Comprehensive review of the applications of Thymol and the methods used for synthesizing it using Meta Cresol

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Abstract

Thymol, an isomer of carvacrol and a phenol monoterpene derivative of cymene, is a principal constituent of thyme essential oils, renowned for their therapeutic properties. Thymol is extensively utilized in dental hygiene products, food, fragrances, and cosmetics due to its functional attributes. It is also employed in aromatherapy, traditional medicine, and the food industry for flavoring and preservation, as well as in mosquito repellents for its natural repelling effects. The global thymol market, valued at USD 48.6 million in 2022, is projected to reach USD 56.2 million by 2028, exhibiting a compound annual growth rate (CAGR) of 2.4%. Most industrial processes synthesize thymol from meta-cresol using an isopropylating agent and a catalyst, typically following a Friedel-Crafts alkylation pathway. Researchers have conducted extensive experiments to identify suitable catalysts for this process, utilizing various zeolites, acidic catalysts, nitrating mixtures, basic catalysts, and mixed-metal oxide catalysts. This review article addresses the chemical processes for synthesizing thymol from meta-cresol and discusses its applications.

Keywords: *Thymol; 2-isopropyl-5-methylphenol; Friedel-Craft; m-cresol; meta cresol*

1.0 Introduction:

Thymol has traditionally been derived from plant sources including eucalyptus, mint, and thyme; however, more recently, synthetic production of thymol has commenced. Thymol is a phenolic monoterpene predominantly found in thyme species. It is a recognized antioxidant and one of the most frequently utilized compounds in the beauty and health industries. Various essential oils, often extracted from plant sources such as thyme and mint, are synthesized using thymol (M. Mesbah et.al., 2023)

Thymol is also known by several alternative nomenclatures: IPMP, 2-Isopropyl-5-methylphenol, 5-Methyl-2-isopropylphenol, 5-Methyl-2-(1-methylethyl) phenol, and Thyme camphor. The chemical structure of thymol is shown in Fig 1. (Jafar et al., 2024). It is employed in mouthwash as an anesthetic, antibacterial agent, and halothane preservative. When administered in combination with chlorhexidine, it has reportedly demonstrated enhanced efficacy in reducing plaque and gingivitis compared to its individual use. Additionally, dental creams such as Johnson & Johnson's Euthymol utilize thymol as the primary antibacterial ingredient. It has been effectively employed to control varroa mites, inhibit fermentation, and prevent mold growth in bee colonies. It is also utilized as a non-repellent, rapidly degrading pesticide. Thymol can be employed in the formulation of both general-purpose and medical disinfectants. The projected annual global demand for thymol in 2003 was 4,500 metric tons. Thymol production costs at that time were approximately $ 3.4/kg, with a $ 9/kg sales price. Its substantial market value was evidenced by the relatively wide margin between production costs and the selling price (Merwe J.et.al 2014).

Thymol serves as a precursor in the synthesis of menthol, which is the most widely sold aroma chemical globally in terms of volume. Menthol is extensively utilized in respiratory treatments, cosmetics, and pharmaceutical formulations for pain relief (Rozza, A.L et.al 2021). Previous research has demonstrated that menthol possesses antinociceptive, antibacterial, and antiulcerogenic properties. Table 1. shows the physical and chemical properties of thymol. According to most projections, the demand for synthetically produced menthol is expected to increase, a prediction supported by the double-digit annual growth in demand observed in recent years. Thymol undergoes additional reactions with menthol, including hydrogenation to menthone, as well as the formation of chlorothymol and thymol iodide (Helander.et.al 1998).

1.1 Pharmacological uses of Thymol:

Thymol has been utilized in traditional medicine for an extended period and has been demonstrated to possess a diverse range of pharmacological properties, including antioxidant, free radical scavenging, anti-inflammatory, analgesic, antispasmodic, antibacterial, antifungal, antiseptic, and anticancer activities. It represents one of the potential natural options for pharmaceutical development, having exhibited notable therapeutic potential, pharmacological properties, molecular mechanisms, and pharmacokinetic features. The capacity of thymol to effectively scavenge superoxide anion, hydroxyl, and DPPH radicals and reduce them in a concentration-dependent manner has been established (Nagoor Meeran.et.al.2017). Thymol has demonstrated its potential as a chemopreventive or anticancer agent in several types of cancers by exhibiting anticancer characteristics in numerous cell lines that model human cancer (Mohamed Fizur.et.al 2012)

1.2 Therapeutic uses of Thymol:

One of the key constituents of thyme essential oil is thymol. The thyme plant, its essential oils, and their primary volatile components, carvacrol and thymol, have been extensively utilized for medicinal purposes. The chemical constituents of thyme essential oil (EO) encompass monoterpenes, monoterpene alcohols, phenol derivatives, ketones, aldehydes, ethers, and esters (Kowalczyk A. et.al 2020). Historically, thyme herb and its volatile oil have been employed to treat upper respiratory tract infections, bronchitis symptoms, parasitic infections, pruritus induced by dermatitis, bruises, and sprains. In contemporary practice, it is predominantly utilized as a disinfectant in dentistry and as an expectorant for cough associated with the common cold (Thosar N. et.al 2013). Research conducted by Piombino et al. has demonstrated that thymol and its derivatives can be encapsulated in microcapsules composed of natural polymers. Furthermore, thymol exhibits promising anti-tumor activity through various mechanisms, including those associated with the induction of apoptosis and the inhibition of proliferation (Piombino, C. et.al.2020)

1.3 Antibacterial applications of Thymol:

Herbal extracts have garnered significant attention in recent years for various medical applications, particularly in wound treatment. Thymol, a naturally occurring phenolic

monoterpene found in essential oils primarily extracted from Thymus, Origanum, and Coridithymus, is one of the naturally occurring substances with therapeutic properties in this domain (R. Najafloo.et.al 2020). When Lee et al. investigated the efficacy of thymol against biofilm formation, they observed that thymol treatment resulted in significant bacterial mortality and inhibition of biofilm growth (Lee JH.et.al 2017). Currently, both marketing efforts and research initiatives are focusing considerable attention on the development of wound management products. Several recent studies have examined the potential of Thymol in wound healing, highlighting its significant promise in this field. The findings indicate that thymol exhibits combinatorial mechanisms of action during the healing process (Müller RH.et.al 2002).

1.4 Food preservation applications of Thymol:

Thymol exhibits the capacity to disrupt the lipid bilayer of cell membranes, potentially enhancing membrane permeability. Consequently, thymol has demonstrated antibacterial efficacy against a diverse range of microorganisms, including bacteria, fungi, and yeasts. As a result, the application of thymol as a treatment is considered efficacious for both food preservation and the prevention of postharvest deterioration in fresh produce (Yibo Zhang.et.al 2019).

1.5 Thymol applications in production of animals and fish:

The herbal food ingredient thymol is utilized to enhance immunological function, feed utilization, performance metrics, and resistance against infectious diseases. Supplementing livestock, fish, and poultry diets with medicinal plants containing potent compounds and natural antioxidants in thymol has demonstrated the significant potential of thymol to improve productive and reproductive performances, nutrient bioavailability, immunity, and overall health of livestock, as well as mitigate issues associated with various animal diseases, adverse effects of chemical drugs, synthetic materials, and cancer (Mohamed Ezzat Abd El-Hack,et.al 2016).

2.0 Synthetic Production Methods:

Thymol was first synthesized in 1882. The cuminal utilized in this conventional synthesis of thymol is converted into nitro-cuminal, with the nitro group occupying a position adjacent to the aldehyde group. Upon treatment with phosphorus

pentachloride, this substance was transformed into nitro-cymyline chloride, which was subsequently reduced with zinc and hydrochloric acid to produce 3-aminocymene. This compound was then diazotized and hydrolyzed to yield thymol (Phillips,et.al 1920). Both liquid phase and vapor phase processes can be employed for the synthesis of thymol (Malkar, et.al 2017). The reaction predominantly follows the Friedel-Crafts Alkylation pathway. The primary limitation of this process is the requirement for high pressure and temperature. Heterogeneous catalysis is generally preferred due to its environmental advantages.

2.1 Vapor Phase Synthesis of Thymol:

H. Grabowska et al. investigated the alkylation of m-cresol with isopropanol using zinc aluminate spinel ($ZnAl_2O_4$) catalysts with different loadings and properties to produce Thymol. Reactions were conducted continuously at atmospheric pressure and temperatures between 470 and 590 K. Results showed thymol as the main product at higher temperatures, while both O and C alkylated products appeared at lower temperatures. Two hydrothermal methods were used for catalyst preparation, differing in synthesis mixture and reagents. The catalyst was placed on quartz wool in a vertical quartz reactor with a 6 mm inner diameter. The reactant mixture had molar ratios of 5:1:1 (isopropanol: m-cresol: water). The first hydrothermal method produced a catalyst with superior efficiency, yielding approximately 69.1% thymol and achieving about 88% thymol selectivity. This study suggests that gas-phase alkylation with this catalyst is an effective method for synthesizing thymol (H. Grabowska, et.al 2001).
K. Shanmugapriya et al. developed a method to produce thymol via vapor phase reaction of m-cresol with isopropyl acetate. Fig 2. shows the reaction of m-cresol with isopropyl acetate to form thymol. Silica-alumina mesoporous molecular sieves with varying Al to Si ratios were hydrothermally synthesized. The isopropylation was conducted in a fixed-bed, vertical-flow reactor with a 2 cm internal diameter at atmospheric pressure. They studied the effects of reaction temperature, feed ratio, and time-on-stream. Conversion of m-cresol exceeded 60% at all temperatures, with a consistent m-cresol to isopropyl acetate feed ratio of 1:3. The highest m-cresol conversion (80.9%) and thymol selectivity (83.7%) were achieved at 300°C. Other products included Isothymol, 2-isopropyl-5-methylphenyl acetate, and isopropyl-3-methylphenyl ether. The study concluded that higher temperatures increase

conversion and selectivity to thymol, and that the catalysts' hydrophilic and hydrophobic properties, along with their acid sites, significantly influence the reaction (K. Shanmugapriya, et.al 2004).

M. Nitta et al. alkylated meta cresol with propylene over γ-alumina catalyst at atmospheric pressure in a flow system, producing an ortho-rich thymol mixture. The study found that catalytic activity varied with temperature and used acids and bases to examine the alumina catalyst's active sites. The catalyst's activity was assessed by m-cresol conversion, typically measured two hours after reaction initiation. At temperatures above 250 °C, thymol selectivity remained constant above 90%, and even at 250 °C, the catalyst showed high selectivity for thymol synthesis (Nitta, et.al 1974). Selvaraj and S. Kawi studied the isopropylation of m-cresol with isopropyl alcohol in a vapor phase using mesoporous Zn-Al-MCM-41 catalysts. They examined the effects of temperature, reactant mole ratio, and recyclability on the reaction. The reaction, conducted in a fixed-bed vertical-flow reactor at atmospheric pressure, achieved a high m-cresol conversion of approximately 90.7% at 350 °C with a 75% catalytic loading, yielding over 90% thymol with 100% selectivity. In comparison, mesoporous Al-MCM-41 with 21% loading showed a 76.3% conversion and 88.4% thymol selectivity at 350 °C, resulting in a 67.4% thymol yield. Thus, mesoporous Zn-Al MCM-41(75) demonstrated superior performance in m-cresol conversion and thymol selectivity (M. Selvaraj.et.al 2008).

R. S. Malkar et al. utilized meta cresol for the selective synthesis of thymol, employing novel zirconia-titanium mixed sulfated oxides as a catalyst. The hydrothermal method was employed to produce various unique zirconia-titanium mixed sulfated oxides, which were subsequently evaluated for their efficacy in isopropylating m-cresol to generate thymol. In a continuous fixed bed vapor phase reactor, a sulfated catalyst with a 2:1 mole ratio of zirconia to titania demonstrated the highest conversion and selectivity for thymol. A significant advantage of this catalyst is its ability to maintain stability and functionality for up to 20 hours. During the time on stream testing, no decrease in m-cresol conversion or thymol selectivity was observed for up to 10 hours, indicating the catalyst's reliability and potential for extended use. With an m-cresol to isopropanol feed mole ratio of 1 to 3, the maximum conversion of meta cresol was observed at 220 °C, reaching 73.12%. In this experiment, the yield and selectivity achieved were 75.31% and 55.07%, respectively. Thus, a key advantage of this process is that the reaction occurs in the vapor phase at a relatively low temperature

of 220 °C, which is lower than the majority of other reported methods (Amandi, et.al 2005). S. Velu and S. Sivasanker investigated the alkylation of m-cresol with methanol and 2-propanol over calcined magnesium aluminum hydrotalcites. Magnesium-aluminum hydrotalcites with varying magnesium to aluminum atomic ratios of 2, 3, and 4 were synthesized using the coprecipitation method. The catalyst samples were calcined at 720K and subsequently subjected to vapor phase alkylation with methanol to produce m-cresol in the temperature range of 520 - 720K at atmospheric pressure. The reaction yielded 3-methyl anisole, 2,5- and 2,3-dimethylphenols, and 2,3,6-trimethylphenol, along with various other byproducts, including O- and C-alkylated compounds. It was determined that the m-cresol/methanol feed ratio, temperature, and contact periods influenced the selectivity of these products. At 673 K and an atomic ratio of 3.0, the alkylation of m-cresol with 2-propanol resulted in approximately 80% selectivity towards thymol with only about 40% m-cresol conversion. Consequently, it can be inferred that a selective synthesis of thymol may be achieved using an alkylation process employing a magnesium aluminum hydrotalcites catalyst (Velu, et.al 1998). Zeolites constitute a well-established family of nanoporous materials that play crucial roles in various chemical reactions as heterogeneous catalysts with shape- and size-selective properties. In the chemical industry, hydroxylation, alkylation, oxidation, and epoxidation are examples of zeolite-catalyzed processes currently in use (Yilmaz, et.al 2009). The shape-selective qualities of zeolites are widely recognized and enable the overcoming of thermodynamic constraints. The alkylation of phenol and meta cresol over zeolites was investigated by C. T. O'Connor et al. Results of this research study into the alkylation of phenol and m-cresol using propene and methanol, respectively, are presented in this paper. The selected zeolite catalysts were H-ZSM-5 and H-MCM-22.

The selectivity over H-ZSM-5 for thymol in the instance of m-cresol propylation exceeded 90% at conversions of approximately 50% and 80% at conversions of approximately 85%. The results of this study indicate that reaction temperature is the sole parameter directly affecting selectivity. Reaction temperature has a significant impact on selectivity, which decreases with increasing temperature at a given conversion (O’Connor, et.al 2003).

At a constant temperature of 250 ºC and atmospheric pressure, M. Nitta et al. examined the alkylation of meta cresol using propylene as the propylating agent over supported metal sulphate catalysts. The aqueous sulphate solution was added to the

carrier for a day to impregnate it, and subsequently dried at 120 ºC in the air to create the sulphate catalysts. All reactions were conducted at atmospheric pressure in a continuous flow system reactor. The liquid products of this alkylation included Isothymol, thymol, and its three other isomers as well as an insignificant quantity of unidentified compound (Nitta, et.al 1974). The results indicate that the yield of thymol was approximately 70%, which is considered satisfactory given the low reaction temperature (of 220 oC), and further research can be conducted to enhance thymol selectivity by increasing the temperature (Nitta, et.al 1974). The widely used industrial process for producing thymol utilizes solvents such as nitrobenzene and CS2 in excess of homogenous acid catalysts like AlCl3, H2SO4, and HF and presents inherent challenges such as equipment corrosion, pollution, and low selectivity to the desired product (Afreen, et.al 2017). The kinetics and reaction mechanisms of the gas phase alkylation of biomass-derived meta cresol using isopropanol as an isopropylating agent over zinc modified zeolite catalysts were investigated by G. Afreen and colleagues.

In a continuous flow fixed-bed reactor, the kinetic tests of the gas phase alkylation of m-cresol with iso-propanol were conducted. At 200 °C, the conversion of m-cresol reached 50%; at 250 °C, it increased to 93%. The decrease in conversion (69% at 300 °C) caused by coke production was induced by further temperature increase. At 250 °C, the highest conversion of m-cresol (93%) was achieved. However, according to the results, the conversion decreased over time for every temperature, demonstrating the catalyst's deactivation characteristic (G. Afreen, et.al 2020).

Mesoporous Al-MCM-41 Molecular Sieves were employed to investigate the isopropylation of m-Cresol by V. Umamaheswari et al. Three distinct silica to alumina ratios—59, 103, and 202—were examined, with temperatures ranging from 250 °C to 400 °C. Thymol was identified as the primary product of this reaction, accompanied by secondary products including isopropyl-3-methylphenyl ether (IMPE) and isopropyl-(2-isopropyl-5-methylphenyl) ether (IIMPE). The molar ratio of meta cresol to isopropanol was also determined to be a significant factor. The maximum m-cresol conversion, observed at a ratio of 1:4 with thymol selectivity of 75.3%, was 55%. Three catalysts, Al-MCM-41 (59), Al-MCM-41 (103) and Al-MCM-41 (202), were evaluated, with Al-MCM-41 (59) demonstrating the highest efficacy. The experimental results are presented in Table 2, including additional products and byproducts, as well as the conversion and selectivity of thymol with respect to temperature variation. As

evidenced in Table 2, at 300 °C, 55% of the m-cresol is converted, with a thymol selectivity of approximately 75% (V. Umamaheswari, et.al 2002).

2.2 Liquid Phase synthesis of Thymol:

G. D. Yadav et al. investigated the activity and selectivity of novel mesoporous solid super acidic catalysts in the synthesis of thymol by isopropylation of meta cresol, utilizing 2-propanol as a propylating agent. The three newly developed catalysts, designated as UDCaT-4, UDCaT-5, and UDCaT-6, were modified forms of zirconia that demonstrated superior catalytic activity, stability, and reusability compared to traditional sulfated zirconia when used in the presence of water. The three catalysts were synthesized using distinct methodologies. UDCaT-4 was developed using aluminum nitrate and zirconium oxychloride, while UDCaT-5 was prepared by adding ammonia solution to zirconium oxychloride (ZrOCl2.8H2O) solution. UDCaT-6 was synthesized by employing the incipient wetness approach, wherein zirconium oxychloride was added to precalcined hexagonal mesoporous silica.

A four-bladed turbine impeller was utilized for agitating the contents of the stainless-steel Parr autoclave used for all the trials. The autoclave was loaded with known quantities of reactants and catalyst, the temperature was increased to the desired level, and agitation was initiated. G. D. Yadav et al. withdrew the initial samples for the purpose of analysis, in contrast to other publications where they were not (Yadav, et.al 2005).

Under autogenous pressure, the temperature was maintained at 180 °C, and the agitation was operated at 1000 rpm. One of the primary advantages of the process was that all reactions were conducted without the necessity of a solvent or co-solvent. The results indicated that UDCaT-5 exhibited superior efficacy in converting meta cresol compared to other catalysts, with UDCaT-5 demonstrating higher activity than UDCaT-4 and UDCaT-6. Moreover, when evaluating all three catalysts, it was observed that an increase in catalyst loading corresponded to an increase in m-cresol conversion. Furthermore, an increase in the mole ratio of m-cresol to IPA resulted in enhanced conversion of isopropyl alcohol, accompanied by increased selectivity for the C-alkylated product. The reusability of UDCaT-5 was verified through two separate experiments (Teodorescu F, et.al 2017). Following each experimental run, the catalyst was filtered, washed with isopropyl alcohol, dried at 130 °C for two hours, and weighed

prior to utilization in the subsequent batch. Although the catalyst underwent washing after filtration to remove adsorbed reactants and products, the possibility remained that a small quantity of adsorbed reactant and product species may have been retained, potentially obstructing the catalyst's active sites. This study concluded that optimal thymol yield could be achieved by conducting the reaction at 180 °C with a catalyst loading of 0.05 g cm-3 and a mole ratio of 5:1 between m-cresol and isopropyl alcohol. [31].

F. Teodorescu and colleagues investigated the selective alkylation of m-cresol with isopropyl alcohol using both microwave irradiation and conventional heating under solvent-free conditions over a strong acid resin catalyst. Two heterogeneous catalysts, CT-151 DR Resin and Nation NR-50, were employed in the process. The impact of reactant mole ratio on conversion and selectivity was examined by varying the mole ratio of m-cresol to IPA from 1:1 to 3:1 and 5:1, while maintaining other conditions constant. The results obtained under microwave irradiation further confirmed that the 5:1 molar ratio was optimal for achieving the highest selectivity in C-alkylated products, yielding up to 92.8% of mono-alkylated products compared to 7.2% di-alkylated products (Rozza, et. Al 2021). Under conventional heating, an increase in selectivity for the C-alkylated products was observed as the mole ratio of m-cresol to IPA was increased up to 5:1. It was determined that O-alkylation is more favorable at lower temperatures than C-alkylation, which predominates at 423 K. The selectivity of thymol as well as other reaction byproducts is influenced by reaction time under conventional heating, as shown in Table 3 below.

The minimum time required for the synthesis of alkylated products in the case of a microwave-assisted process was observed to be a few minutes, with approximately 87% of C-alkylated products already formed at the 10-minute point. Selectivity towards C-alkylated products increased with subsequent increases in reaction time, while selectivity towards O-alkylated compounds decreased concurrently.

The effect of reaction time on the selectivity of thymol under microwave irradiation is shown in Table 4. In conclusion, due to the short reaction time, it can be inferred that microwave-assisted synthesis of thymol using meta cresol is more advantageous compared to the traditional heating method (Teodorescu F, et.al 2017).

In the liquid phase isopropylation of meta cresol with propylene, T. Yamanaka investigated the catalytic characteristics of metal sulphates supported on gamma-

alumina catalyst. The liquid phase isopropylation of m-cresol utilized catalysts composed of γ-alumina that had been treated with various metal sulphates and subsequently calcined. Under propylene pressure ranging from 15 kg/cm2 to 80 kg/cm2, the reaction temperature varied from 250 oC to 300 ºC. (Yamanaka, et.al 1976). The isopropylation reaction was conducted in a 100 ml autoclave reactor without the use of a solvent. Upon completion of the reaction, the autoclave was cooled to room temperature using a cold-water bath system, and the unreacted components were subsequently filtered. Additionally, the reaction mixture was dissolved in ether. Thymol was the primary product of the reaction, accompanied by several additional byproducts including 4-isopropyl-5-methylphenol, 2,6-diisopropyl-5-methylphenol, 2,4-diisopropyl-5-methylphenol, and a negligible quantity of isopropyl ethers. Ultimately, FeSO4/Al2O3 was identified as the catalyst that exhibited the highest selectivity for Thymol, demonstrating a very high activity that remained unaffected by calcination temperatures (Yamanaka, et.al 1976).

2.3 Other Methods for Thymol synthesis

H. Jordan et al.'s invention describes condensing alkyl phenols and ketones at low temperatures using a condensing agent like hydrochloric acid to synthesize thymol and its isomers. The method suggests treating the condensation products with hydrogen at elevated temperatures using hydrogenation catalysts to directly synthesize thymol and its isomers without thermal decomposition. The condensation product of m-cresol and acetone is hydrogenated under pressure, if required, until 4 hydrogen atoms have combined, in the presence of 0.1% aluminum-3-methyl-6-isopropylene phenolate and 1% nickel catalyst. Thymol is isolated from the reaction product using conventional methods, with an optimal temperature range of 180 °C to 190 °C (Hans, et.al 1930).

S. Siegfried et al.'s invention outlines synthesizing thymol by reacting propylene with meta cresol. The primary product of this reaction is thymol when conducted at temperatures between 300 °C and 400 °C. Propylene and m-cresol are combined at a pressure above thymol's vapor pressure. Fractional distillation separates thymol from by-products after the reaction. K. Schollkopf et al. demonstrated that heating propylene-yielding compounds with m-cresol, possibly under pressure, produces propyl or isopropyl derivatives of m-cresol. Typically, 1 mol of propylene-yielding

material is used per mole of meta cresol. An excess of m-cresol promotes multiple propylated addition products, while an excess of propylene-yielding chemical inhibits them. (Siegfried, et.al 1935). They propose that metal oxides like zinc oxide or magnesium oxide can retain hydrogen halide acids formed when propyl or isopropyl halides are used in the reaction mixture. Thymol can be the primary product with appropriate reaction parameters (Karl, et.al 1933).

M. S. Carpenter et al. developed a method for synthesizing alkylated phenols, particularly thymol, via the Friedel-Crafts reaction. This method allows for the cost-effective production of pure thymol using a mixture of 80% meta-cresol and 20% para-cresol. Favorable results are achieved if the inert liquid is used in minimal quantities when reacting m-cresol with specific isopropylating agents at temperatures between -20 °C and 0 °C, in the presence of certain inert liquids and a Friedel-Crafts catalyst, yielding up to 84.6% thymol (Scott, et.al 1942). W. E. Huggett and G. F. Duffin's invention involves gradually adding concentrated sulfuric acid while maintaining a temperature between 50 and 55 °C, then heating the mixture to complete sulfonation at 120 °C. After cooling to around 80 °C, absolute isopropanol is added and reheated to 120 °C. Steam distillation at 140 °C desulfonated the sulfonic acids, producing an oily distillate containing meta-cresol, thymol, and other propylated meta-cresols. The distillation leaves a non-volatile tarry substance. Upon drying and distilling the oily distillate, the unreacted m-cresol and a mixture containing thymol are obtained. The mixture is cooled to about 15 °C to crystallize thymol, with further cooling to -20 °C depositing thymol crystals (Edward, et.al 1949). R. R. Bottoms' innovation outlines a method for synthesizing thymol from its isomers through sulfonation, isomerization, and desulfonation of the resulting sulfonic acids. This process converts undesired thymol isomers into thymol. The invention asserts that no thymol can be extracted from the phenolic mixture if the thymol isomers are sulfonated, heated, and desulfonated.

One mole of water is released per mole of m-cresol during isopropylation with isopropyl alcohol. Using m-cresol and isopropyl alcohol in the sulfonation mixture generates two moles of water per mole of phenolic substance. The methodology for thymol synthesis and separation in this study closely follows that developed by W. E. Huggett and G. F. Duffin (Edward, et.al 1949), (Bottoms, et.al 1958). W. Biedermann et al. continuously synthesized thymol by reacting m-cresol with propylene using aluminum oxide catalysts and a nitrogen base. Most thymol synthesis methods from m-cresol face limitations like short-lived catalysts, the need for catalyst regeneration,

and prolonged reaction times preventing continuous operation. These issues can be resolved by using an aluminum oxide catalyst with a nitrogen base. The invention produces crude thymol of consistent quality, from which thymol with over 99.5% purity can be easily isolated, even with trace water in m-cresol, regardless of the starting material. The method employs ammonia and its basic or salt-forming substitutes as nitrogen bases. It involves increasing the basic nitrogen content of meta cresol, combining it with propylene, introducing the mixture to the reactor, adding the catalyst from the bottom, and extracting crude thymol from the top. This process, at 365 °C and 50 bars, yields 10 tons of crude thymol daily (Biedermann. et.al 1978).

Wimmer et al.'s process reacts m-cresol with propene on broad and medium-pored zeolites to synthesize thymol. Due to inadequate catalyst efficacy at atmospheric pressure, all known procedures require liquid-phase reactions under super atmospheric pressure for satisfactory conversions and selectivity. High pressure requirements make it challenging and economically unviable for industrial-scale implementation. The reactor was made of a glass tube with an inner diameter of 25 mm and a length of 35 cm that was heated by electric resistance. Different zeolites with varying SiO to Al_2O_3 ratios were tested, including H-ZSM 5, H-mordenite, H-ZSM 23, and H-erionite. At a reaction temperature of 250 °C, the combination of H-mordenite zeolite and a meta cresol to propene molar ratio of 1: 2 yielded the highest conversion of about 53% and the highest selectivity of about 84% (Wimmer, et.al 1991).

Z. Guangyou's invention in drug synthesis involves a thymol production process using m-cresol, isopropyl chloride, concentrated sulfuric acid, and an ionic liquid catalyst. The reaction lasts 2 hours, after which the product is dissolved in n-heptane, washed with water, and crystallized. Benefits include lower production costs and easier separation of by-products (Guangyou, et.al 2022).

Y. Kai et al. synthesized 4,7-diformazan butylcoumarin by combining ethyl acetoacetate and m-cresol, which is then hydrolyzed and decarboxylated in alkaline conditions, yielding 5-(propyl-1-alkene-2-base) phenol. This organic phase is reduced to produce thymol. The method is cost-effective and suitable for industrial production (Kai, et.al 2021).

W. Guisheng developed a gas-solid phase reaction using isopropanol and meta cresol with a CaO-ZnO-Al2O3 catalyst in a fixed bed. At 280 °C, the maximum m-cresol conversion was about 52%, with thymol selectivity at 88.22%. The catalyst offers high

activity and is suitable for industrial-scale thymol synthesis (Guisheng, et.al 2020).
Z. Chunyong et al. synthesized thymol using m-cresol and isopropanol, with a catalyst introduced after initial agitation. Under microwave radiation (400–800 W) at 150–200 °C for 5–15 minutes, the mixture converts to thymol. Optimal conditions (600 W, 180 °C, 5 minutes) achieved 98.34% m-cresol conversion and 96.82% thymol selectivity (Chunyong, et.al 2020). Z. Yuhong et al. introduced a synthetic process for thymol production. Existing methods often suffer from low selectivity or difficult operating conditions, and some use highly corrosive catalysts that create significant waste and are non-recyclable. This new method uses m-cresol and propylene as starting materials and employs an aluminium oxide catalyst, prepared via the sol-gel method and doped with cobalt. At around 220°C, the process achieves 90-97% thymol selectivity and over 90% m-cresol conversion. The inventors claim this method is easy to manage, environmentally friendly, and the catalyst is stable and long-lasting (Yuhong, et.al 2018).
Y. Zhenghao et al. describe a new thymol synthesis method using super acidic catalysts made from pairs like concentrated sulfuric acid with aluminium trichloride, polyphosphoric acid with aluminium chloride, concentrated sulfuric acid with zinc chloride, or polyphosphoric acid with zinc chloride. Propylene gas is continuously fed into the reactor to facilitate m-cresol isopropylation while maintaining reaction temperature. The continuous reaction was tested for 2-20 hours, achieving about 80% thymol yield and 99.5% selectivity. This method is cost-effective, simple, and easily implementable (Zhenghao, et.al 2017).

Conclusion:

The review delineates the broad applications of thymol in fields such as pharmacology, pharmaceuticals, medicine, therapeutics, antibacterial uses, food preservation, and more. Market forecasts suggest that thymol will remain a highly valuable chemical. This review includes over 90% of the vapor and liquid phase synthesis methods used across industries, employing various catalysts like acidic, basic, super acidic, and mixed metal oxides. Each method has pros and cons concerning reaction times, energy needs, and catalyst regeneration. A major challenge in thymol synthesis is separating thymol from its isomers and complex reaction byproducts, such as isopropyl-3-methylphenyl ether, Isothymol, 2-isopropyl-5-methylphenyl acetate, and

isopropyl-(2-isopropyl-5-methylphenyl) ether. Industrial-scale synthesis under high temperature and pressure is difficult due to high energy demands. To address this, heterogeneous active catalysts like gamma alumina and CaO-ZnO-Al2O3 mixed oxide are used industrially. When activated at high temperatures, these catalysts reduce reaction times and can be easily separated by basic processes like settling post-reaction. Additionally, some researchers have explored ultrasound and irradiation methods. Although these require significant energy and are not cost-effective, they necessitate short reaction times (10-15 minutes). Further research is needed to scale up these processes and reduce energy consumption. Process optimization is also essential at the industrial level to reduce reaction times, catalyst use, and byproduct formation, thereby improving thymol yield and meta cresol conversion.

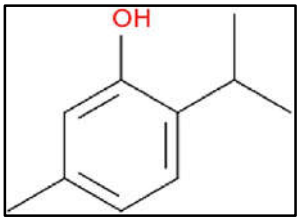

Fig 1 Chemical Structure of Thymol.

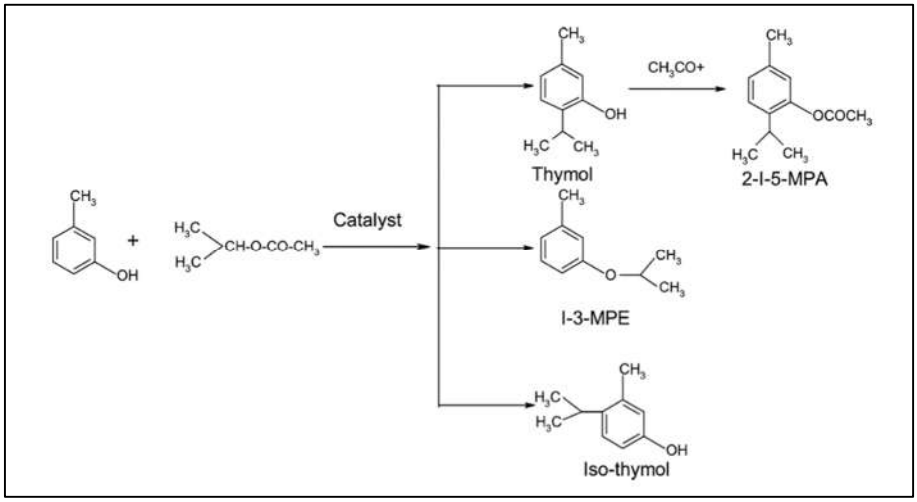

Fig 2 Reaction of m-cresol with isopropyl acetate

Table. 1. Physical and Chemical properties of Thymol.

Sr. No	Properties	Description
1	Chemical Formula	$C_{10}H_{14}O$
2	Physical State (at room temperature)	Crystalline
3	Appearance	Colorless to White
4	Melting Point Range	48 ^oC to 51 ^oC (per liter)
5	Boiling Point (100% purity)	232 ^oC (per liter)
6	Flash Point	116 ^oC
7	Water Solubility (at room temperature)	0.8 gram per liter
8	Vapor Pressure (at room temperature)	0.022 hPa
9	Density (at room temperature)	0.965 gram per cm^3

Table. 2. Effect of Temperature on the Conversion & Selectivity of Thymol for Mesoporous Al-MCM-41 Catalyst.

Temperature (in ^oC)	**Meta Cresol Conversion (in %)**	**Thymol Selectivity (in %)**	**IIMPE Selectivity (in %)**	**IMPE Selectivity (in %)**
275	40.4	56	14	30
300	55	75.3	9.4	15.3
325	52.5	81	9	10.3
350	47.6	87.2	4.8	8
375	42.1	100	-	-
400	40.2	100	-	-

Table. 3. Effect of Reaction Time on the Selectivity of Thymol under Conventional Heating

Reaction Time (in minutes)	thymol Selectivity (in %)	di-alkylated products Selectivity (in %)	para-thymol Selectivity (in %)	vic-thymol Selectivity (in %)	sym-thymol Selectivity (in %)
60	59.8	5.9	28	1.1	5.2
120	59.9	4.7	24.4	1.2	9.8
180	60	4.8	23.4	1.2	10.8
240	57.9	3.6	23	1.1	14.1

Table. 4. Effect of Reaction Time on the Selectivity of Thymol under Microwave Irradiation

Reaction Time (in minutes)	Thymol Selectivity (in %)	Sym thymol Selectivity (in %)	vic-thymol Selectivity (in %)	para-thymol Selectivity (in %)	di-alkylated products Selectivity (in %)	O-alkylated products Selectivity (in %)
1	28.6	0.1	21	15.8	4.4	30.5
5	28.8	0.3	22	18.5	4.7	25.8
10	31.2	0.8	23	23.2	5.9	15.9
20	34.3	0.9	26.2	23.7	6.8	8.1
30	34.5	1.2	26.4	26.8	10.6	0.8
60	34.6	1.3	26.6	27	10.2	0.3

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