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The Ethnobotany and Modern Pharmacology of Gandhapura (*Gaultheria fragrantissima* Wall.): Opportunities and Risks

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ABSTRACT

The present study aims to evaluate various medicinal properties of *Gaultheria fragrantissima* W. The genus *Gaultheria*, comprising approximately 134 species, is most commonly used in the traditional systems of medicine to treat rheumatism and alleviate pain. Recent research has established that these plants exhibit anti-inflammatory, antioxidant, antibacterial, and analgesic activities. Studies have reported about 109 compounds from this genus, which chiefly include methyl salicylate derivatives. Methyl salicylate (Oil of Wintergreen) is a common ingredient in most of the famous topical analgesic balms. It is an organic ester naturally produced by many species of plants, particularly wintergreens. The present study aims to present a methodical study on the selected medicinal plant with reference to its classification, morphology, cultivation, potential functions, applications, health risks, and future opportunities.

Keywords: *Gaultheria fragrantissima* W., Ayurveda; Medicinal plants and Balm.

INTRODUCTION

Ayurveda and other Indian literature mentioned the used of plants in the treatment of various ailments. Out of an estimated 2,50,000 higher plants, less than 1% have been screened pharmacologically. There is a growing need to find the most suitable and efficient treatment options for disorders coupled with pain. *Gaultheria fragrantissima* W., which belongs to family Ericaceae and is one of the common plant that has been used in the treatment of arthritis, sciatica, neuralgia and rheumatic pain, in addition, it is used as an antiseptic and carminative. Furthermore, *G. procumbens* is utilized as a folk medicine in America and Canada, and *G. fragrantissima* is used in India (Simon et. al., 1984, Shiva et. al., 2000). This therapeutic plant is commonly known as *Gandhpura* in Ayurveda and the Indian Traditional system of medicine, while the trade name is Indian Wintergreen.

In Indian subcontinent this plant is found mainly in two regions i.e. Eastern Himalayas and Western Ghats. (Bantawa and Mondal, 2008) Furthermore, it is found freely in the Nilgiris hills, hills of Travancore and Toungoo hills in Burma, and Ceylon; also from Nepal, Bhutan and Khasia hills of Assam at the altitudes above 1,500m (Nadkarni and Nadkarni, 1994).

Systematic classification, morphology, habitat and propagation

Gaultheria fragrantissima Wall., (Gandhapura) belongs to family Ericaceae. It is also known as winter-berry, tea-berry, box-berry, deer-berry, checker-berry, spice berry, wax cluster and partridgeberry. It is an endangered aromatic, small, woody, stout shrub containing wintergreen oil. Fragrant Wintergreen is a vigorous shrub with ovate-lance shaped evergreen leaves, and with numerous spike-like clusters of small fragrant white or pink globular flowers (Polunin and Stainton, 1990; Venugopal and W. Langstang, 2011).



***Gaultheria fragrantissima*, (Wintergreen)**

Source: <http://www.star-ayurveda.com/>

It is a branched shrub up to 1.75 m tall. It prefers a moist but not boggy humus-rich soil in shade or semi- shade. It is a peat and moisture-loving species; it requires a lime-free soil shade (Bean, W., 1981; Thomas, 1992). The plantlets form roots in late summer or spring (Sheat, 1948). The bruised leaves have a strong camphor-like odor (Genders, R., 1994). The general habitat of the plant is forests and as shrub undergrowth (Polunin and Stainton, 1984), usually on dry slopes (Gamble, 1972), at elevations of 1,200 - 2,700 metres in the Himalayas. The propagation of *G. fragrantissima* occurs mostly by seed that requires a phase of cold stratification. Berries are 6 mm, with dark violet-blue fleshy pointed sepals.

It Flowers from April-May (Nadkarni and Nadkarni, 1994). Panda (2012) reported the detailed morphology of the flower and flower parts.



***Gaultheria fragrantissima*, (Wintergreen)**

Picture courtesy: Jan Thomas Johansson (2014)

Utilization

1. Pain-reliever: Oil of wintergreen is obtained by distilling leaves and sometimes the whole herb of *G. procumbens*, a plant indigenous to the United of America. Puran singh (1917) studied the distillation products of *G. fragrantissima* Wall., with a vision to its exploitation on a commercial level. Wintergreen essential oil is obtained by steam distillation of the leaves of the plant, subsequent to maceration in warm water. Methyl salicylate, the chief chemical constituent of the oil, is not there in the plant until created by enzymatic action from a glycoside within the leaves as they are macerated in warm water. He established that only the herb that is found in Assam has ample oil for commercial purposes. The characteristics of the Indian wintergreen oil have also found to be extremely comparable to those obtained from other countries. The constants of the Assam oil are as follows: specific gravity 1.185; optimally inactive; soluble in 6 parts of 70% acohol; methyl-salicylate content 99.1 %. Refractive index at 20° C., 1.537 to 1.539, colourless or nearly colorless with a characteristic strong odour and sweet, aromatic pungent taste. A similar oil is has been further discovered in many plants of the families Betulaceae, Rosaceae, Polygalaceae, Leguminosae etc in different parts of the world, but the active principle in some of them is present in too small quantities to be of any commercial value.

The pain-relieving properties of wintergreen essential oil is similar to aspirin (salicylate is the principal component of aspirin) (Balch 2002). While an infusion of wintergreen leaves is occasionally consumed, the pre-dominate use of wintergreen is the topical use of its essential oil in ointments or liniments for rheumatism, sprains, sciatica, neuralgia and muscular pain (Wren 1994). It is also used in the "Dencorub Extra Strength" heat cream, which is used to treat joint and muscular pain and is a product of the Dencorub company. Studies undertaken by Mason et. al. (2004) report that the topical application of rubefacient that have salicylates may be effective in cure of acute pain.

They have reported that trials of musculoskeletal and arthritic pain suggest moderate to reduced efficacy. Adverse events were rare in studies of acute pain and weakly reported in those of chronic pain. But, in absence of good clinical trials efficacy estimates for rubefaciants are still unpredictable. Topical salicylates work in strains, sprains, and sport injuries; the same has been shown for topical non-steroidal anti-inflammatory drugs (Moore et. al., 1998).

Most of the famous balms like Lessentiel repairing balm by Druide, Zandu Balm by Zandu Pharmaceuticals, Rumalaya-Gel by Himalaya wellness pharmaceuticals, X Pain by Jhawar Chemicals Pvt. Ltd. and Strong balm by Lead pharmaceuticals have wintergreen oil as the major constituent. The active ingredient of wintergreen is methyl salicylate, is used as a topical pain-reliever in creams such as BENGAY®. Ichiyama and Ragan (2002) reported that *Gaultheria fragrantissima* have potent analgesic activity. The pain reliever gels like Rumalaya gel depresses cutaneous sensory pain receptors and acts directly to diminish or obliterate pain. It also reduces swelling associated with inflammatory conditions, shortens recovery time and increases mobility of joints (Cross, and Megwa, 1999). The essential oil from wintergreen leaves contains about 98% methyl salicylate and is a good analgesic and anti-inflammatory agent (Zhang, 2007). Indigenous communities of America utilize brewed tea from the leaves to ease symptom of rheumatic pain, headache, fever, sore throat and various other aches and pains. Although the essential/volatile oils are excessively strong to be consumed internally, the leaves, which have much of the identical properties in less proportions, can be utilized to treat influenza, colds, and various bacterial infections. By the use of an infusion of wintergreen leaves, advantages similar to the easing of stomach pain, earaches and fever have also been well documented. It is possible that this therapeutic outcome occur due to the fact that the key metabolite of methyl salicylate is salicylic acid, a proven Non-Steroidal Anti-Inflammatory Drug (NSAID) that is also the metabolite of acetylsalicylic acid, commonly known as aspirin (Rainsford, 2007).

2. Chronic rheumatism and arthritis: The plant has been used in treatment of arthritis, sciatica, neuralgia and rheumatic pain, in addition as an antiseptic and carminative. Applying few drops of Wintergreen oil with carrier oils like Jojoba oil or sesame oil will help clearing impediments in the blood flow, checks rheumatism and helps in removal of toxins, reduce excess weight, salts and excess water by penetrating deeply into the tissues and muscles through the skin (Yao, et. al., 2005).

3. As a flavoring agent: Oil of wintergreen is also used as a flavoring agent (in confectionaries, herbal tea, toothpaste etc) in commercial food products. Methyl salicylate, although it is sourced from plants but they are not true mints and is used as substitute to mint (the common peppermint and spearmint oils are utilized) in some kinds of chewing gum and candy (Steffen, 1994).

4. In pharmaceutical and perfumery industry: The diuretic attribute of Wintergreen oil aids in eliminating the excess water, salt, fat and uric acid in the body through urine, which makes it a promising natural remedy for treating bladder infections, hypertension, edema, obesity and water logging. The studies have reported that the plant is utilized for the volatile oil extracted from its leaves. This essential oil is rich in methyl salicylate and is in high demand in pharmaceutical and perfumery industry (Chopra, 1932).

5. Antiseptic: Essential oil of Wintergreen is extremely noxious and it acts as a defensive screen against bacteria, virus, fungi, microbes and other harmful organisms. It is a good antiseptic and defends the skin from being septic in case of open wounds/cuts that are microbes' prone, and other skin infections. This oil is very powerful and kills *Staphylococcus Aureus* bacteria and heals septic problems. Essential oils and extracts from *Gaultheria* spp. have been studied for their antibacterial activity. A considerable inhibitory effect was established for extracts of *Gaultheria Leucocarpa* var. *yunnanensis* against *Escherichia coli*. (Ma et al., 2001a, b). Gentle application on the skin is useful for curing all types of skin disorders as this oil has the capability to penetrate into the skin and is simply absorbed by tissues and blood stream for quicker relief. (Karuppusamy and Rajasekaran, 2009).

6. Respiratory problems and other spasmodic disorders: The anti-spasmodic features of Wintergreen oil assist in treating the entire varieties of spasms in the respiratory, digestive, nervous system, circulatory systems and muscles. As per the Ayurvedic claims adding few drops of Wintergreen essential oil in steam inhalation, warm baths, gentle massaging and few other topical applications on the affected parts gives total relief from respiratory disorders like asthma, chest congestion, breathing problems and spasmodic coughs. In addition to the above mentioned disorders other disorders that can be effectively cured with wintergreen oil are Nervous afflictions, muscular contractions and certain other health disorders that result due to spasms.

7. Anti-herbivore: James and Price (2004) have reported that by using controlled-release dispensers of methyl salicylate may play an important role as an aid in the conscription of useful insects to kill the herbivorous insects. Plants produce methyl salicylate mainly as a possible anti-herbivore resistance process. Further, reports suggests that compounds of the oil may also be used by plants as a pheromone to notify other plants of pathogens such as tobacco mosaic virus thus can act as a biochemical insect & animal repellent (Vladimir et. al., 1997).

8. As natural nematicides: *G. fragrantissima* in combination with essential oil of other species like *Zanthoxylum alatum* emerge to be very useful as natural nematicides against *Bursaphelenchus xylophilus*, a pine wood nematode. For commercialization and realistic use of the essential oils and their components as new nematicides additional studies that focus on systemic action, phytotoxicity and formulation for improving nematicidal potency are required (Kim et al., 2011). Plants in this genus are notably resistant to honey fungus (Huxley, 1992).

9. As mouth freshener/Mouth wash: Herbs and plant extracts are employed in oral hygiene products for several years. Numerous herbs have been suggested to help and maintain dental health. Hiora mouthwash (A product of Himalaya Ayurveda) is a herbal preparation, made from natural herbs including *Gaultheria fragrantissima* with their beneficial properties like anti-cariogenic and anti-plaque. Studies undertaken by Bhat et. al. (2013) established that Hiora herbal mouthwash has a good potential as an anti-plaque agent in dental care. Wintergreen essential oil improves logical thinking and stimulates mental power. Apart from all these natural benefits, this oil is used as a flavoring agent in candies, root beer, chewing gums, smokeless tobacco, mouth fresheners, mouthwash like Listerine, in toothpastes and certain other oral care products. The potent antioxidants and the antioxidant activity of Wintergreen essential oil adds synergism to the anti-inflammatory property It is also used as a solvent in printmaking (Battino and Ferreiro 2002).

10. In Women's health: Jain (2006) reported that the essential oil from *Gaultheria fragrantissima* being a natural emmenagogue, helps in curing ample of womanly problems like delayed menstruation, uterine ulcers, dysmenorrhea, blocked menses, pain in the pelvic region, hair fall, hemorrhages, fatigue, vomiting and stress related to menstruation.

11. Miscellaneous uses: The additional applications of methyl salicylate are as a transmit mechanism for creating manual copies of images on a surface due to its similar physical & chemical properties as of sulfur mustard during research experiments (Bartelt et. al., 2008). One surprising use of wintergreen oil is rust elimination and degreasing of equipments. Wintergreen is mainly successful for breaking through sea water corrosion as well.



***Gaultheria fragrantissima*, (Wintergreen)**

Picture courtesy: Jan Thomas Johansson (2014)

Chemical composition of wintergreen oil

Till date, widespread studies on the chemical composition from 34 species of the genus *Gaultheria* have led to the detection of 110 compounds, typically assigned to five structural types that include methyl salicylate derivatives, C₆-C₃ constituents, Terpenoids, steroids and other compounds. The C₆-C₃ constituents' chiefly are 19 flavonoids, 10 lignans and seven simple phenylpropanoids in the genus *Gaultheria*. Among the Terpenoids there are four diterpenes and 18 triterpenoids found in the genus *Gaultheria*. Till date only two steroids have been reported in the genus *Gaultheria*. And which include benzoic acid derivatives, alkaloids, anthraquinones, dilactones and hydrocarbons, etc (Liu et. al., 2013).

The oil extracted from *Gaultheria* sp. exhibits following important constituents methyl-salicylate (approximately 98%), α -pinene, delta-3 myrcene, careen, limonene, 3,7-guaiadiene and delta – cadinene (Cecilia, 2000). Methyl salicylate, the main chemical constituent of the oil, is not present in the plant until formed by enzymatic action from a glycoside within the leaves as they are macerated in warm water (Sylla, 1995).

Commercial synthesis

Methyl salicylate is the active ingredient in Oil of Wintergreen. It has a very distinct minty odor. As mentioned earlier it is a derivative of salicylic acid and is frequently used in ointments for the aid of muscle pain, spasms because it can penetrate the skin. Previously chemists isolated salicylic acid from plants subsequently they started transforming it by creation of acyl derivatives, in particular esters since the target of manufacturing these derivatives was to get the salicylic acid derivative into the individual body and then have it revert to salicylic acid. For example, wintergreen is a liquid and is incorporated in "aspirin" creams as it is hydrolyzed to salicylic acid while absorbed through the skin. Aspirin is less acidic and irritating in comparison to salicylic acid, and now it is encrusted to make it further bearable on intake. Ironically, with all its biological properties and side effects, that including blood thinning, it should be noted that salicylic acid and its derivatives would most likely not be permissible in the market by existing regulatory agencies.

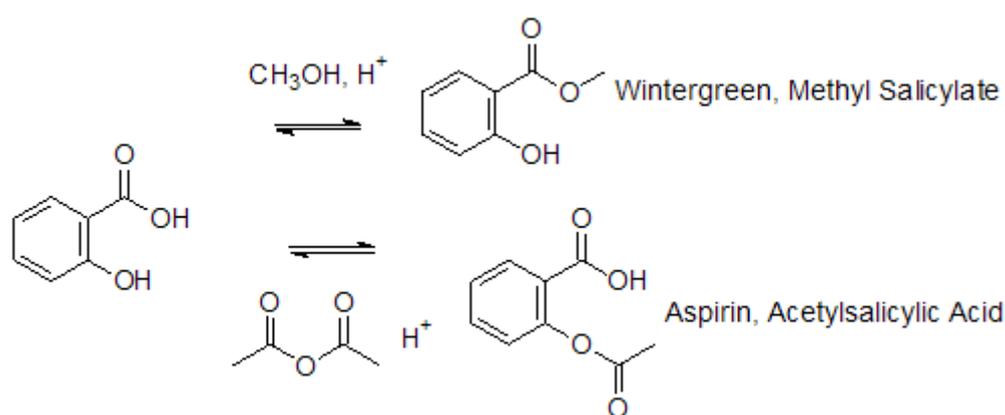


Fig. 1. The reaction between salicylic acid and methanol to form methyl salicylate and its reversion to salicylic acid after absorption in skin.

Pharmacological activity and associated Health risks

Wintergreen essential oil (methyl salicylate) is extremely toxic and is supposed to be applied externally only. Approximately 30 ml (about 1 fl oz) of oil of wintergreen is equal to 55.7 g of aspirin, or about 171 adult aspirin tablets. This conversion demonstrates the strength and possible toxicity of oil of wintergreen even in minute quantities (Botma 2001). High doses of topically applied wintergreen oil can be toxic, as salicylates can be absorbed transdermally. To mitigate the chance of toxicity, wintergreen essential oil should not be applied for more than 3 continuous days per month, and it should not be used among people with chronic kidney or liver conditions. Also, it should not be applied to the skin of a child under the age of 12 unless advised to do so by a physician (Balch 2002). Ingestion of as little as 4 ml in a child can be fatal. The pleasant smell of methyl salicylate may also entice children to ingest products containing methyl salicylate (Botma, 2001). When ingested, the highly concentrated liquid methyl salicylate in the form of wintergreen oil, as with other volatile oils, can induce vomiting and is a notorious source for severe, often fatal, poisonings (Howrie et. al., 1985; Bell and Duggin, 2002). Wintergreen oils too have blood-thinning effect like aspirin. People who take blood thinners such as Warfarin, or those who are susceptible to aspirin are advised for not taking wintergreen essential oil.

Other caution related with Methyl Salicylate includes using with care if the person suffers from nasal polyps, asthma, or sensitivities to aspirin. And to be careful in its application after strenuous exercise, during hot and sultry weather, or using a heating pad in combination with products containing this ingredient can increase systemic absorption and the increase its risk level. The Chronic Effects associated with Humans are: The substance is toxic to blood, lungs, the nervous system, mucous membranes. It could be very hazardous in case of ingestion, in case of skin contact or inhalation it act as an irritant, thus urgent medical help is required. It acts as a permeator so is slightly hazardous in case of skin contact therefore medical may be required (MSDS, Sciencelab.com, 2005).

Methyl Salicylate may be absorbed rapidly through intact skin. Bowel absorption is somewhat erratic and it is absorbed at least in part as the intact ester and small amount are even excreted as such by the kidneys. Orally ingested salicylates are absorbed rapidly, partly from the stomach but mostly from the upper small intestine. Appreciable concentrations are found in plasma in less than 30 min; after a single dose, a peak value is reached in about 2 hr and then gradually declines. Salicylates are excreted in the urine as free salicylic acid (10%), salicyluric acid (75%), salicylic phenolic (10%) and acyl (5%) glucuronides, and gentisic acid (less than 1%). However, excretion of free salicylate is extremely variable and depends upon both the dose and the urinary pH. In alkaline urine, more than 30% of the ingested drug may be eliminated as free salicylate, whereas in acidic urine this may be as low as 2%. (Gosselin, et.al. 1984).

Generally, ingestion of salicylates at doses larger than 150 mg/kg (or 70 mg/lb) can produce toxic symptoms such as tinnitus, nausea, and vomiting. Serious toxicity can be seen with ingestions greater than 400 mg/kg (approximately 180 mg/lb), with severe vomiting, hyperventilation, hyperthermia, confusion, coma, convulsions, hyper- or hypoglycemia, and acid-base disturbances such as respiratory alkalosis or metabolic acidosis. In severe cases, the clinical course may progress to pulmonary edema, hemorrhage, acute renal failure, or death. It is important to note that the salicylate -overdose patient can progress to a more serious condition over time as additional drug is absorbed from the gastrointestinal tract. Chronic salicylism presents clinically in a similar fashion to the acute situation, although it is often associated with a higher morbidity and mortality as well as more pronounced hyperventilation, dehydration, coma seizures, and acidosis (Amdur et. al. 1991). The prolonged and excessive ingestion of analgesic mixtures containing salicylates in combination with acetaminophen or salicylamide can produce papillary necrosis and interstitial nephritis (Gilman et.al. 1990).

Essential Symptoms of Salicylate/Aspirin Allergy?

Aspirin is one of the oldest medicines recognized, and is frequently used in various traditional medicine remedies. Aspirin was initially extracted from plants however is now prepared synthetically. Numerous analogous medicines have now been created, and this collection of drugs is known as Non-Steroidal Anti-Inflammatory Drugs or NSAIDs.

NSAIDs can be very effective medicines for pain and fever. They work by inhibiting the production of compounds in the body which are involved in tissue inflammation and fever.

Aspirin also 'thins' the blood by interfering with the ability of the blood to clot, and is used by health professionals in those at risk of heart attacks and strokes. There is also emerging evidence that aspirin may even reduce the risk of certain cancers (Hirsh, 1985).

Like all medicines, aspirin and NSAIDs have side effects. Common side effects include bruising and stomach upset (or even ulcers or bleeding from the bowel), at high dose. Very high doses may cause confusion or ringing in the ears (tinnitus). Aspirin should not be used in children, as it can trigger severe liver damage (known as Reye's syndrome). Ibuprofen (Nurofen) and other NSAIDs are safe to use in children (Levy, 1974).

Salicylates are chemicals present naturally in plants and are a chief constituent in aspirin and other pain-relieving medicines. They are also found in many fruits and vegetables, as well as in many common health and beauty products. Foods containing high levels of salicylate include tea (except fruit and chamomile tea), coffee, dried herbs and spices, black pepper, sharp green apples, cherries, strawberries, dried fruit, tomatoes (fresh, puree and ketchup), fruit juices, cider, wine, peppermints and liquorice. Medicines which can contain aspirin include:

- Cold & flu remedies
- Medicines used for pain from headache, periods, sinus
- Some antacids
- Drugs used for inflammatory bowel disease
- Many complementary and alternative medicines, especially those used for pain and joint problems
- Teething gels

The degree of reaction to salicylates can differ on the basis of numerous factors. Characteristically, the amount of salicylates may vary from one part to another and even between bunch of the same part from the similar source. Additionally, the degree of salicylate sensitivity varies from individual to individual. People with a small salicylate tolerance may have an allergic reaction if more than a small amount of salicylate is consumed. Indication of a salicylate allergy varies but may include:

- Asthma-like symptoms, such as trouble breathing and wheezing
- Headaches
- Nasal congestion
- Changes in skin color
- Itching, skin rash, or hives
- Swelling of the hands, feet, and face
- Stomach pain

In severe cases, a salicylate allergy can direct to anaphylaxis, an acute reaction involving a sudden drop in blood pressure, loss of consciousness, and organ system failure. Avoiding products that have salicylates is the greatest defense against an allergic reaction.

CONCLUSIONS

The following points may be concluded from the present paper:

- There should be efforts to initiate and support for conservation, management and sustainable utilization of *Gaultheria fragrantissima* for human and livestock health care.

- The collection of medicinal plants for livelihood support of the local communities should not be overlooked. The conservation of wild medicinal plants shall be based on sustainable harvesting techniques and by implementation of various conservation techniques must not be ignored.
- Micro-propagation has been an alternative technique to conventional methods of propagation and has found wide commercial application in the propagation of many commercially viable medicinal plants. However, there is no proper study on the micro-propagation of *Gaultheria fragrantissima* except a report of preliminary studies (Ranyaphi et. al., 2010).
- The therapeutically significant plants like *Gaultheria fragrantissima* require being cultivated with an organized approach to meet Indian traditional system-based drug industry and to authenticate the efficacy of all ethno medical claims pharmacologically.
- A coordinated effort is required which could only be achieved by pooling research and development sectors, research institutions, NGOs and communities together to standardize these efforts towards protection of selected plant species that are facing threat due to human interference or anthropogenic activities.
- The author anticipates that this comprehensive review will present important record for the investigation and advanced research on *Gaultheria* species.

Future research prospects

The tremendous potential of *Gaultheria fragrantissima* Wall. Makes it a very suitable for studies like: Optimum growth conditions requirements, gene improvement, documentation of variation in morphology with changing altitude, unexplored role if some incurable diseases, development of Synergic medicine (ingredients of plants all interact simultaneously, so their uses can complement or damage others or neutralize their possible negative effects), Further, the deep knowledge of folk belief and the conventional remedial technique that herbal therapeutics embrace can be exploited for the discovery and isolation of pharmacologically active phytochemical constituents which may unlock new outlook in modern system through prospective investigations.

Although the view of the commercial exploitation of the natural product from *G. fragrantissima* of India doesnot seems very vivid, there is no reason why the existing resources should be permitted to go waste and why proper investigation should not be taken up. According to Puran Sigh (1917) the yield of the oil from the Indian plant is rather low, but by improved methods of distillation the yield of the oil could probably be increased. Experiments carried out in Germany by Ziegelmann show that by macerating the material some time before distillation a better yield is obtained. This is evident form the following statement:

	Yield of oil % (Sweet birch Bark)	Yield of oil % (<i>Gaultheria</i> leaves)
1.	0.20 (No maceration)	0.70
2.	0.41 (Maceration 12 hours at 40° C.)	1.30

It is likely, therefore that if enhanced methods of extraction are utilized as in Germany, *Gaultheria* oil production in India may be also become a profitable proposal with cultivation

to ensure regular supplies, the oil could be produced in Assam at Rs 1-10 as compared to Rs 4 per lb. for the synthetic methyl-salicylate (Rs 2-8 per lb.) still there is handsome margin of the profit left for the producers. India can at least bring in her own needs of oil of Wintergreen from the resources existing in her own soil (Chopra and Chopra, 1933). As the yield of wintergreen oil from the flora of North-East region is accounted to be superior than the other parts of India, therefore it presents is great potential for commercial cultivation in the North-Eastern hill states of India (Chopra, 1958). The cultivated area can be taken up as tea-gardens and the leaves can be collected for oil extraction.

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