

# Protective Effects of Thymol on Inflammatory Bowel Disease

Subjects: [Agriculture, Dairy & Animal Science](#)

Contributor: Yao Liu , Hui Yan , Bing Yu , Jun He , Xiangbing Mao , Jie Yu , Ping Zheng , Zhiqing Huang , Yuheng Luo , Junqiu Luo , Aimin Wu , Daiwen Chen

Inflammatory bowel disease (IBD) is a gastrointestinal disease that involves chronic mucosal or submucosal lesions that affect tissue integrity. Although IBD is not life-threatening, it sometimes causes severe complications, such as colon cancer. The exact etiology of IBD remains unclear, but several risk factors, such as pathogen infection, stress, diet, age, and genetics, have been involved in the occurrence and aggravation of IBD. Immune system malfunction with the over-production of inflammatory cytokines and associated oxidative stress are the hallmarks of IBD. Dietary intervention and medical treatment suppressing abnormal inflammation and oxidative stress are recommended as potential therapies. Thymol, a natural monoterpene phenol that is mostly found in thyme, exhibits multiple biological functions as a potential adjuvant for IBD.

gastrointestinal disease

gut health

natural anti-oxidant

## 1. Introduction

Inflammatory bowel disease (IBD) is a chronic and relapsing inflammatory disorder of the gastrointestinal tract (GIT) <sup>[1]</sup>. It is not fatal, but imposes a burden on global healthcare and greatly reduces the quality of life of patients. From 1990 to 2017, the number of IBD patients increased from 37 million to more than 68 million, and the global prevalence of IBD increased by 85.1% <sup>[2]</sup>. The United States has the highest age-standardized prevalence rate in the world, accounting for nearly a quarter of all global IBD patients in 2017. Among European countries, the United Kingdom has the highest age-standardized prevalence. The prevalence of IBD in the United States ranges from 252 to 439 cases per 100,000 people <sup>[3]</sup>. Compared with western countries, the incidence of IBD in Asia is relatively low, but it has risen from 0.54 to 3.44 per 100,000 individuals across eight Asian countries <sup>[4][5]</sup>. The prevalence and incidence of IBD are continuing to increase worldwide in different races and countries <sup>[6]</sup>.

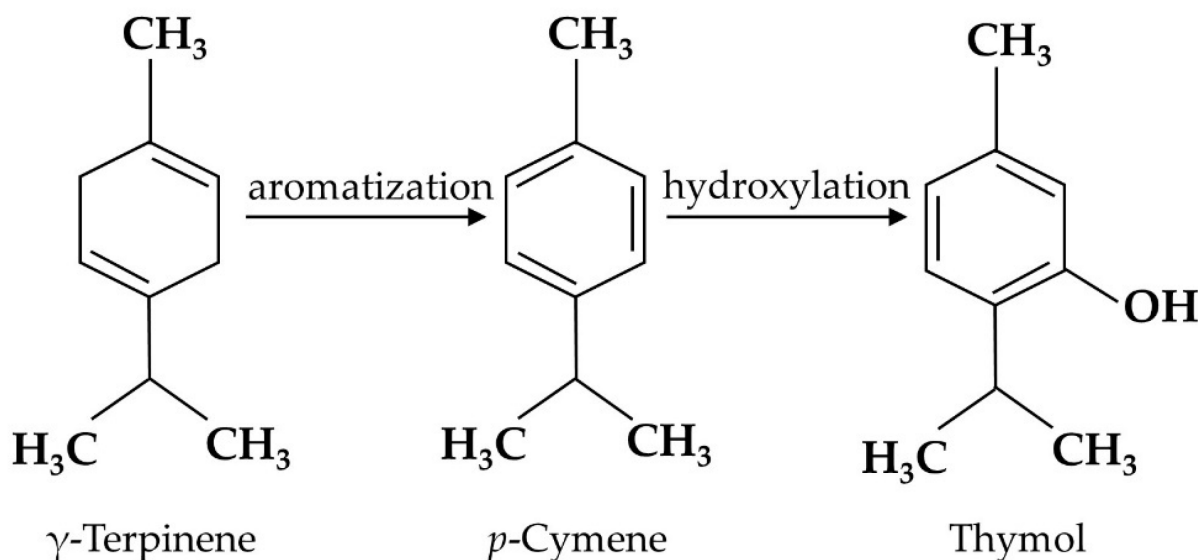
IBD includes Crohn's disease (CD) and ulcerative colitis (UC). UC involves long-lasting inflammation and ulcers along the superficial lining of the large intestine (rectum and colon), while CD is characterized by the discontinuous transmural inflammation in deeper layers of most regions of the GIT <sup>[7][8]</sup>. The exact cause of IBD remains unknown, but malfunction in the immune system is its hallmark. In IBD patients, an abnormal immune response to pathogen infection or stress causes chronic inflammation in the GIT contributing to the incidence of the disease <sup>[9]</sup>. Some genetic factors involved in an inappropriate immune response are a reason for IBD <sup>[10]</sup>. Oxidative stress (OS) with excessive accumulation of reactive oxygen species (ROS) has been reported to correlate with intestinal chronic inflammation and incidence of IBD <sup>[11]</sup>. Moreover, alteration in the gut microbiota has been associated with

the pathogenesis of IBD [12]. Unfortunately, there is currently no cure for IBD. Anti-inflammation medicines are used to relieve inflammation and even surgery is required to remove damaged parts of the GIT when patients suffer. Recently, advances in dietary regulation of inflammation, OS, and gut microbiota have resulted in dietary intervention against IBD incidence being recommended as a long-term prevention and therapy technique [13]. Currently, more research is focusing on natural plant extracts, such as phenol compounds, for the prevention and relief of IBD [14].

Thymol (2-isopropyl-5-methylphenol), a natural monoterpene phenol compound, is the major component of the essential oils extracted from plants of thyme species, such as *Thymus vulgaris*, *Coridothymus capitatus*, and *Origanum vulgare* [15]. Thymol exhibits multiple biological and pharmacological properties, including anti-inflammation, anti-oxidation, anti-bacteria, anti-fungal, and anti-tumor potential [16]. A high dose of thymol up to 500 mg/kg diet has been shown to have no toxicity [17].

## 2. Pharmacokinetics and Pharmacological Properties of Thymol

Thymol is the secondary metabolite produced by the aromatization of  $\gamma$ -terpinene to *p*-cymene, followed by the hydroxylation of *p*-cymene in plants [18] (Figure 1), including *Thymus zygis* [19], *Thymbra capitata* [20], *Thymus vulgaris* [21], *Satureja thymbra* [22], *Nigella sativa* seeds [23], and *Monarda didyma* [24]. Pure thymol has low solubility in water, high volatility, and a strong bitter/irritating taste [25]; thus, it is usually encapsulated in electrospun nanofibers to enhance its water solubility and high temperature stability [26]. Emulsification is also used for thymol processing. Both encapsulation and emulsification have been shown to improve the anti-oxidant activity of thymol [27].



**Figure 1.** Thymol biosynthesis in plants. Thymol is synthesized by the hydroxylation of *p*-cymene, which originates from the aromatization of  $\gamma$ -terpinene.

Thymol administered orally can be rapidly absorbed in the stomach and small intestines, and then transported to various organs via the circulation system in animals [28]. Thymol can be metabolized to thymol sulfate and thymol glucuronide by sulfation and glucuronidation in the intestines, liver, kidney, and other organs, respectively [29]. Thymol and its metabolites reach the maximum concentration in the blood 30 min after oral administration and then are slowly eliminated in about 24 h [25]. They also present in the lungs, kidneys, mucosa of the small and large intestines, and other organs, suggesting that they may function directly in these organs. It is difficult to determine which compound is the active form of thymol, because thymol metabolites can be deconjugated to thymol locally and export its pharmacological activity in this way [30]. Recently, scientists have focused on the pharmacological activities of thymol.

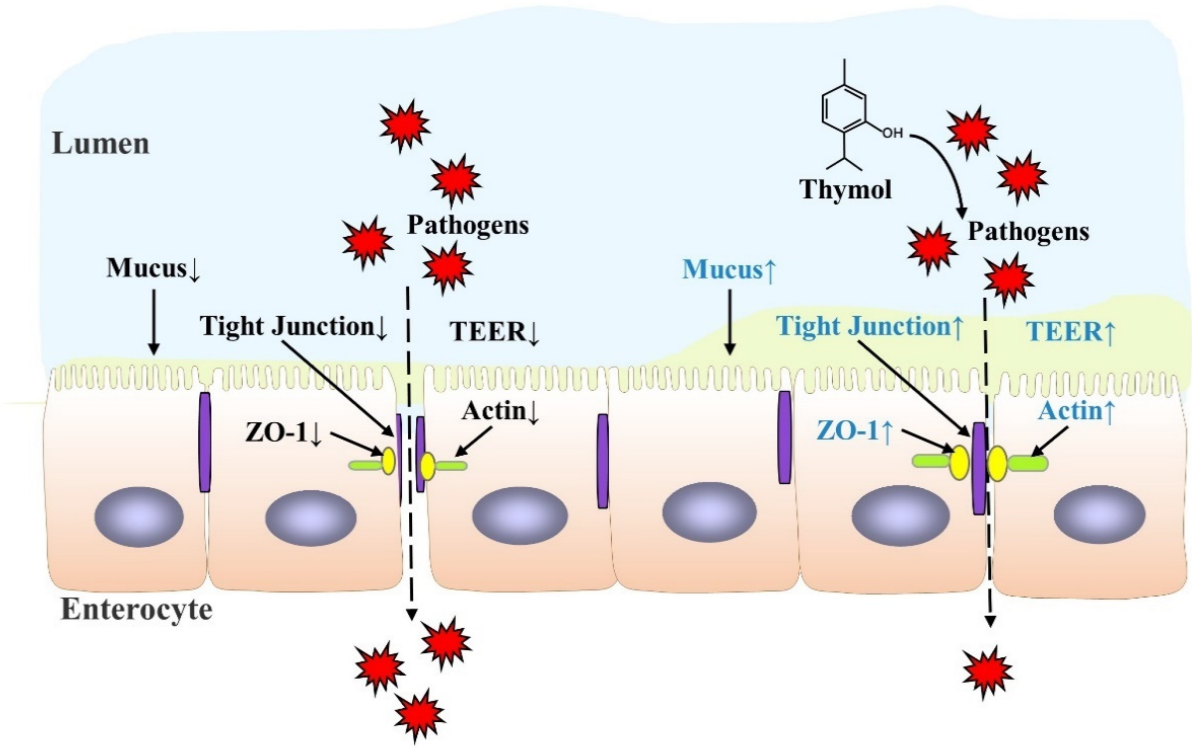
Thymol-containing plants have long been used in traditional Chinese medicine due to its pharmacological properties. Thymol acts as a potent inhibitor of the release of inflammatory cytokines, such as interleukin (IL)-6, IL-1 $\beta$ , and IL-8 [31]. Thymol enhances anti-oxidative capacity to alleviate OS in different tissues [32]. As a spectrum anti-bacterial agent, thymol reduces the activities of microorganisms belonging to the Enterobacteriaceae, Streptococcus, and Saccharomycetaceae families, involving membrane rupture, inhibition of biofilm formation, and other pathways [33][34]. Thymol shows anti-viral potential to inhibit virus colonization, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-298), by docking with the S1 receptor-binding domain of spike glycoprotein [35]. Thymol also exhibits other pharmacological functions, such as analgesia, anti-malarial, and anti-fungal properties [36][37][38][39][40].

### 3. Thymol Protects Intestinal Barrier Function against IBD

The intestinal barrier, mainly composed of intestinal epithelial cells (IECs) and immune cells, maintains the balance between the luminal contents and mucosa. The disturbance of this balance has been associated with gastrointestinal diseases, such as IBD [41]. Although the exact pathogenesis of IBD remains unclear, a “leaky gut” with impaired intestinal barrier function is the main feature. The intestinal barrier is the first line of defense against pathogen infection, and injury to the intestinal barrier aggravates the disease. Thus, understanding how thymol protects the intestinal barrier is important for relieving IBD.

Thymol has exhibited a protective function for the intestinal barrier in both in vivo and in vitro studies, as illustrated in **Table 1**, and its specific mechanism is shown in **Figure 2**. Thymol attenuates weaning stress-induced diarrheal and intestinal barrier dysfunction in weanling pigs by reducing the serum diamine oxidase level, an indicator of intestinal integrity, and increasing the expression of the tight junction protein zonula occludens-1 (ZO-1) and occludins [42]. Thymol alleviates dextran sulfate sodium (DSS)-induced intestinal damage and increases tight junction claudin-3 expression [43]. Increased plasma endotoxin and D-lactic acid levels are markers of increased intestinal permeability. The latest study found that dietary thymol reduced the plasma endotoxin and D-lactic acid concentrations on days 7 and 14 post-weaning [44]. The intestinal mucus layer is the first line of defense maintaining bacterial symbiosis with the host and preventing bacterial penetration into epithelial cells [45]. Thymol increases mucus secretion to relieve ethanol-induced ulcer mucosal damage in rats [46]. In IPEC-J2 cells, thymol alleviates lipopolysaccharide (LPS)-induced decrease in trans-epithelial electrical resistance (TEER), indicating an

increase in the integrity of the single cell layer [47]. In Caco-2 cells, thymol increases the integrity of the tight junction and up-regulates cyclooxygenase-1 (COX1) activity to maintain GIT homeostasis, which is beneficial for intestinal health [48]. In addition, thymol changes the expressions of 120 and 59 genes in the oxyntic and pyloric mucosa, respectively, which are associated with gastric epithelium proliferation and maturation activities in weaned pigs [28].



**Figure 2.** Action of thymol to protect intestinal barrier function. Pathogen infection in the intestinal lumen reduces mucus secretion and the expressions of tight junction proteins, and increases intestinal permeability, resulting in a “leaky gut”, which increases the risk of intestinal disease. Thymol has been shown to defend against pathogen invasion, promote mucus secretion, and enhance intestinal barrier integrity.

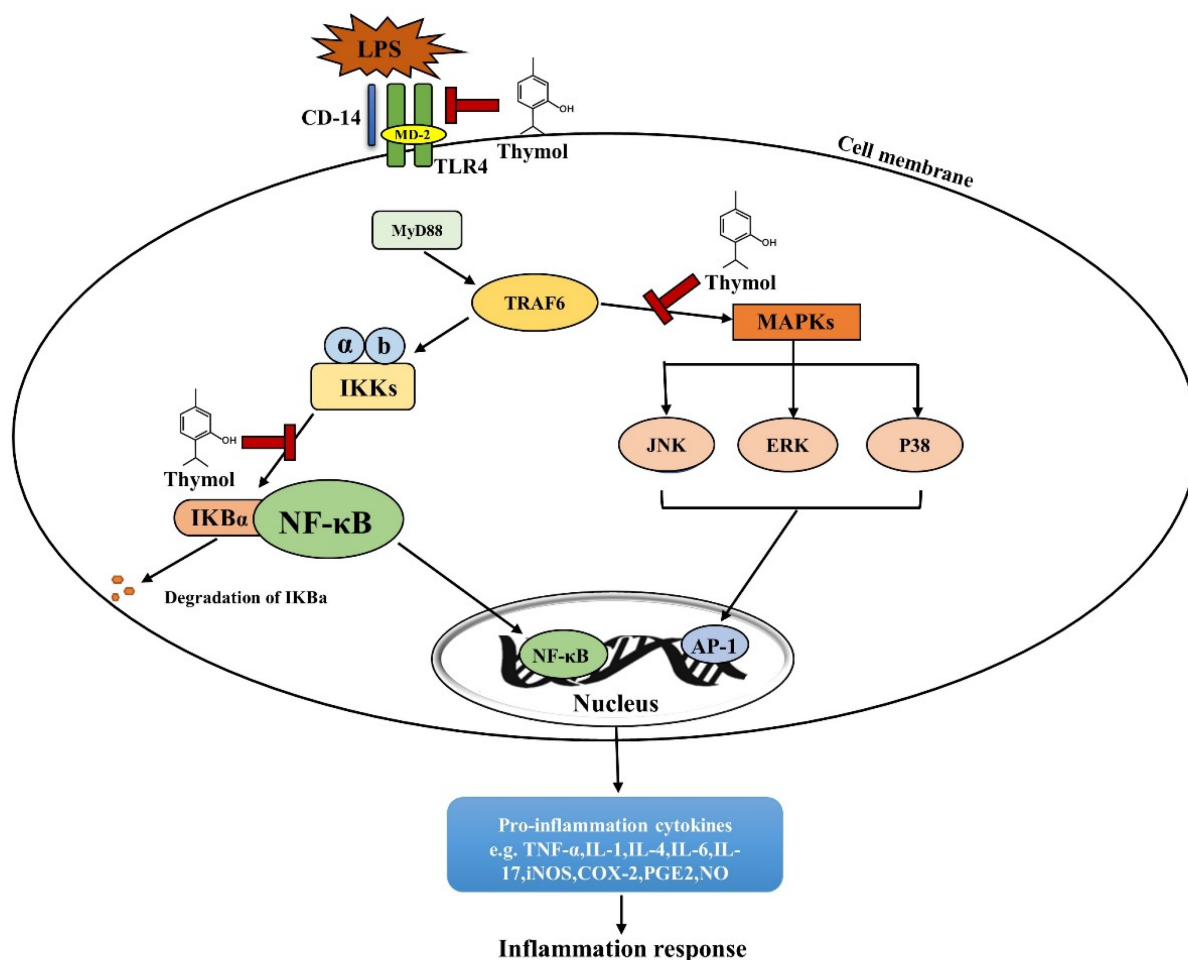
**Table 1.** Protective function of thymol on the intestinal barrier.

Model	Thymol Dose	Effects	Ref.
In vivo			
Weaned pigs	50 mg/kg diet	Enrichment of 120 and 59 gene sets in oxyntic and pyloric mucosa↓	[28]
Ethanol-induced acute ulcer	10–100 mg/kg diet	Mucosal damage↓ Amount of mucus↑	[46]
Chicken infected with <i>Clostridium perfringens</i>	30 mg/kg diet	Intestinal lesions and mortality↓ <i>Lactobacillus salivarius</i> and <i>L. johnsonii</i> ↓ <i>L. crispatus</i> , <i>L. agilis</i> , and <i>Escherichia coli</i> ↑	[49]

Model	Thymol Dose	Effects	Ref.
Weaned pigs	100 mg/kg diet	Expression of ZO-1 and occludins in jejunal mucosa↓ <i>Enterococcus</i> genus and <i>E. coli</i> ↓ Plasma diamine oxidase concentration↓ Weaning-induced intestinal OS↓	[42]
In vitro			
IPEC-J2	50 μM	TEER↑ Cell permeability↓ ZO-1and actin staining↑	[47]
Caco-2 cells	15 mg/L	COX1 transcription↑ COX1:COX2 ratio↑ TEER↑	[48]

The dysregulation of innate and adaptive immune responses leads to chronic intestinal inflammation in IBD patients [50][51][52]. Transcription factor nuclear factor κB (NF-κB) is the key mediator regulating the inflammatory response. The activation of NF-κB signaling induces the expression of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), inducible nitric oxide synthase (iNOS), interleukin (IL-1β), and IL-6 [53]. The over-production and accumulation of inflammatory cytokines cause intestinal epithelial apoptosis and the disruption of intestinal homeostasis, resulting in the dysfunction of the intestinal epithelial barrier in IBD patients [54]. Currently, the suppression of inflammation is the mainstay of IBD treatment.

Thymol shows strong anti-inflammatory properties in in vivo and in vitro studies [55]. A schematic diagram of thymol's action is depicted in **Figure 3**. Toll-like receptors (TLRs) are the main sensors used to detect various dangerous signals and activate innate immune responses. The classic TLR signaling pathway activates NF-κB to regulate the expressions of a series of cytokines [56]. In mice and macrophages, thymol inhibits TLR4 expression and then inhibits the activation of NF-κB signaling, which reduces the production of inflammatory cytokines, such as TNF-α and IL-1β [57][58]. NF-κB is a master mediator of inflammatory responses. Inactive NF-κB binds to IκB, an inhibitory subunit of NF-κB, and presents in the cytoplasm. When activated by a variety of signals, such as cytokine receptors and pattern-recognition receptors (PRRs), IκB is phosphorylated and degraded to release RelA (p65) from the NF-κB complex. p65 is then translocated to the nucleus to induce pro-inflammatory cytokine expression as a transcription factor [59]. Thymol has been shown to inhibit NF-κB activation by reducing p65 translocation and abundance in the colons of acetic acid-induced colitis rats and in LPS-activated macrophages, respectively, with decreased cytokine production [60][61]. The activation of NF-κB induces the expressions of iNOS and COX-2, which further promote vigorous inflammation. In ulcerative colitis rats, thymol reduces the COX-2 expression and nitric oxide (NO) levels produced by iNOS in the rats' colon [62]. These studies showed the anti-inflammatory function of thymol through the inhibition of the NF-κB signaling pathway.



**Figure 3.** Mechanism of thymol in relieving inflammation. Cells receive various stimuli and activate IκB kinases (IκBs) through the TLR4 signaling pathway, and then IκB proteins are phosphorylated, ubiquitinated, and degraded, and NF-κB dimers are released. The NF-κB dimer is then further activated through various post-translational modifications and translocated into the nucleus to bind to target genes to promote pro-inflammatory gene transcription. In addition, by activating the MAPKs family, it can promote the expression of c-jun terminal kinases (JNK) 1/2, extracellular signal-regulated kinase (ERK), and p38 for activation, thereby promoting the nuclear entry of activator protein 1 (AP-1) to regulate the expression of pro-inflammatory genes. Thymol inhibits the dissociation of the IκB protein and NF-κB dimer and the activation of the mitogen-activated protein kinase (MAPK) signaling pathway to relieve inflammation.

Studies have reported that proteins in the MAPK family, such as JNK1/2, p38α, and ERK, are activated in the colonic mucosa of IBD patients [63]. The suppression of the MAPK signaling pathway is an approach for alleviating inflammation and thus IBD [63]. It has been reported that thymol inhibits p38 phosphorylation and interferes with the activation of the MAPK signaling pathway to maintain the immune balance [64]. Thymol also suppresses LPS-induced activation of p-p38, p-JNK, and p-ERK, and correspondingly inhibits the production of NO, IL-6, TNF-α, COX-2, and other inflammatory cytokines [65]. Therefore, thymol can also reduce the inflammatory response by inhibiting the MAPK signaling pathway.



Cytokines are synthesized and secreted by activated immune cells, such as macrophages, T cells, B cells, dendritic cells (DCs), and natural killer cells. Among them, the regulatory T cell (Treg) is essential to control autoimmunity. Treg is defined by the expression of CD4, CD25, and transcription factor forkhead box P3 (Foxp3) [66]. Thymol promotes the differentiation of naïve T cells to CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> Treg cells and induces Foxp3 expression [67]. Meanwhile, thymol also maintains the balance of the Th1/Tregs and Th17/Tregs ratios to prevent autoimmunity as a result of suppressed inflammation [67][68]. Additionally, thymol exerts inhibitory effects on DCs' maturation and T cell activation [69]. Although thymol has influenced the immune cell population in some studies, more information is required on how thymol modulates immune cell differentiation and whether the changes in the immune cell population by thymol contribute to the relief of IBD.

## References

1. Duerr, R.H.; Taylor, K.D.; Brant, S.R.; Rioux, J.D.; Silverberg, M.S.; Daly, M.J.; Steinhart, A.H.; Abraham, C.; Regueiro, M.; Griffiths, A.; et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 2006, 314, 1461–1463.
2. Sudabeh Alatab, S.G.S. Kevin Ikuta, Homayoon Vahedi, Catherine Bisignano. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020, 5, 17–30.
3. Kaser, A.; Zeissig, S.; Blumberg, R.S. Inflammatory bowel disease. *Annu. Rev. Immunol.* 2010, 28, 573–621.
4. Loftus, E.V., Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004, 126, 1504–1517.
5. Ng, S.C. Epidemiology of inflammatory bowel disease: Focus on Asia. *Best Pract. Res. Clin. Gastroenterol.* 2014, 28, 363–372.
6. Kaplan, G.G.; Ng, S.C. Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. *Gastroenterology* 2017, 152, 313–321.
7. Corridoni, D.; Arseneau, K.O.; Cominelli, F. Inflammatory bowel disease. *Immunol. Lett.* 2014, 161, 231–235.
8. Walfish, A.; Sachar, D. Phenotype classification in IBD: Is there an impact on therapy? *Inflamm. Bowel Dis.* 2007, 13, 1573–1575.
9. Geremia, A.; Biancheri, P.; Allan, P.; Corazza, G.R.; Di Sabatino, A. Innate and adaptive immunity in inflammatory bowel disease. *Autoimmun. Rev.* 2014, 13, 3–10.

10. Van Limbergen, J.; Russell, R.K.; Nimmo, E.R.; Satsangi, J. The genetics of inflammatory bowel disease. *Am. J. Gastroenterol.* 2007, 102, 2820–2831.
11. Zhao, Y.; Guo, Q.; Zhu, Q.; Tan, R.; Bai, D.; Bu, X.; Lin, B.; Zhao, K.; Pan, C.; Chen, H.; et al. Flavonoid VI-16 protects against DSS-induced colitis by inhibiting Txnip-dependent NLRP3 inflammasome activation in macrophages via reducing oxidative stress. *Mucosal Immunol.* 2019, 12, 1150–1163.
12. Matsuoka, K.; Kanai, T. The gut microbiota and inflammatory bowel disease. *Semin. Immunopathol.* 2015, 37, 47–55.
13. Lee, D.; Albenberg, L.; Compher, C.; Baldassano, R.; Piccoli, D.; Lewis, J.D.; Wu, G.D. Diet in the pathogenesis and treatment of inflammatory bowel diseases. *Gastroenterology* 2015, 148, 1087–1106.
14. Martin, D.A.; Bolling, B.W. A review of the efficacy of dietary polyphenols in experimental models of inflammatory bowel diseases. *Food Funct.* 2015, 6, 1773–1786.
15. Hazzit, M.; Baaliouamer, A.; Faleiro, M.L.; Miguel, M.G. Composition of the essential oils of *Thymus* and *Origanum* species from Algeria and their antioxidant and antimicrobial activities. *J. Agric. Food Chem.* 2006, 54, 6314–6321.
16. Salehi, B.; Mishra, A.P.; Shukla, I.; Sharifi-Rad, M.; Contreras, M.D.M.; Segura-Carretero, A.; Fathi, H.; Nasrabadi, N.N.; Kobarfard, F.; Sharifi-Rad, J. Thymol, thyme, and other plant sources: Health and potential uses. *Phytother. Res.* 2018, 32, 1688–1706.
17. Geyikoglu, F.; Yilmaz, E.G.; Erol, H.S.; Koc, K.; Cerig, S.; Ozek, N.S.; Aysin, F. Hepatoprotective Role of Thymol in Drug-Induced Gastric Ulcer Model. *Ann. Hepatol.* 2018, 17, 980–991.
18. Poulou, A.J.; Croteau, R. Biosynthesis of aromatic monoterpenes: Conversion of gamma-terpinene to p-cymene and thymol in *Thymus vulgaris* L. *Arch. Biochem. Biophys.* 1978, 187, 307–314.
19. Ocaña, A.; Reglero, G. Effects of Thyme Extract Oils (from *Thymus vulgaris*, *Thymus zygis*, and *Thymus hyemalis*) on Cytokine Production and Gene Expression of oxLDL-Stimulated THP-1-Macrophages. *J. Obes.* 2012, 2012, 104706.
20. Machado, M.; Dinis, A.M.; Salgueiro, L.; Cavaleiro, C.; Custódio, J.B.; Sousa Mdo, C. Anti-Giardia activity of phenolic-rich essential oils: Effects of *Thymbra capitata*, *Origanum virens*, *Thymus zygis* subsp. *sylvestris*, and *Lippia graveolens* on trophozoites growth, viability, adherence, and ultrastructure. *Parasitol. Res.* 2010, 106, 1205–1215.
21. Nikolić, M.; Glamočlija, J.; Ferreira, I.C.F.R.; Calhella, R.C.; Fernandes, Â.; Marković, T.; Marković, D.; Giweli, A.; Soković, M. Chemical composition, antimicrobial, antioxidant and antitumor activity of *Thymus serpyllum* L., *Thymus algeriensis* Boiss. and Reut and *Thymus vulgaris* L. essential oils. *Ind. Crops Prod.* 2014, 52, 183–190.



22. Karousou, R.; Koureas, D.N.; Kokkini, S. Essential oil composition is related to the natural habitats: *Coridothymus capitatus* and *Satureja thymbra* in NATURA 2000 sites of Crete. *Phytochemistry* 2005, 66, 2668–2673.
23. Maulidiani, M.; Sheikh, B.Y.; Mediani, A.; Wei, L.S.; Ismail, I.S.; Abas, F.; Lajis, N.H. Differentiation of *Nigella sativa* seeds from four different origins and their bioactivity correlations based on NMR-metabolomics approach. *Phytochem. Lett.* 2015, 13, 308–318.
24. Laquale, S.; Avato, P.; Argentieri, M.P.; Bellardi, M.G.; D'Addabbo, T. Nematotoxic activity of essential oils from *Monarda* species. *J. Pest. Sci.* 2018, 91, 1115–1125.
25. Nieddu, M.; Rassu, G.; Boatto, G.; Bosi, P.; Trevisi, P.; Giunchedi, P.; Carta, A.; Gavini, E. Improvement of thymol properties by complexation with cyclodextrins: In vitro and in vivo studies. *Carbohydr. Polym.* 2014, 102, 393–399.
26. Celebioglu, A.; Yildiz, Z.I.; Uyar, T. Thymol/cyclodextrin inclusion complex nanofibrous webs: Enhanced water solubility, high thermal stability and antioxidant property of thymol. *Food Res. Int.* 2018, 106, 280–290.
27. Sedaghat Doost, A.; Van Camp, J.; Dewettinck, K.; Van der Meeren, P. Production of thymol nanoemulsions stabilized using Quillaja Saponin as a biosurfactant: Antioxidant activity enhancement. *Food Chem.* 2019, 293, 134–143.
28. Colombo, M.; Priori, D.; Gandolfi, G.; Boatto, G.; Nieddu, M.; Bosi, P.; Trevisi, P. Effect of free thymol on differential gene expression in gastric mucosa of the young pig. *Animal* 2014, 8, 786–791.
29. Pisarčíková, J.; Ocel'ová, V.; Faix, Š.; Plachá, I.; Calderón, A.I. Identification and quantification of thymol metabolites in plasma, liver and duodenal wall of broiler chickens using UHPLC-ESI-QTOF-MS. *Biomed. Chromatogr.* 2017, 31, e3881.
30. Lugarà, R.; Grześkowiak, Ł.; Zentek, J.; Meese, S.; Kreuzer, M.; Giller, K. A High-Energy Diet and Spirulina Supplementation during Pre-Gestation, Gestation, and Lactation do Not Affect the Reproductive and Lactational Performance of Primiparous Sows. *Animals* 2022, 12, 1171.
31. Pandur, E.; Micalizzi, G.; Mondello, L.; Horvath, A.; Sipos, K.; Horvath, G. Antioxidant and Anti-Inflammatory Effects of Thyme (*Thymus vulgaris* L.) Essential Oils Prepared at Different Plant Phenophases on *Pseudomonas aeruginosa* LPS-Activated THP-1 Macrophages. *Antioxidants* 2022, 11, 1330.
32. Ahmed, O.M.; Galaly, S.R.; Mostafa, M.M.A.; Eed, E.M.; Ali, T.M.; Fahmy, A.M.; Zaky, M.Y. Thyme Oil and Thymol Counter Doxorubicin-Induced Hepatotoxicity via Modulation of Inflammation, Apoptosis, and Oxidative Stress. *Oxid. Med. Cell. Longev.* 2022, 2022, 6702773.
33. Yin, L.; Liang, C.; Wei, W.; Huang, S.; Ren, Y.; Geng, Y.; Huang, X.; Chen, D.; Guo, H.; Fang, J.; et al. The Antibacterial Activity of Thymol Against Drug-Resistant *Streptococcus iniae* and Its

- Protective Effect on Channel Catfish (*Ictalurus punctatus*). *Front. Microbiol.* 2022, 13, 914868.
34. Yao, Z.; Feng, L.; Zhao, Y.; Zhang, X.; Chen, L.; Wang, L.; Zhang, Y.; Sun, Y.; Zhou, T.; Cao, J. Thymol Increases Sensitivity of Clinical Col-R Gram-Negative Bacteria to Colistin. *Microbiol. Spectr.* 2022, 10, e0018422.
35. Kulkarni, S.A.; Nagarajan, S.K.; Ramesh, V.; Palaniyandi, V.; Selvam, S.P.; Madhavan, T. Computational evaluation of major components from plant essential oils as potent inhibitors of SARS-CoV-2 spike protein. *J. Mol. Struct.* 2020, 1221, 128823.
36. Hassan, H.F.H.; Mansour, A.M.; Salama, S.A.; El-Sayed, E.M. The chemopreventive effect of thymol against dimethylhydrazine and/or high fat diet-induced colon cancer in rats: Relevance to NF- $\kappa$ B. *Life Sci.* 2021, 274, 119335.
37. Mendes, S.S.; Bomfim, R.R.; Jesus, H.C.; Alves, P.B.; Blank, A.F.; Estevam, C.S.; Antonioli, A.R.; Thomazzi, S.M. Evaluation of the analgesic and anti-inflammatory effects of the essential oil of *Lippia gracilis* leaves. *J. Ethnopharmacol.* 2010, 129, 391–397.
38. Mohammadi, A.; Mahjoub, S.; Ghafarzadegan, K.; Nouri, H.R. Immunomodulatory effects of Thymol through modulation of redox status and trace element content in experimental model of asthma. *Biomed. Pharmacother.* 2018, 105, 856–861.
39. Raghuvanshi, D.S.; Verma, N.; Singh, S.V.; Khare, S.; Pal, A.; Negi, A.S. Synthesis of thymol-based pyrazolines: An effort to perceive novel potent-antimalarials. *Bioorg. Chem.* 2019, 88, 102933.
40. Robledo, N.; Vera, P.; López, L.; Yazdani-Pedram, M.; Tapia, C.; Abugoch, L. Thymol nanoemulsions incorporated in quinoa protein/chitosan edible films; antifungal effect in cherry tomatoes. *Food Chem.* 2018, 246, 211–219.
41. Franzosa, E.A.; Sirota-Madi, A.; Avila-Pacheco, J.; Fornelos, N.; Haiser, H.J.; Reinker, S.; Vatanen, T.; Hall, A.B.; Mallick, H.; McIver, L.J.; et al. Gut microbiome structure and metabolic activity in inflammatory bowel disease. *Nat. Microbiol.* 2019, 4, 293–305.
42. Wei, H.K.; Xue, H.X.; Zhou, Z.X.; Peng, J. A carvacrol-thymol blend decreased intestinal oxidative stress and influenced selected microbes without changing the messenger RNA levels of tight junction proteins in jejunal mucosa of weaning piglets. *Animal* 2017, 11, 193–201.
43. Mueller, K.; Blum, N.M.; Mueller, A.S. Examination of the Anti-Inflammatory, Antioxidant, and Xenobiotic-Inducing Potential of Broccoli Extract and Various Essential Oils during a Mild DSS-Induced Colitis in Rats. *ISRN Gastroenterol.* 2013, 2013, 710856.
44. Wang, Y.; Yang, Z.; Zhou, Y.; Tan, J.; Sun, H.; Sun, D.; Mu, Y.; Peng, J.; Wei, H. Effects of different amino acid levels and a carvacrol-thymol blend on growth performance and intestinal health of weaned pigs. *J. Anim. Sci. Biotechnol.* 2022, 13, 22.

45. Fernández-Tomé, S.; Ortega Moreno, L.; Chaparro, M.; Gisbert, J.P. Gut Microbiota and Dietary Factors as Modulators of the Mucus Layer in Inflammatory Bowel Disease. *Int. J. Mol. Sci.* 2021, 22, 10224.
46. Ribeiro, A.R.S.; Diniz, P.B.F.; Pinheiro, M.S.; Albuquerque-Júnior, R.L.C.; Thomazzi, S.M. Gastroprotective effects of thymol on acute and chronic ulcers in rats: The role of prostaglandins, ATP-sensitive K<sup>+</sup> channels, and gastric mucus secretion. *Chem. Biol. Interact.* 2016, 244, 121–128.
47. Omonijo, F.A.; Liu, S.; Hui, Q.; Zhang, H.; Lahaye, L.; Bodin, J.C.; Gong, J.; Nyachoti, M.; Yang, C. Thymol Improves Barrier Function and Attenuates Inflammatory Responses in Porcine Intestinal Epithelial Cells during Lipopolysaccharide (LPS)-Induced Inflammation. *J. Agric. Food Chem.* 2019, 67, 615–624.
48. Putaala, H.; Nurminen, P.; Tiihonen, K. Effects of cinnamaldehyde and thymol on cytotoxicity, tight junction barrier resistance, and cyclooxygenase-1 and -2 expression in Caco-2 cells. *J. Anim. Sci.* 2017, 26, 274–284.
49. Yin, D.; Du, E.; Yuan, J.; Gao, J.; Wang, Y.; Aggrey, S.E.; Guo, Y. Supplemental thymol and carvacrol increases ileum *Lactobacillus* population and reduces effect of necrotic enteritis caused by *Clostridium perfringens* in chickens. *Sci. Rep.* 2017, 7, 7334.
50. Choy, M.C.; Visvanathan, K.; Cruz, P.D. An Overview of the Innate and Adaptive Immune System in Inflammatory Bowel Disease. *Inflamm. Bowel Dis.* 2017, 23, 2–13.
51. Iliev, I.D.; Funari, V.A.; Taylor, K.D.; Nguyen, Q.; Reyes, C.N.; Strom, S.P.; Brown, J.; Becker, C.A.; Fleshner, P.R.; Dubinsky, M.; et al. Interactions between commensal fungi and the C-type lectin receptor Dectin-1 influence colitis. *Science* 2012, 336, 1314–1317.
52. Roy, U.; Gálvez, E.J.C.; Iljazovic, A.; Lesker, T.R.; Błażejowski, A.J.; Pils, M.C.; Heise, U.; Huber, S.; Flavell, R.A.; Strowig, T. Distinct Microbial Communities Trigger Colitis Development upon Intestinal Barrier Damage via Innate or Adaptive Immune Cells. *Cell. Rep.* 2017, 21, 994–1008.
53. Natarajan, K.; Abraham, P.; Kota, R.; Isaac, B. NF-κB-iNOS-COX2-TNF α inflammatory signaling pathway plays an important role in methotrexate induced small intestinal injury in rats. *Food. Chem. Toxicol.* 2018, 118, 766–783.
54. Salim, S.Y.; Söderholm, J.D. Importance of disrupted intestinal barrier in inflammatory bowel diseases. *Inflamm. Bowel Dis.* 2011, 17, 362–381.
55. Chauhan, A.K.; Kang, S.C. Thymol disrupts the membrane integrity of *Salmonella ser. typhimurium* in vitro and recovers infected macrophages from oxidative stress in an ex vivo model. *Res. Microbiol.* 2014, 165, 559–565.
56. Peng, Y.; Zhang, X.; Zhang, T.; Grace, P.M.; Li, H.; Wang, Y.; Li, H.; Chen, H.; Watkins, L.R.; Hutchinson, M.R.; et al. Lovastatin inhibits Toll-like receptor 4 signaling in microglia by targeting

- its co-receptor myeloid differentiation protein 2 and attenuates neuropathic pain. *Brain Behav. Immun.* 2019, 82, 432–444.
57. Khazdair, M.R.; Ghorani, V.; Alavinezhad, A.; Boskabady, M.H. Pharmacological effects of *Zataria multiflora* Boiss L. and its constituents focus on their anti-inflammatory, antioxidant, and immunomodulatory effects. *Fundam. Clin. Pharmacol.* 2018, 32, 26–50.
  58. Gholijani, N.; Gharagozloo, M.; Farjadian, S.; Amirghofran, Z. Modulatory effects of thymol and carvacrol on inflammatory transcription factors in lipopolysaccharide-treated macrophages. *J. Immunotoxicol.* 2016, 13, 157–164.
  59. Jin, B.R.; Chung, K.S.; Cheon, S.Y.; Lee, M.; Hwang, S.; Noh Hwang, S.; Rhee, K.J.; An, H.J. Rosmarinic acid suppresses colonic inflammation in dextran sulphate sodium (DSS)-induced mice via dual inhibition of NF- $\kappa$ B and STAT3 activation. *Sci. Rep.* 2017, 7, 46252.
  60. Chamanara, M.; Abdollahi, A.; Rezayat, S.M.; Ghazi-Khansari, M.; Dehpour, A.; Nassireslami, E.; Rashidian, A. Thymol reduces acetic acid-induced inflammatory response through inhibition of NF- $\kappa$ B signaling pathway in rat colon tissue. *Inflammopharmacology* 2019, 27, 1275–1283.
  61. Liu, D.-M.; Zhou, C.-Y.; Meng, X.-L.; Wang, P.; Li, W. Thymol exerts anti-inflammatory effect in dextran sulfate sodium-induced experimental murine colitis. *Trop.J. Pharm. Res.* 2018, 17, 1803–1810.
  62. Tahmasebi, P.; Abtahi Froushani, S.M.; Afzale Ahangaran, N. Thymol has beneficial effects on the experimental model of ulcerative colitis. *Avicenna J. Phytomed.* 2019, 9, 538–550.
  63. Waetzig, G.H.; Seegert, D.; Rosenstiel, P.; Nikolaus, S.; Schreiber, S. p38 Mitogen-Activated Protein Kinase Is Activated and Linked to TNF- $\alpha$  Signaling in Inflammatory Bowel Disease. *J. Immunol.* 2002, 168, 5342–5351.
  64. Liang, D.; Li, F.; Fu, Y.; Cao, Y.; Song, X.; Wang, T.; Wang, W.; Guo, M.; Zhou, E.; Li, D.; et al. Thymol inhibits LPS-stimulated inflammatory response via down-regulation of NF- $\kappa$ B and MAPK signaling pathways in mouse mammary epithelial cells. *Inflammation* 2014, 37, 214–222.
  65. Chen, J.; Li, D.-L.; Xie, L.-N.; Ma, Y.-R.; Wu, P.-P.; Li, C.; Liu, W.-F.; Zhang, K.; Zhou, R.-P.; Xu, X.-T.; et al. Synergistic anti-inflammatory effects of silibinin and thymol combination on LPS-induced RAW264.7 cells by inhibition of NF- $\kappa$ B and MAPK activation. *Phytomedicine* 2020, 78, 153309.
  66. Tanaka, A.; Sakaguchi, S. Regulatory T cells in cancer immunotherapy. *Cell Res.* 2017, 27, 109–118.
  67. Namdari, H.; Izad, M.; Rezaei, F.; Amirghofran, Z. Thymol as a reciprocal regulator of T cell differentiation: Promotion of regulatory T cells and suppression of Th1/Th17 cells. *Int. Immunopharmacol.* 2019, 67, 417–426.

68. Gholijani, N.; Amirghofran, Z. Effects of thymol and carvacrol on T-helper cell subset cytokines and their main transcription factors in ovalbumin-immunized mice. *J. Immunotoxicol.* 2016, 13, 729–737.
  69. Amirghofran, Z.; Ahmadi, H.; Karimi, M.H.; Kalantar, F.; Gholijani, N.; Malek-Hosseini, Z. In vitro inhibitory effects of thymol and carvacrol on dendritic cell activation and function. *Pharm. Biol.* 2016, 54, 1125–1132.
- 

Retrieved from <https://encyclopedia.pub/entry/history/show/73777>