Octochem Pharma and Flavours Pvt. Ltd.

Proposed Project

2021

This manufacturing unit will manufacture –

ACTIVE PHARMACEUTICALS INGREDIENT (API)
L-MENTHOL

These are considered as the quasi-drugs (Used in pharmaceuticals and cosmetics)

INsDEX

Introduction:

Menthol:

Mentha oil is one of the important **agricultural** essential oils and is extracted from the **medicinal botanical herb** of Mentha Arvensis through distillation process by the farmers.

It is widely used in **pharmaceuticals**, foods and flavorings. In addition to being a popular flavoring agent in food and confectionery preparation, natural menthol has cooling and soothing effect on skin and mucous membrane of human body, making it a useful ingredient in pharmaceuticals and cosmetics industry.

We are setting up our manufacturing unit in **Chandausi**, which is the heart of "Mint and Essential Oil Growing belt" in India and is blessed with ideal soil and climatic conditions for the cultivation of these herbs.

India produces 90% of the world's menthol production and of which 85% of share is produced in Uttar Pradesh.

Chandausi, District- Sambhal is considered the main market for quoting mentha sprice in the world.

Key Properties:

Menthol is one of the most widely used **API** (Active Pharmaceutical ingredients).

Menthol has local anesthetic and counterirritant qualities, and it is widely used to relieve minor **throat irritation**. Menthol also acts as a weak kappa opioid receptor agonist.

Menthol's ability to chemically trigger the cold-sensitive TRPM8 receptors in the skin is responsible for the well-known cooling sensation it provokes when inhaled, eaten, or applied to the skin. In this sense, it is similar to capsaicin, the chemical responsible for the spiciness of hot chilis (heat sensors).

Uses and Applications: 1/2

Menthol's analgesic properties are mediated through a selective activation of κ-opioid receptors. Menthol also blocks voltage-sensitive sodium channels, reducing neural activity that may stimulate muscles.

Menthol oil has a very wide spread use in different pharmaceutical preparations and it has analgesic, antibacterial, antifungal, anesthetic and penetration-enhancing effects.

It can demonstrate chemo preventive and immunomodulation actions, which are also well known.

What is menthol used to treat?

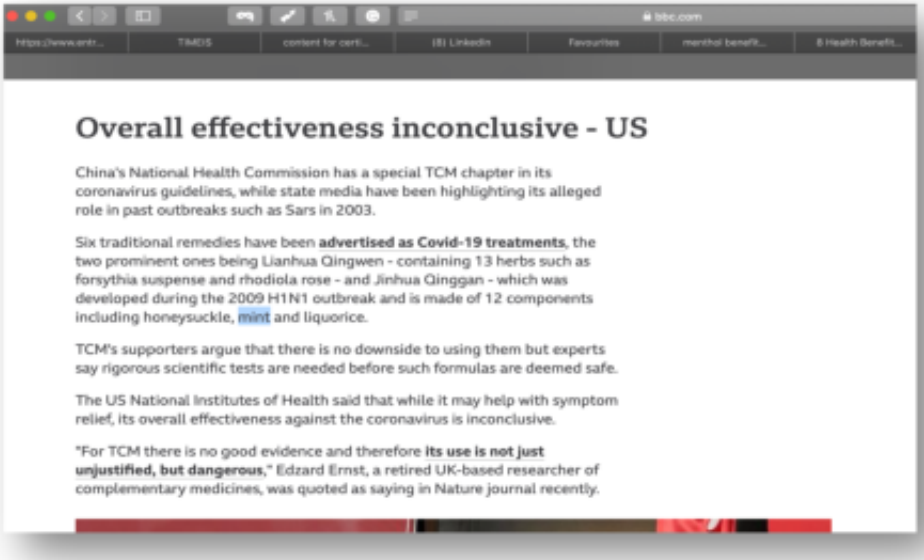
- In nonprescription products for short-term relief of minor sore throat and minor mouth or throat irritation.
  Examples: lip balms and cough medicines.
- As an antipruritic to reduce itching.
- As a topical analgesic, it is used to relieve minor aches and pains, such as muscle cramps, sprains, headaches and similar conditions, alone or combined with chemicals such as camphor, eucalyptus oil or capsaicin.
  Examples: Tiger Balm, or IcyHot patches.
- As a penetration enhancer in transdermal drug delivery.
- In decongestants for chest and sinuses (cream, patch or nose inhaler).
  Examples: Vicks VapoRub, Mentholatum, VapoRem, Mentisan.
- In certain medications used to treat sunburns, as it provides a cooling sensation (then often associated with aloe).
- In aftershave products to relieve razor burn.
- As a smoking tobacco additive in some cigarette brands, for flavor, and to reduce throat and sinus irritation caused by smoking. Menthol also increases nicotine receptor density, increasing the addictive potential of tobacco products.

Uses and Applications: 2/2

- Commonly used in oral hygiene products and bad-breath remedies, such as mouthwash, toothpaste, mouth and tongue sprays, and more generally as a food flavor agent; such as in chewing gum and candy.
- As a pesticide against tracheal mites of honey bees.
- In perfumery, menthol is used to prepare menthyl esters to emphasize floral notes (especially rose).
- In first aid products such as "mineral ice" to produce a cooling effect as a substitute for real ice in the absence of water or electricity (pouch, body patch/sleeve or cream).
- In various patches ranging from fever-reducing patches applied to children's foreheads to "foot patches" to relieve numerous ailments (the latter being much more frequent and elaborate in Asia, especially Japan: some varieties use "functional protrusions", or small bumps to massage one's feet as well as soothing them and cooling them down).
- In some beauty products such as hair conditioners, based on natural ingredients (e.g., St. Ives).
- As antispasmodic and smooth muscle relaxant in upper gastrointestinal endoscopy.
- Some studies show that menthol acts as GABAA receptor positive allosteric modulator and increases Gabaergic transmission in PAG neurons. Menthol also shares anaesthetic properties similar to propofol, by modulating the same sites of the GABAA receptor.

Major Drugs- Menthol as raw material

1) Currently, This is being used as an **API** in a **Chinese medicine** named **Lianhua Qingwen** for treating **COVID-19 patients** in China and Philippines. Study conducted on how Chinese medicine works on the novel coronavirus, China'top epidemiologist Zhong Nanshan and his team wrote that Lianhua Qingwen exhibits anti-viral and anti-inflammatory activity against the novel SARS-CoV-2 virus. The drug "significantly inhibited SARS-CoV-2 replication in Vero E6 cells and markedly reduced pro-inflammatory cytokines (TNF-α, IL-6, CCL-2/MCP-1, and CXCL-10/IP-10) production at the mRNA levels," the paper stated.



Overall effectiveness inconclusive - US

China's National Health Commission has a special TCM chapter in its coronavirus guidelines, while state media have been highlighting its alleged role in past outbreaks such as Sars in 2003.

Six traditional remedies have been **advertised as Covid-19 treatments**, the two prominent ones being Lianhua Qingwen - containing 13 herbs such as forsythia suspense and rhodiola rose - and Jinhua Qinggan - which was developed during the 2009 H1N1 outbreak and is made of 12 components including honeysuckle, mint and liquorice.

TCM's supporters argue that there is no downside to using them but experts say rigorous scientific tests are needed before such formulas are deemed safe.

The US National Institutes of Health said that while it may help with symptom relief, its overall effectiveness against the coronavirus is inconclusive.

"For TCM there is no good evidence and therefore **its use is not just unjustified, but dangerous**," Edzard Ernst, a retired UK-based researcher of complementary medicines, was quoted as saying in Nature journal recently.

Lianhua Qingwen capsules or granules were used in 284 patients with mild and moderate **COVID-19** symptoms at 23 hospitals across nine provinces.

Results show that **treatment using the drug for 14 days leads to a higher rate of recovery for mild and moderate cases, in that it helps reduce the proportion of mild cases developing into severe cases and shorten the duration in which patients go from testing positive to testing negative.** "It's proven effective in mitigating such symptoms as fever, fatigue, coughing, and breathing difficulties in patients," noted Zhang. "The experimental group showed signs of improvement in chest CT images compared with the control group.

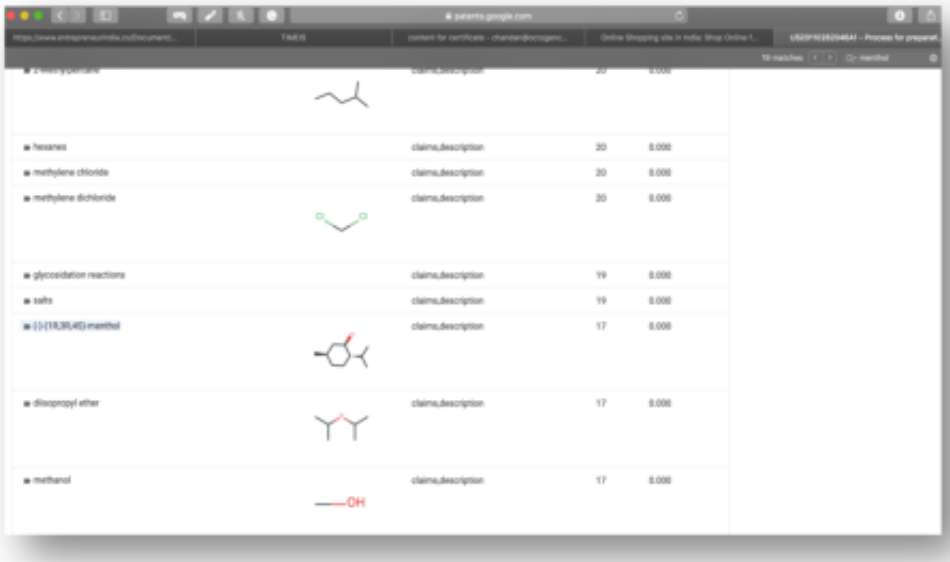
Continued..

"Moreover, Zhang Boli, academician of the Chinese Academy of Engineering, added that Lianhua Qingwen could repair patients' damaged organs in their recovery phase and relieve symptoms in critically ill patients when combined with Western remedies. So far, **Lianhua Qingwen has made inroads into eight countries** and two regions under different categories, including Chinese medicine, Chinese patent drug, botanical drug products, dietary supplement, food additive, etc.

References: -

- Link: https://www.bbc.com/news/world-asia-53094603,
- Link:https://news.cgtn.com/news/2020-06-24/COVID-19-and-TCM-How-Chinese-medicine-makes-scientific-inroads-RAxPK45qco/index.html,
- Link: https://www.globaltimes.cn/content/1187794.shtml,

2) Menthol is used in the manufacturing of the drug Lamivudine, Emtricitabine



that is used to treat **Hepatitis B, HIV** patients.

Brand name: Epivir, Epivir-HBV exists in the markets.

Reference: -

- Link: https://patents.google.com/patent/US20110282046A1/en

Medicine Brands Containing Menthol:

For cough and sore throat:

- Buckley's®
- Cēpacol®
- Fisherman's Friend®
- Sucrets®
- Vicks®

For minor aches and pains:

- Absorbine Jr.®
- Aspercreme®
- BENGAY®
- BOROLEUM®
- Deep Heating®
- Icy Hot®
- Mentholatum®
- Salonpas®
- Satogesic®
- Stopain®

For plaque or bacteria in the mouth:

- Chloraseptic®
- LISTERINE®

For irritated lips and skin:

- Blistex®
- Carmex®
- GOLD BOND®
- Palmer's®

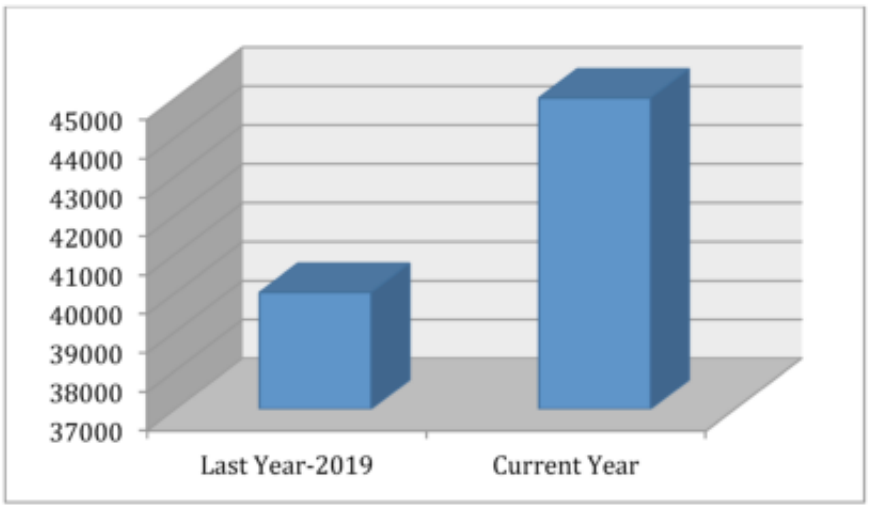
For oral discomfort:

- Orajel™

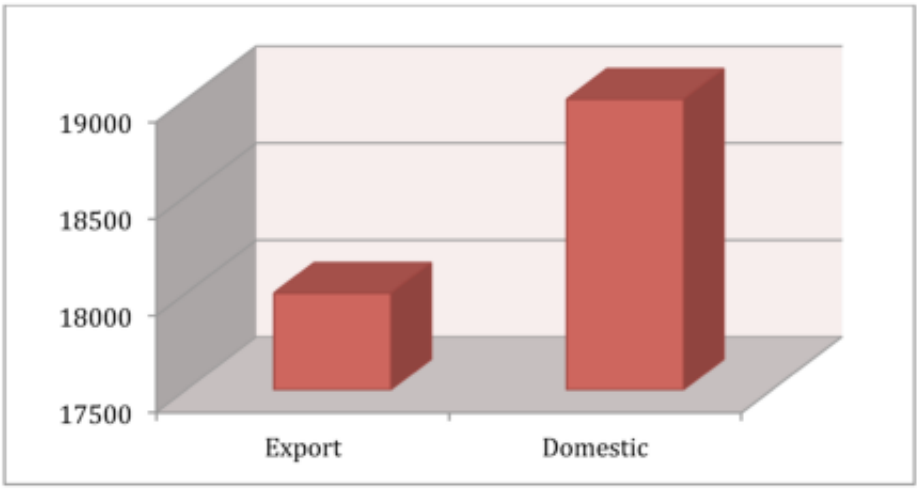
Market Potential:- 1/3

Mentha oil is a colorless or pale yellow, clear liquid. It has a characteristic, pleasant aroma and has a pungent taste, followed by a cool aftertaste.

- India is the world's largest producer of mints and its derivatives. In 2019 total production of mentha arvensis oil is approximately 40,000 Tonnes. In year 2020 total production of mentha arvensis oil is aprox. 45,000 Tonnes.

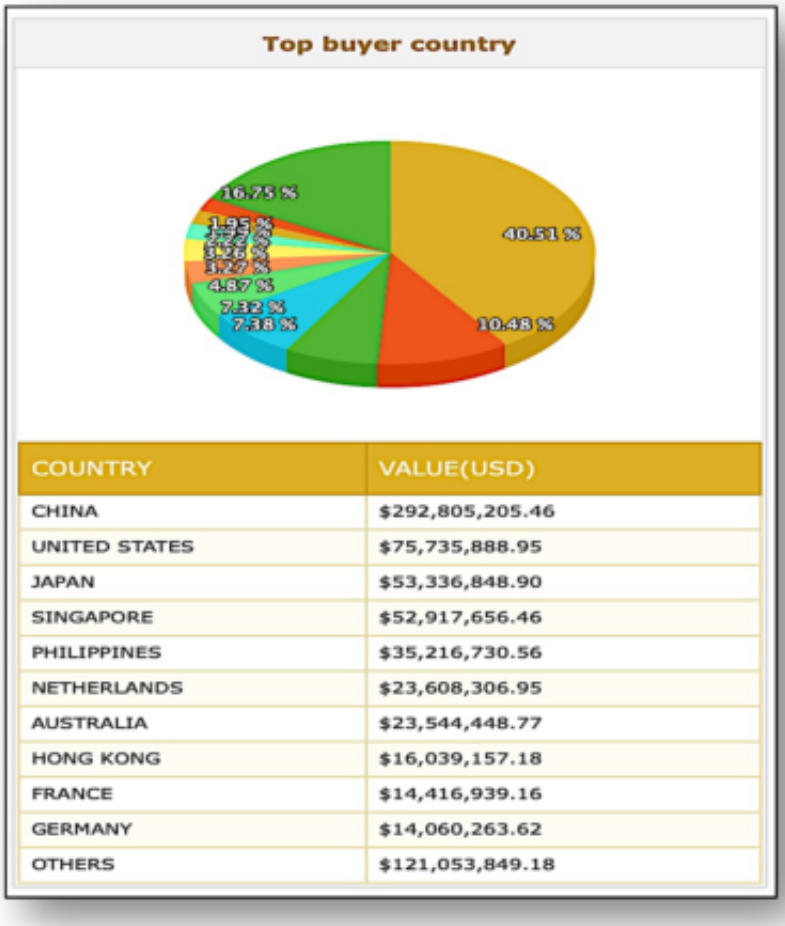


- Also, India is exporting mints and its derivatives throughout the world and last year total export of menthol oil is 18,000 Tonnes and domestic consumption is aprox. 19,000 Tonnes



Market Potential:- 2/3

Export data and list of countries buying menthol irrespective to the amount for the year 2019.



COUNTRY	VALUE(USD)
CHINA	$292,805,205.46
UNITED STATES	$75,735,888.95
JAPAN	$53,336,848.90
SINGAPORE	$52,917,656.46
PHILIPPINES	$35,216,730.56
NETHERLANDS	$23,608,306.95
AUSTRALIA	$23,544,448.77
HONG KONG	$16,039,157.18
FRANCE	$14,416,939.16
GERMANY	$14,060,263.62
OTHERS	$121,053,849.18

Fig- Reference https://www.thedollarbusiness.com/

Market Potential:- 3/3

The consumption pattern of mentha in India has made it an important crop. Mentha in India has reached out to almost all the households and has made a major impact because of the qualities present in it.

The global demand for mentha oil can be attributed to the increased usage of mentha oils owing to the high demand in pharmaceuticals, fragrances in personal care products such as cosmetics, oral care, cigarettes, and flavoring segments. The growing consumer preference for natural and organic personal care products due to increasing awareness regarding the potential side effects of inorganic products is expected to further fuel the growth of this market.

The increasing demand for natural and organic personal care products is a key growth driver for the mentha oil market. The popularity of organic and natural products has increased due to rising awareness of adverse effects of chemical-based products and the health benefits of using organic products.

Organic and natural personal care products are made using natural ingredients, which includes mentha oil because of its characteristics of being a denaturant, flavoring agent, and fragrance ingredient.

India exports different types of mint-oil to countries including China, U.S., Singapore, Netherlands, Germany, UK, France, Brazil and Japan. The major export varieties include Mentha Arvensis oil, Peppermint oil (Mentha pipertia), De-mentholised mint-oil, and Spearmint oils.

Technical Aspects:-

Process of Manufacturing-
The formation of menthol crystals involves:

- Freezing of the mentha oil.
- Removal of the oil crystals from the residual oil by centrifuging.
- Drying of the crystals.

After collection of the mint oil from farmers/brokers, it should be filtered prior to cooling as it usually contains some water and mucilaginous impurities, which prevent ready formation of the menthol crystals. For crystallization some producers use filter and centrifuge the oil.

(I) Crystallization

Purified oil is slowly and gradually cooled progressively to lower temperature whereby menthol crystals form in each operation. The freezing process usually comprises three steps (I) cool at 14 C (II) 10 C and (III) –5OC for hours. Some times, actual process takes 48 hours and cooling up to -20 C temperature. Some manufacturers employ large refrigerators compartment. The large plants are equipped with regular freezing rooms. The gradual and slow cooling permits the formation of large and more regular crystals.

(II) Separation of Menthol Crystals from the Dementholised Oil

This is performed by first decanting the remaining liquid oil from the crystal and centrifuging the crystals in large centrifuges rotating at the speed of about 1200 RPM. Some producers wash the crystals with small amount of water during the centrifuge process.

(III) Drying of the Menthol Crystals

The centrifuged crystals are spread upon the trays in large compartments or Special room dried for approximately 36 hours in a slow current of air at a temperature of about 26 C. This operation must be undertaken very carefully. Now the crystal is ready for packing and marketing.

Quality Control and Standards
Menthol crystals are to be made as per IS 3134.

Lookalike Machinery:- (1/2)

Fig 3- Crystal Freezers

Fig 4- Flakes Freezers

Fig 5- Machines Motor

Fig 6- Crystal Accessories

Fig 7- GLC Testing Machine

Fig 8- Centrifugal machines

Lookalike Machinery:- (2/2)

Fig 9- Distillation Tank

Fig 10- Fractional Columns

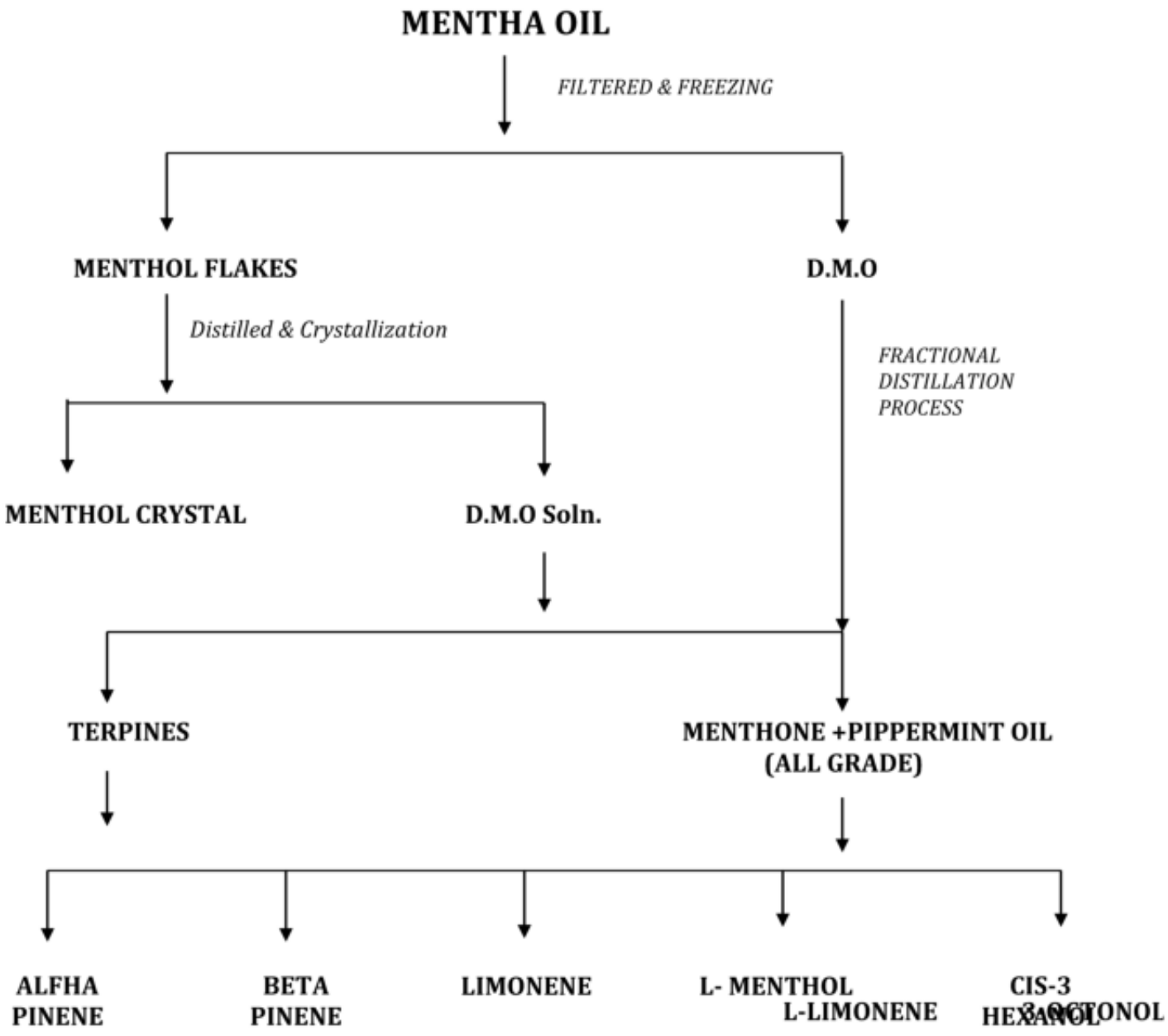
Fig 11- SS Tank

Fig 12- SS Reactor

Fig 13- Forklift

Fig 14- Generator set

Flow Chart: -



(Fig 1- Process of Mentha oil)

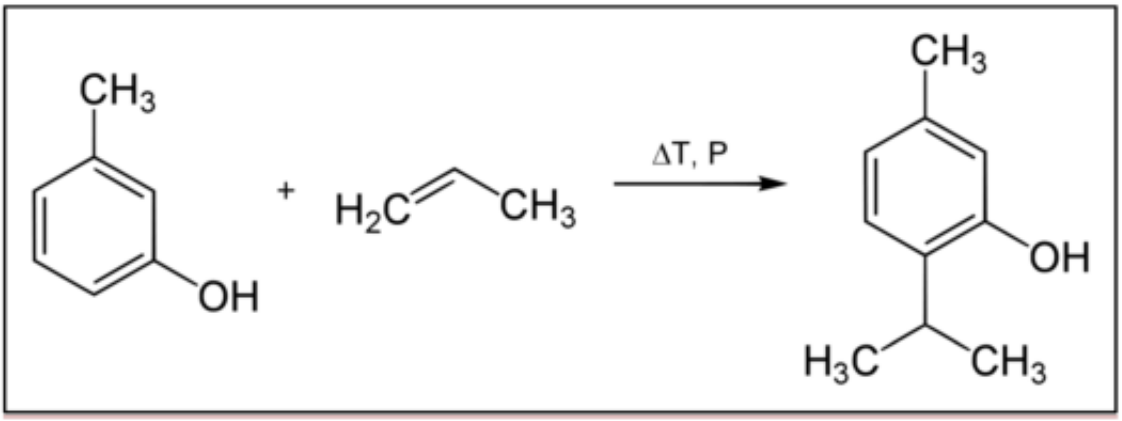
Thymol

Thymol (also known as **2-isopropyl-5-methylphenol**, IPMP) is a natural monoterpenoid phenol derivative of cymene, $C_{10}H_{14}O$, isomeric with carvacrol, found in oil of thyme, and extracted from *Thymus vulgaris* (common thyme), Ajwain[3] and various other kinds of plants as a white crystalline substance of a pleasant aromatic odor and strong antiseptic properties. It can be synthetically manufactured from meta-cresol also.

Uses:

Thymol has been used in alcohol solutions and in dusting powders for the treatment of tinea or ringworm infections, and was used in the United States to treat hookworm infections. People of the Middle East continue to use za'atar, a delicacy made with large amounts of thyme, to reduce and eliminate internal parasites. It is also used as a preservative in halothane, an anaesthetic, and as an antiseptic in mouthwash. When used to reduce plaque and gingivitis, thymol has been found to be more effective when used in combination with chlorhexidine than when used purely by itself. Thymol is also the active antiseptic ingredient in some toothpastes, such as Johnson & Johnson's Euthymol. Thymol has been used to successfully control varroa mites and prevent fermentation and the growth of mold in bee colonies, methods developed by beekeeper R. O. B. Manley. Thymol is also used as a rapidly degrading, non-persisting pesticide. Thymol can also be used as a medical disinfectant and general purpose disinfectant. Thymol is also an active ingredient in Listerine mouthwashes.

Synthesis of Thymol:



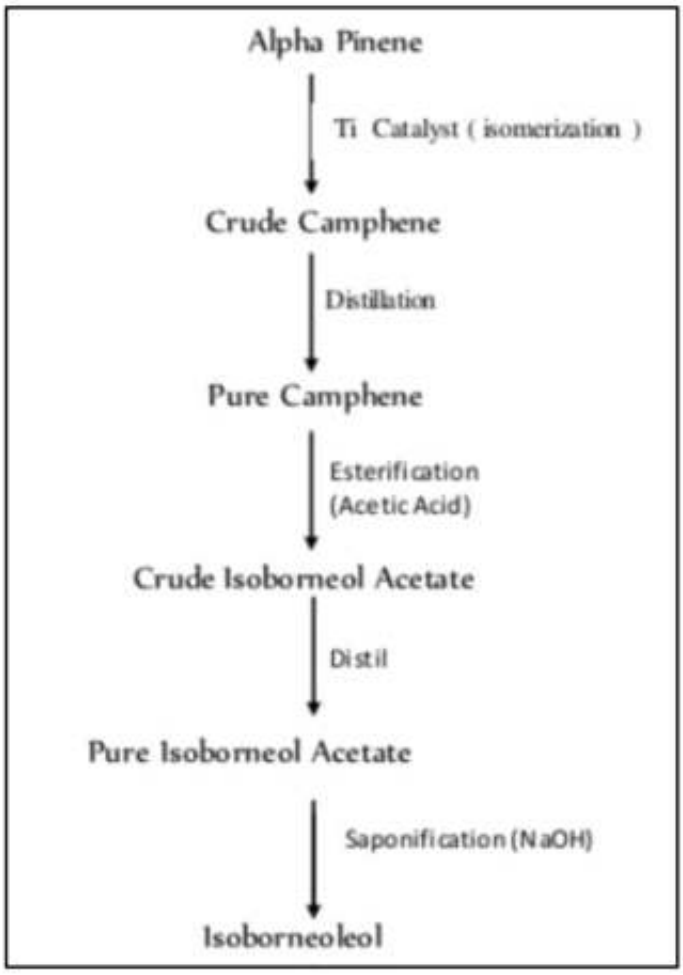
Isoborneol

Isoborneol is a bicyclic organic compound and a terpene derivative. It is found in many essential oils and is a natural insect repellent. The structural isomer fenchol is also a widely used compound derived from certain essential oils.

Uses:

It is used as an aroma chemical in perfumery and has a balsamic odour type with pine, woody and camphoraceous facets. It is used in traditional Chinese medicine. An early description is found in the Bencao Gangmu. Further, It is used to manufacture camphor which is a major active ingredient in **Vicks VapoRub** and has been used as a flavour by many flavours and fragrances industries.

Synthesis of Isoborneol:



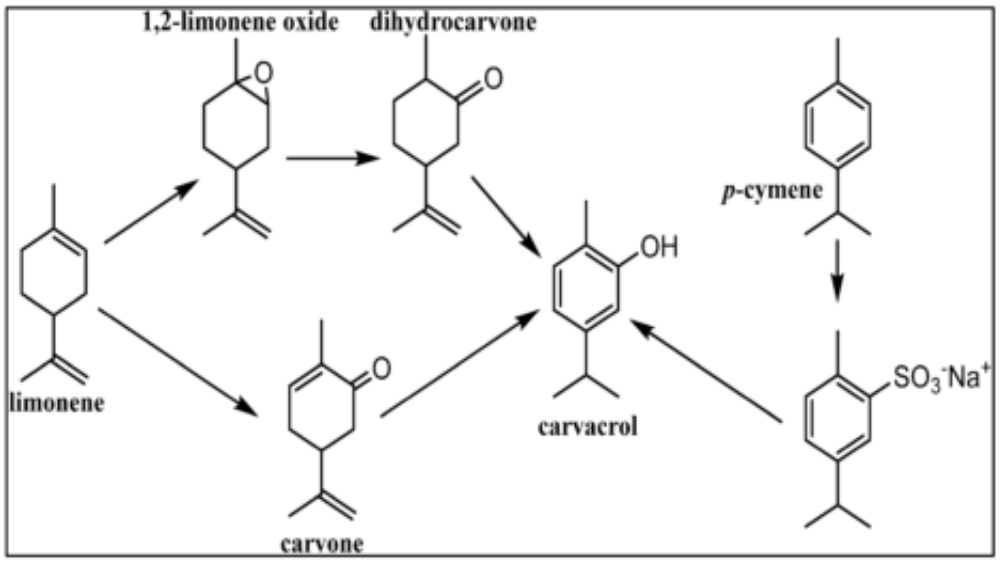
Carvacrol

Carvacrol, or cymophenol, $C_6H_3(CH_3)(OH)C_3H_7$, is a monoterpenoid phenol. It has a characteristic pungent, warm odor of oregano. Carvacrol is present in the essential oil of Origanum vulgare (oregano), oil of thyme, oil obtained from pepperwort, and wild bergamot. The essential oil of thyme subspecies contains between 5% and 75% of carvacrol, while Satureja (savory) subspecies have a content between 1% and 45%.[3] Origanum majorana (marjoram) and Dittany of Crete are rich in carvacrol, 50% and 60–80% respectively.

Uses:

Cavacrol is mainly used in food, spice and pharmaceutical industries. Carvacrol is responsible for the biological activities of oregano. Many diverse activities of carvacrol such as antimicrobial, antitumor, antimutagenic, antigenotoxic, analgesic, antispasmodic, antiinflammatory, angiogenic, antiparasitic, antiplatelet, AChe inhibitory, anti elastase, insecticidal, antihepatotoxic and hepatoprotective activities and uses such as feed additive, in honeybee breeding and in gastrointestinal ailments have been shown.

Synthesis of Carvacrol:



Annexure

References:-

1. Link: https://www.bbc.com/news/world-asia-53094603,
2. Link:https://news.cgtn.com/news/2020-06-24/COVID-19-and-TCM-How-Chinese-medicine-makes-scientific-inroads-RAxPK45qco/index.html,
3. Link: https://www.globaltimes.cn/content/1187794.shtml,
4. Link: L-Menthol In Lamivudine and Emtricitabine
5. Link: IsoBorneol in Chinese medicine