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Antimicrobial, anticancer, antidiabetic, antineurodegenerative, and antirheumatic activities of thymol: clarification of mechanisms

Qassim Hassan Aubais Aljelehawy[1*], Shadieh Mohammadi[2], Elham Mohamadian[3], Osamah Raji Mal Allah[4], Alireza Mirzaei[5], Mobin Ghahremanlou[6]

[1]*Department of Chemistry, College of Education, University of Al-Qadisiyah, Iraq*

[2]*Environmental Health Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Kurdistan, Iran*

[3]*Department of Biology, Faculty of Science, Razi University, Kermanshah, Iran*

[4]*Ministry of Education, General Directorate for Education in Al-Qadisiyah, Iraq*

[5]*Department of Agronomy and Plant Breeding, Faculty of Agriculture and Natural Resources, University of Mohaghegh Ardabili, Ardabil, Iran*

[6]*Australasian Nanoscience and Nanotechnology Initiative, Melbourne, Australia*

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ABSTRACT

Thymol is monoterpenic phenol with a wide range of therapeutic properties. Various pharmacological properties including antimicrobial, antineoplastic, anti-inflammatory, antidiabetic, antirheumatic, and antineurodegenerative have been found for this metabolite. The severity of peripheral nerve dysfunction in diabetes mellitus can be ameliorated by thymol treatment via decreasing tumor necrosis factor-α (TNF- α) and nitric oxide levels. In the case of the anticancer mechanism, thymol can increase the expression of the tumor suppressor of p53, Bcl-2-associated X protein (Bax), and apoptosis. Moreover, in this review, three main neurodegenerative diseases of Alzheimer's disease (AD), multiple sclerosis (MS), and Parkinson's disease (PD) have been discussed with respect to antineurodegenerative activities of thymol. Recent studies show that novel formulations of thymol in the nanoscale can improve therapeutic activities such as thymol release *in vitro* and *in vivo*. Antimicrobial and antioxidant activities of thymol against both Gram-negative and Gram-positive bacteria can be augmented by various nanoformulations. Therefore, we have tried to discuss the advantages and disadvantages of micro and nanoformulations of this bioactive material according to recent investigations.

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Introduction

Therapeutic application of bioactive compounds isolated from medicinal plants is augmented due to their bioavailable, biocompatible, and biodegradable properties inside the body [1]. Thymol (2-isopropyl-5-methylphenol; $C_{10}H_{14}O$), isomeric of carvacrol (Figure 1a) can be extracted mainly from various plant species involving *Thymus vulgaris* [2], *Origanum vulgare* [3], *Ocimum gratissimum* [4], *Carum copticum* [5], *Oliveria decumbens* [6], and *Trachyspermum ammi* [7]. This metabolite is soluble in ethanol by a value of ~900 mg/g at ~40°C and other organic solvents such as ether and chloroform [8]. This bioactive compound has demonstrated pleotropic pharmacological activities involving antimicrobial, anticancer, antidiabetic, antineurodegenerative, and antirheumatic. By oral administration, thymol is rapidly absorbed and eliminated within ~24 h. Thymol sulfate can be found in oral bioavailability (~16%) or plasma (half-life ~1.5 h) and two conjugated forms of thymol sulfate and thymol glucuronide (only at high doses) may be detected in the urine (Figure 1b and c) [9].

Antimicrobial activity

Antibacterial, antifungal, antiviral, and antiparasitic properties have been reported for thymol and essential oils containing thymol. Antibiofilm, antifungal, and antiviral mechanisms of thymol are illustrated in figure 2a-c [9]. Various nanomaterials including self-

*Corresponding author. E-mail: qassim.hassan@qu.edu.iq

assembled nanostructures, liposomes, nanoemulsions, solid lipid nanoparticles (SLNs), metal/metal oxide NPs, and polymer NPs have obtained promising attention to effective formulations of therapeutic compounds [10-12]. A combination of soy lecithin and gelatin was employed to incorporate thymol as a nanoemulsion formulation, followed by incorporation into gelatin film. This nanoemulsion with size range of 137.9 nm to 180.3 nm provided a sustained release (for 72 h at 25 °C) of thymol with increased antibacterial activity. *Bacillus subtilis* and *Escherichia coli* O_{157}:H_7 exhibited 25.28 and 23.07 mm after 4h incubation under this nanoformulation [13].

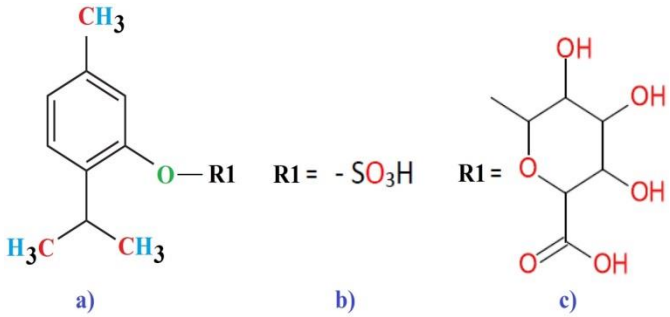

Fig 1. Chemical structure of thymol (a) and two conjugated forms of thymol sulfate (b) and thymol glucuronide (c) (adopted with modification from [9]).

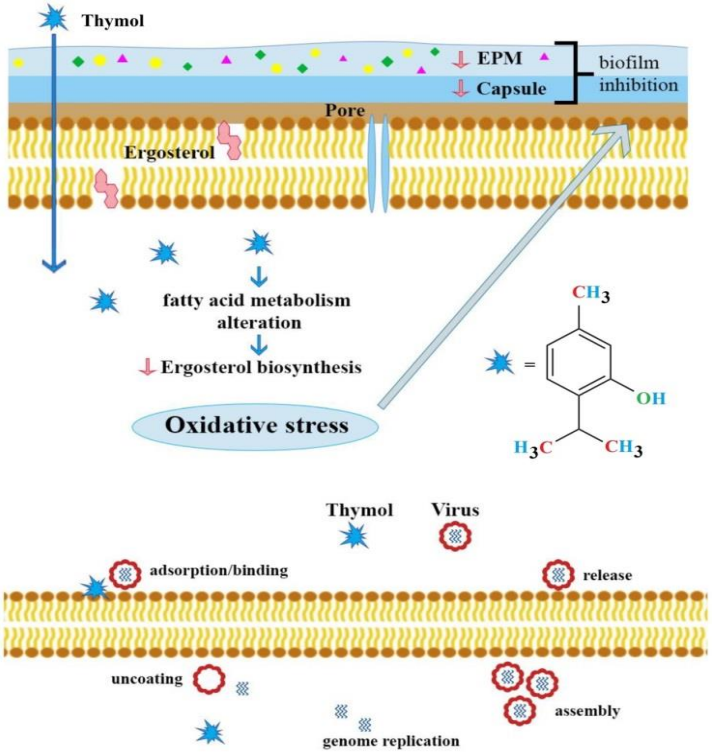

Fig 2. Thymol can bind to membrane ergosterol (a sterol of fungal cell membranes similar to mammalian cholesterol) and augment ionic leakage, finally leading to cell death due to a lack of essential nutrients and biological macromolecules (b). Antiviral mechanisms of thymol as inhibition of the virus-cell membrane fusion and viral assembly inside cells (b) (adopted with modification from [9].

Also, studies demonstrate the antibacterial activities of thymol are different against various gram-positive bacteria. Moreover, investigations evaluated that loading of thymol by nanoemulsion and alginate carrier provided better diffusion in the colloidal medium for the development of antibacterial goal than free thymol due to a reduction in size and more uniform shapes [14, 15]. In this regard, some recent studies showed that the nanoemulsion of thymol, caused high antibacterial activity against *Streptococcus mutans* and
prevent tooth decay [14]. In a comparative study, by the spray-drying technique, thymol was encapsulated layer-by-layer and monolayer. Biofilm formation of *Salmonella* Enteritidis was inhibited and removed under the stress of a combination of two encapsulated thymol after 5 h incubation [16].

Anticancer activity

In most countries, about 8.8 million deaths per year have been reported for patients with malignant neoplasm [17]. Cancer disease remains a major concern owing to the low efficiency of conventional cancer therapies. Cancer is a major problem in many parts of the world. Many anticancer drugs in current clinical use are isolated from plant species. Severe side effects and emerging drug resistance are two main complicated issues for effective cancer therapy. In the case of human U-87 malignant glioblastoma cells (U-87), thymol treatment augmented the expression of p53, Bcl-2-associated X protein (Bax), and apoptosis by excessive reactive oxygen species (ROS) production. The main mechanism for the anticancer of thymol was the arresting of the cell cycle at the G_0/G_1 interface, which was synergized by combination with the temozolomide drug [18]. In 2020, Elbe et al. studied the antiproliferative activity and apoptotic effect of thymol on prostate cancer (PC-3, DU145), breast cancer (MDA-MB-231), and lung cancer (KLN205) cell lines. Their results showed that thymol significantly induces apoptosis in all groups in a dose-dependent manner. Statistical analysis showed a significant difference between different thymol cell lines compared to the control group, and the resulting data showed that thymol has anti-apoptotic and anti-proliferative properties in lung, breast, and prostate cancer cell lines [19]. However, the hydrophobic properties of thymol prevent its wider use. Therefore, new derivatives (acetic acid thymol ester, thymol β-D-glucoside) have been synthesized according to their hydrophilic properties. New thymol derivatives significantly increase ROS production. The results confirmed that the effect of thymol derivatives on tumor cells depends on their chemical structure and dose. However, thymol and its derivatives have great potential in the prevention and treatment of colon cancer, which is one of the most common cancers in the world [20]. In ovarian cancer, which is the seventh most common cancer worldwide among women, many anticancer drugs that are currently used clinically have been isolated from plant species. Thymol and carvacrol act on the SKOV-3 ovarian cancer cell line through anti-proliferative and apoptotic effects and significantly transfer anti-proliferative properties to ovarian cancer cells in a concentration-dependent manner [21].

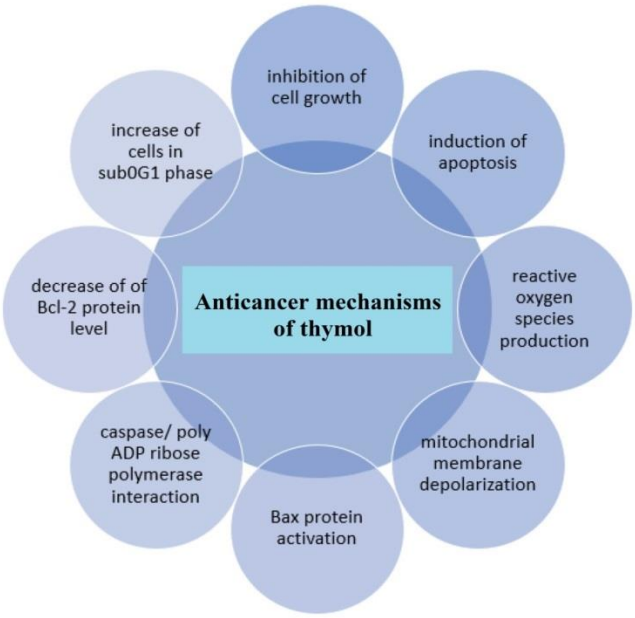

Fig 3. The main antineoplastic mechanisms of thymol (adopted with modification from [9]).

Antidiabetic

Patients with diabetes mellitus, a metabolic disorder, demonstrate a dysfunctional condition of the peripheral nerve named diabetic neuropathy [22]. Thymol isolated from *R. ammi* plant species at concentrations of 20 mg/kg and 10 mg/kg exhibited a reduction of diabetic neuropathy in Streptozotocin-induced diabetic Wistar rats by blocking the elevated cytokines, restoration of levels of Na^+K^+ATPase, decreasing of tumor necrosis factor-α (TNF-α) and NO level. Additionally, the lipid peroxidase enzyme (a marker of oxidative stress levels) was reduced as values of 2.71 nM/mg of protein [7]. Advanced glycation end products (AGE) are glycated proteins or lipids in the bloodstream that can lead to apoptosis in human podocytes (epithelial cells covering the outer surfaces of glomerular capillaries). Thymol can inhibit AGE-induced cell injury in human podocytes via blocking the Ras homolog family member A (RhoA)-Nuclear factor kappa B (NF-κB) pathway. Moreover, thymol demonstrated restoration of the expression of Rho kinase (ROCK), nephrin, vimentin, and podocin [23]. Nanoformulations of bioactive materials specifically herbal metabolites are a novel and effective strategy for improving therapeutic effects. In one study, polymeric NPs modified by oleic acid were used to load thymol. This formulation on high and low doses showed respectively a reduction and increase in brain-derived neurotrophic factor (BDNF) expression on

rat's olfactory ensheathing cells in both high glucose and normal conditions [24]. Type 2 diabetes is a multifaceted metabolic syndrome caused by pancreatic β-cell dysfunction and genetic and environmental factors. Insulin resistance, mediated by interleukins and other inflammatory elements, is one of the key factors in the development of diabetes. Many essential oils obtained from dietary plants are effective against chronic diseases. Plant essential oil compounds such as cinnamaldehyde, carvacrol, zingerone, sclareol, zerumbone, myrtenol, thujone, geraniol, citral, eugenol, thymoquinone, thymol, citronellol, α-terpineol, and linalool have strong antidiabetic effects by modulating different signal transmission pathways related to glucose metabolism. Thymol and other essential oils can significantly inhibit the production of thiobarbituric acid reactive substance (TBARS) and lipid peroxidation (MDA), reduce oxidative stress, increase the level of insulin, adiponectin, and glycoprotein enzymes, and enhance antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase. Also, reduce glutathione and vital glycolytic enzymes. In addition, thymol can significantly reduce the level of liver enzymes and lipid profile markers [25]. Saravanan et al. 2015 showed that thymol is a monoterpene phenol with anti-hyperglycemic and anti-hyperlipidemic medicinal activities and can show promising anti-diabetic activity [26]. Research results have shown that thymol can be safe and beneficial against diabetes and its related complications by affecting different signaling pathways and molecular targets related to glucose metabolism.

Neurodegenerative diseases

Alzheimer's disease (AD)

Unfortunately, there is poor etiology for neurodegenerative diseases such as Alzheimer's disease (AD), multiple sclerosis (MS), and Parkinson's disease (PD). Neuronal damage and protein aggregation followed by the activation of damage-associated molecular patterns (DAMPs) and disease-associated microglia (DAM) lead to oxidative stress and neuroinflammation and are the main hallmarks of neurodegenerative diseases [27]. In addition, microglia respond to DAMPs molecules released from damaged cells by sustained ROS generation. In this way, finding and comprehensive understanding of the molecular mechanisms of neuroinflammation and oxidative stress are the main parameters to improving effective antioxidant therapies. In the case of AD, neuropathologic features are the extracellular accumulation of amyloid β (Aβ), intracellular formation of neurofibrillary tangle formation, and loss of neuronal connections in multiple brain regions [28].

Multiple sclerosis (MS)

Covenantal therapies for MS have not demonstrated inadequate efficiency. This common neurodegenerative disease results from axonal degeneration and loss of myelin (chronic demyelination) as atrophy of the central nervous system [29]. The imbalance between pro-inflammatory (produced by macrophages contributed to the up-regulation of inflammatory reactions such as interferon gamma (IFN-γ), interleukin 17 (IL-17), and IL-6) and anti-inflammatory cytokines such as Transforming growth factor beta (TGF-β), IL-10, and IL-4 can lead to experimental autoimmune encephalomyelitis (EAE) and MS. Biological metabolites such as thymol having antioxidant properties may be the suitable option to attenuate clinical and pathological symptoms of MS disease. *T. vulgaris* (thyme) having thymol has shown significant antioxidant and anti-inflammatory activities. The level of IL-6 and IFN-γ produced by splenocytes was decreased in thyme-treated EAE compared to the control group. Furthermore, TGF-β and IL-10 were augmented in extract-treated mice than the control group [30].

Rheumatoid arthritis (RA)

RA is known as an inflammatory and autoimmune rheumatic disease that causes chronic synovial inflammation followed by the destruction of cartilage and bones [31]. In this disease, activation of immune cells is accelerated via the high production of pro-inflammatory cytokines in the synovial membrane responsible for increased osteoclastic bone resorption [32]. Indeed, the interaction between T-cells, cytokines, and macrophages leads to the imbalance of the immune response in this disease [33]. A combination of thymol and nicotine metabolites showed a synergistic impact on the levels of rheumatoid factor, C-reactive protein, nitric oxide, and myeloperoxidase activity in rats having rheumatoid arthritis. In addition, the highest reduction in IL-17 and

IL-1 levels were indicated for combination therapy at half doses compared with monotherapy of each compound at full doses. There was a synergistic effect by the reduction of IFN-γ, TNF-α, and IL-6 for combination therapy. Moreover, thymol caused a higher reduction in the levels of IL-6 and IL-1β compared to nicotine [34].

Conclusions

In the case of neurodegenerative disease, finding and a comprehensive understanding of the molecular mechanisms of neuroinflammation and oxidative stress are the main factors to developing promising antioxidant therapies. In the case of diabetes, thymol illustrated the reduction of diabetic neuropathy by inhibition of the elevated cytokines, restoration of levels of Na^+K^+ATPase, and decreasing of tumor necrosis factor-α (TNF-α) and NO levels. Moreover, loading thymol by modified polymeric NPs on high and low doses showed respectively a reduction and increase in brain-derived neurotrophic factor (BDNF) expression in both normal and high glucose conditions. For anticancer mechanism, the arresting of the cell cycle at the G_0/G_1 interface was found for thymol against human malignant glioblastoma cells.

Study Highlights

- Thymol illustrated reduction of diabetic neuropathy by inhibition of the elevated cytokines, restoration of levels of Na^+K^+ATPase, decreasing of tumor necrosis factor-α (TNF-α) and NO level.
- Loading thymol by modified polymeric NPs on high and low doses showed respectively a reduction and increase in brain-derived neurotrophic factor (BDNF) expression in both normal and high glucose conditions.
- For anticancer mechanism, the arresting of the cell cycle at the G0/G1 interface was found for thymol against human malignant glioblastoma cells.

Abbreviations

AD: Alzheimer's disease
AGE: Advanced glycation end products
Aβ: Amyloid β
Bax: Bcl-2-associated X protein
BDNF: Brain-derived neurotrophic factor
DAM: Disease-associated microglia
DAMPs: Damage-associated molecular patterns
EAE: Experimental autoimmune encephalomyelitis
IFN-γ: Interferon gamma
IL-17: Interleukin 17
MDA: Lipid peroxidation
MS: Multiple sclerosis
NF-κB: Nuclear factor kappa B
PD: Parkinson's disease
RA: Rheumatoid arthritis
RhoA: Ras homolog family member A
ROCK: Rho kinase
ROS: Reactive oxygen species
TBARS: Thiobarbituric acid reactive substance
TGF-β: Transforming growth factor beta
Thyme: *T. vulgaris*
TNF-α: Necrosis factor-α

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Authors' contribution

All authors: conceptualization, preparing the first draft, and revising the manuscript.

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