coloured mobile liquid (the reddish color mentioned in earlier reports derived from the contact with the iron of old stills) of intensely sweet-aromatic odor and flavor (Arctander, 1994).

Wintergreen industry
What is the fate of MS once it gets absorbed?
After oral administration salicylates are in general absorbed rapidly, partly from the stomach (the low pH keeps the molecules in a non-ionized, more lipid-soluble, hence more bioavailable, form) but mostly from the upper small intestine (the alkaline pH keeps the molecules in a ionized, less lipid-soluble, and less bioavailable, form, but the much higher absorptive surface makes this the major absorption site). Appreciable concentrations are found in plasma in less than 30 minutes (Gilman et al, 1990). A very high proportion gets hydrolized by esterase in the intestinal tract, with production of SA, although there remains a proportion of unhydrolyzed ester: 15 minutes after ingestion, 39% of MS was found unchanged in plasma, and after 90 minutes only 21% remained. MS can be excreted as sulfate or glucuronic acid conjugates (Patty, 1963). It is conceivable that the small proportion of unhydrolyzed MS might have a more toxic action than SA.

After cutaneous application with a 3% MS gel, significant levels of salicylate can be detected in the dermis and subcutaneous tissue, at levels 30-fold higher than the plasma concentrations. This data by itself demonstrate that salicylates found in the subcutaneous tissues arrived there by directly penetrating the local tissues, and not by indirect redistribution via the systemic circulation (if this were the case, local tissues and plasma levels would have been equal).

In fact, both *in vitro* (with isolated human skin)(Cross et al, 1998; Moody et al, 2007) and *in vivo* experiments (Morra et al, 1996; Cross et al, 1999) give similar ranges of absorption, 11–32% and 12–20%, respectively, with a 20% absorbed from a bath containing dispersed MS. Once penetrated, most of the MS gets metabolised to salicylic acid in the cutaneous and subcutaneous tissues. Applying MS to the skin would achieve therapeutic levels of salicylate beneath sites of topical application, especially in the leg region (Mills and Cross, 2007). Exercise and heat exposure, by increasing skin temperature, hydration and blood flow, enhance the percutaneous absorption of methyl salicylate (Danon et al, 1986).

Once absorbed the salicylates show a wide distribution, in the cerebrospinal, synovial and peritoneal fluids, in saliva and milk, primarily by pH dependent passive processes. Salicylates are actively transported by a low-capacity, saturable system out of the CSF across the choroid plexus. They cross with ease the placental barrier and they are found at high concentrations in plasma, kidney, liver, heart and lungs. Between 50 and 90% are bound to plasma albumin, and are therefore inactive. Any condition that leads to reduced albumin plasma concentration translates into increased activity. SA gets metabolised in many tissues, but particularly in the hepatic endoplasmic reticulum and mitochondria, which metabolise as much as 80% of SA via conjugation with glycine to form salicyluric acid and with glucuronic acid to form salicyl acyl and phenolic glucuronide. In addition, a small fraction is oxidized to gentisic acid (2,5-dihydroxybenzoic acid) and to 2,3-dihydroxybenzoic and 2,3,5-trihydroxybenzoic acids; gentisuric acid, the glycine conjugate of gentisic acid, is also formed (Gilman et al, 1990) (Fig. 5).
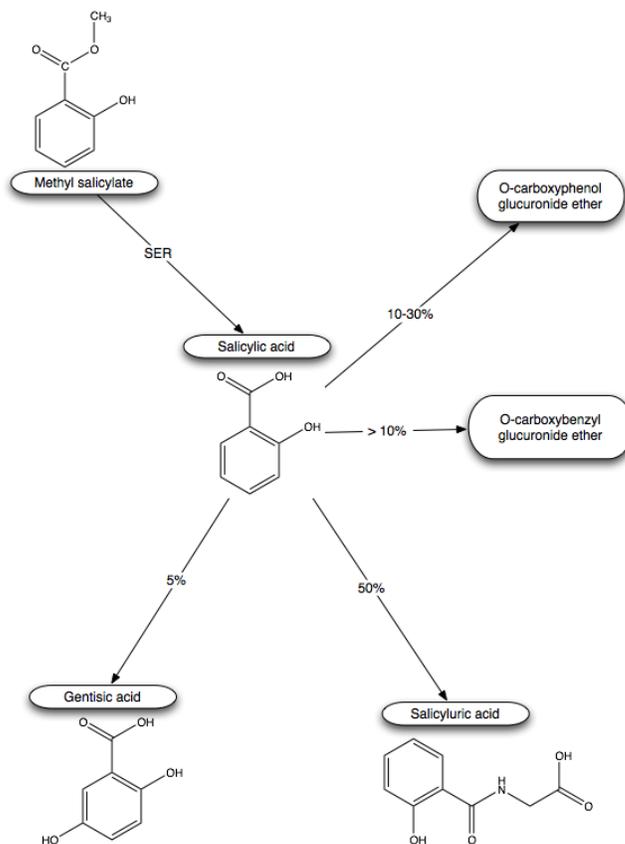

Figure 5.

The two parallel pathways have limited capacity and saturate easily above therapeutic doses (Ellenhorn and Barceloux, 1998). With large or multiple doses the kinetics switch from first-order to zero-order, and renal elimination becomes more important than conjugation (Levy and Tsuchiya, 1972).

At low doses (< 250 mg in an adult) all pathways proceed by first-order kinetics, and the elimination half-life is of about 2.0 to 4.5 hours (Hartwig, 1983). At higher doses (> 4 g) the half-life becomes much longer, 15–30 hours (Chyka et al, 2007), because the biotransformation pathways concerned with the formation of salicyluric acid and salicyl phenolic glucuronide become saturated (Prescott et al, 1982).

Urine analysis shows that salicylates are excreted by the kidneys mainly as free salicylic acid (10%), salicyluric acid (75%), salicylic phenolic (10%), acyl (5%) glucuronides, gentisic acid (less than 1%), and 2,3-dihydroxybenzoic acid (Grootveld and Halliwell, 1988).

The proportion of free salicylic acid excreted depends on urine pH: a 10- to 20-fold increase in renal clearance occurs when urine pH is increased from 5 to 8, from as low as 2% to up to 30%.
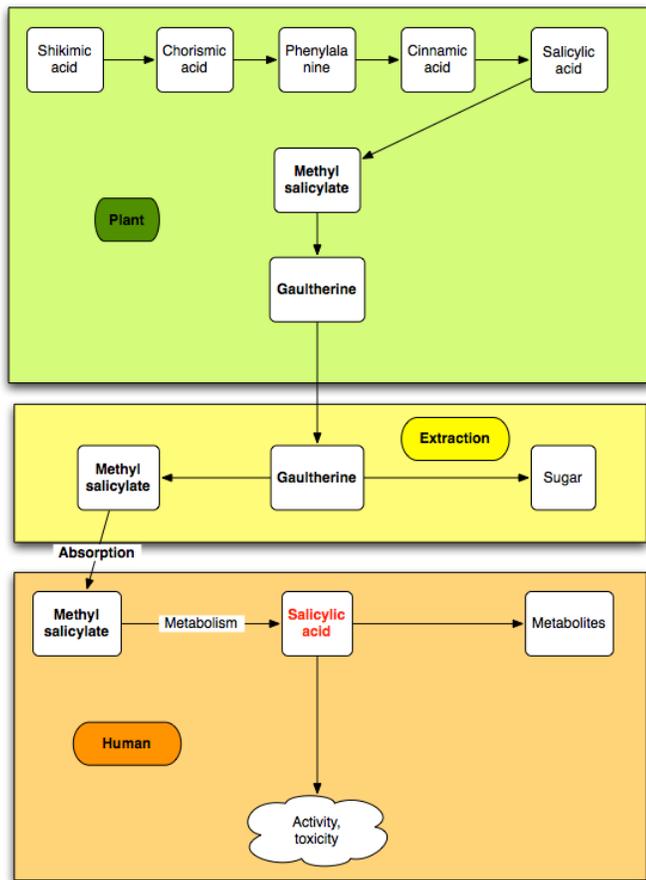
Figure 6.

The use of urinary alkalinization exploits this aspect of salicylate elimination (Dargan et al, 2002).

Toxicology
Terms of comparison

Given that in the past, to make MS toxicity more easily understandable, aspirin toxicity has been used as a term of comparison, we need first to examine the validity of such a comparison.

Aspirin (whose technical name is acetyl salicylic acid) is a synthetic derivative of salicylic acid. It is therefore different from MS. And if we were comparing the topical toxicity of the two molecules we would be making a big mistake. Topically MS is most definitely more aggressive than aspirin.

But when addressing systemic toxicity what we are in fact comparing are the active metabolites of MS and aspirin and their respective toxicity.

As we've seen in the preceding section, once ingested MS gets rapidly hydrolyzed to salicylic acid (although not all of it), just the same, active, molecule that is produced by the metabolism of aspirin.

Given that the active metabolite of the two molecules in the same, we can say that both are pro-drugs, leading to the production of the same active drug, SA. And if this is the case, then we can compare their respective toxicities by taking into account their SA-producing potential.

Let's then review the toxicity data on aspirin: at 150 mg/kg there is no expected toxicity, but we are at the lower limit of the toxic dose (Table 1) at 150–300 mg/kg we would expect mild to moderate toxicity; at 300–500 mg/kg we are in the area of life-threatening toxicity, taking into account that the minimal lethal dose is 450 mg/kg (Amdur et al, 1991). It must be remembered that there are factors that influence toxicity, such as dose, age, renal function, dehydration.

MS toxicity

Using this translation mechanism, we can say that 5 ml (1 teaspoon) of Wintergreen oil at 98% MS contains 7000 mg of salicylates, and produces as much SA as 21 adult aspirin (300–325 mg salicylates per tablet) or as 90 baby aspirins (81 mg salicylates per tablet), and more than 4 times the potentially toxic dose for a baby who weighs 10 kg (Ellenhorn and Barceloux, 1988). Oil of Wintergreen in the form of candy flavoring was ingested by a 21-month-old boy who developed vomiting, lethargy, and hyperpnea but recovered rapidly with parenteral fluids and sodium bicarbonate (Howrie et al, 1985).

Model	Test	Modality	Results: g/kg
Rat	LD_{50}	oral	0.887 and 1.25 g/kg
Mice	LD_{50}	oral	1.11 and 1.44 g/kg
Rabbit	LD_{50}	oral	2.8 g/kg
Guinea pig	LD_{50}	oral	0.7 and 1.06 g/kg
Dog	LD_{50}	oral	2.1 g/kg
Guinea pig	LD_{50}	dermal	0.70 ml/kg
Human child	LDLO (lowest published lethal dose)	oral	0.17 g/kg
Human adult	LD_{50}	oral	0.5 g/kg

Table 1: MS acute toxicity (Tisserand and Young, 2013).

In a retrospective study 80 subjects who had ingested aspirin tablets (n = 42) or topical oil of Wintergreen (n = 38) were compared. The admission plasma salicylate concentrations were generally higher in those who had taken aspirin tablets, but the two

highest readings (4.3 and 3.5 mmol/1) belonged to two of the subjects who had taken oil of Wintergreen (Chan, 1996a).

On the bases of these data it can be seen that LD_{50} tests on rodent models can be misleading, since the toxic dose in those models is much lower than that observed in humans; while the toxic dose of Wintergreen in children of around 35 kg has been estimated to be around 4 ml, and the average lethal dose is 10 ml, the rodent data extrapolated to humans would give a much higher range of 31–50 ml.

In fact MS continues to be a relatively common source of pediatric exposures, and there have been many reports of accidents resulting in the death of children under the age of six ingesting 5 ml or less of Wintergreen oil (Davis, 2007) or medicated oils containing MS (Chan et al, 1995; Chan, 1996b).

Systemic toxicity after dermal absorption
A recent review of the toxicity of salicylates says that the dermal route of exposure for MS does seem of little acute toxicity: in rat models the dermal LD50 for MS is >2 g/kg. In a dermal absorption trial commercial dermal patches containing MS were applied to 8 human volunteers in different numbers (2, 4, or 8) for 8 hours. For the 8-patch group, the average maximum plasma concentrations were 29.5 +/- 10.5 ng/mL, while for the 4-patch group they were 16.8 +/- 6.8 ng/mL. The authors concluded that there seems to be relatively low systemic exposure to MS after application of a high number of dermal patches (Martin et al, 2004).

However, topical MS still has good bioavailability, since salicylate toxicity has been reported with the topical use of salicylate-containing teething gels in infants (Williams et al, 2011), and by the fact that subchronic dermal exposures to undiluted MS are associated with kidney damage, and reproductive and developmental toxicity as a function of blood levels (CIREP, 2003). In a different study, the MS serum levels were measured after the dermal application of a salicylate-containing rubefacient delivered by aerosol. MS was absorbed easily, and serum levels were maximal between 20 and 30 minutes after application. The application caused erythema (maximum effect after 30 minutes) and increased resistance of platelet to clumping (Collins et al, 1974).

A 30 ml-bottle of a liniment with 20% methyl salicylate is equivalent to the above-described fatal dose of Wintergreen for children, and when applied to large areas of skin may cause sufficient dermal absorption to produce toxic serum salicylate levels (Ellenhorn and Barceloux, 1988).

Chronic toxicity seems the most worrying: a subject who was applying a herbal skin cream containing MS for his psoriasis, using occlusion, became quite suddenly and acutely unwell, with tinnitus, vomiting, tachypnoea and typical acid/base disturbance, a classical presentation of salicylate poisoning. The skin lesions and the occlusion certainly enhanced the absorption (Bell and Duggin, 2002).

Not only does MS have good transdermal bioavailability, once in the systemic circulation, it crosses the placental barrier, which makes it potentially harmful to the fetus. The risk is limited, because the amount of salicylates absorbed needs to be high. In a case, a fetus of 33 weeks died in utero 20 hours after the ingestion by the mother of 3 grams of salicylates, which caused a level of 212 mg/l of salicylates in the blood of the fetus (Ellenhorn and Barceloux, 1988). The doses of MS that could reach the systemic circulation after dermal application or inhalation would usually be too low to cause acute fetal damage. However, a low level but prolonged use of salicylates in pregnancy has caused reduced weights at birth, increase in perinatal mortality, anemia, antepartum and postpartum hemorrhage, prolonged gestation, and complicated deliveries (Wilson, 1973).

Dermal toxicity
MS in topical analgesic preparations can cause irritant or allergic contact dermatitis and anaphylactic reactions (Chan, 1996c), although the percentage of dilution makes the difference: it was irritating at a 1% with a 70% ethanol vehicle and at 12% (pain and erythema) whereas a 6% concentration in polyethylene glycol and an 8% solution produced little or no irritation. At 15% or more it caused irritation in atopic patients; however, in subjects with normal skin MS was not a sensitizer (CIREP, 2003).

Laryngeal edema has been attributed to oil of Wintergreen after accidental ingestion (Botma et al, 2001).

Effects of salicylate ingestion

Salicylates directly or indirectly affect most organ systems in the body by uncoupling oxidative phosphorylation, inhibiting Krebs cycle enzymes, and inhibiting amino acid synthesis, and will eventually lead to disturbances of:

• the central nervous system, with tinnitus and hearing loss, and eventually tremors, seizures, confusion, encephalopathy, coma and death.

• the cardiovascular system, with tachycardia, hypotension, dysrhythmias and, with severe intoxication, asystole.

• the respiratory system, with tachypnea and hyperpnea.

• the liver, with hepatitis (in children ingesting doses at or above 30.9 mg/dL) and Reye syndrome.

• the gastrointestinal tract, with nausea and vomiting, and abdominal pain.

• the metabolic systems, with hyperthermia, acid-base disturbances (respiratory alkalosis, metabolic acidosis), dehydration and electrolyte imbalance (hypokalemia, hyponatremia), altered glucose levels

• hematological parameters, with hypoprothrombinemia and platelet dysfunction.

• musculoskeletal system, with rhabdomyolysis.

Dermal adverse effects

Wintergreen can be an irritant but not allergenic (Tisserand and Young, 2013). For this reason it is best not to apply Wintergreen-containing products to burned areas or damaged or inflamed skin.

Interactions

There is a potential for interactions with Warfarin (Chan, 1996b): MS can interact by affecting vitamin K metabolism (Warfarin is a vitamin K antagonist) or by displacing Warfarin from its protein-binding sites. The effects are similar to those derived from ingestion of aspirin [34], and can happen even after small doses applied topically (Morra et al, 1996; Joss and LeBlond, 2000). The antiplatelet effects were observed in a clinical trial after the application of 5 g of a 30% MS topical preparation (Tanen et al, 2008), which is a much higher concentration than it would normally be found in Aromatherapy treatments. However, given the narrow therapeutic window of Warfarin, and the possible severe consequence of an interaction, the risks of an Aromatherapy treatments cannot be discounted right away, especially in the case of occlusion, which enhances dermal absorption.

Conclusions

Toxicological data on their own are rarely sufficient to dictate guidelines. What is a dangerous practice in one case can be an acceptable risk in another. Much depends on how much knowledge the practitioner has of toxicology, physiology and pathology, and on the existence of other, less dangerous practices. However, I believe the data briefly presented here clarify a few things about Wintergreen and all MS-containing oils.

MS is a prodrug that metabolises into salicylic acid in the organism, just like aspirin, but it also has a great facility to penetrate the dermis, thus making it risky not only when taken orally but also when applied topically. It shares all the toxicity problems of aspirin with a higher risk of irritation, and as we have seen we can use this equivalence to make it easier to understand the level of risk. Wintergreen is a special case in Aromatherapy: it's so simple in composition it's almost mono-molecular, and it can be thought of as a pharmaceutical drug, and has caused many deaths in the past, usually after ingestion. I personally am not inclined in using it because of its simplicity (I use herbs and essential oils because they are complex) and its toxicity.

In any event we should be extremely careful with its use and we should actively inform clients and the public about its risks, because it is freely available on the market and it could be easily misused.

In summary

The hazards of the use of Wintergreen are linked to its toxicity, to the risks of interactions with prescription drugs (Warfarin, anticoagulants) and with pathological conditions (hematological disorders and renal problems), and to its teratogenic potential. Particularly problematic is the chronic toxicity, which might develop weeks or months after using the products, and which can be difficult to spot.

It can be safely stated then that MS, Wintergreen and all MS-containing essential oils should never be used on children, pregnant and lactating women, people with renal disease and hematological problems (clotting disorders, hemophilia), and in case of salicylate sensitivity. The usefulness of its application should always be weighed against the risks. ∞

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