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Review

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Tea tree oil, a vibrant source of neuroprotection via neuroinflammation inhibition: a critical insight into repurposing *Melaleuca alternifolia* by unfolding its characteristics

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Abstract: Over the past few decades, complementary and alternative treatments have become increasingly popular worldwide. The purported therapeutic characteristics of natural products have come under increased scrutiny both in vitro and in vivo as part of efforts to legitimize their usage. One such product is tea tree oil (TTO), a volatile essential oil primarily obtained from the native Australian plant, *Melaleuca alternifolia*, which has diverse traditional and industrial applications such as topical preparations for the treatment of skin infections. Its anti-inflammatory-linked immunomodulatory actions have also been reported. This systematic review focuses on the anti-inflammatory effects of TTO and its main components that have shown strong immunomodulatory potential. An extensive literature search was performed electronically for data curation on worldwide accepted scientific databases, such as Web of Science, Google Scholar, PubMed, ScienceDirect, Scopus, and esteemed publishers such as Elsevier, Springer, Frontiers, and Taylor & Francis. Considering that the majority of pharmacological studies were conducted on crude oils only, the extracted data were critically analyzed to gain further insight into the prospects of TTO being used as a neuroprotective agent by drug formulation or dietary supplement. In addition, the active constituents contributing to the activity of TTO have not been well justified, and the core mechanisms need to be unveiled especially for anti-inflammatory and immunomodulatory effects leading to neuroprotection. Therefore, this review attempts to correlate the anti-inflammatory and immunomodulatory activity of TTO with its neuroprotective mechanisms.

Key words: Tea tree oil; Anti-inflammatory; Anti-viral; Antibacterial; Terpinen-4-ol; 1,8-Cineole; Neuroprotective effect

1 Introduction

Plants have long served as an important drug source for various human ailments. Many significant medications that are still in use today, such as artemisinin, vincristine, and gentamicin, were developed using the structural fingerprints of naturally occurring plant compounds (Küpeli Akkol et al., 2021). As a result, plant products constitute an essential basis for creating natural medications, while plant extracts and essential oils (EOs) have been used as genuine sources of useful constituents in agriculture, medicine, foods, cosmetics, and other fields for many years (Ferrentino et al., 2020). EOs are volatile substances produced in various plant organs such as buds, branches, fruits, leaves, flowers, seeds, stems, and roots, and they possess distinctive biological functions (Jain et al., 2022). Their affordability, safety, diversity, and compliance are thought to make them a trusted and dependable source of medicine. There have been claims that a variety of herbal medicines, particularly plant extracts, are used in conventional medicine for neuroprotective, memory-improving, and antiaging purposes. Due

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to consumer worries regarding the harmful and negative consequences of synthetic neuroprotective medications, EOs have become extremely popular as natural therapeutics. *Bacopa monnieri*, *Curcuma longa*, *Ginkgo biloba*, *Panax ginseng*, and *Salvia officinalis* are among the major neuroprotective plants that have been studied extensively to confirm their traditionally claimed effects, with special regard to their mechanisms of neuroprotective action (Kumar et al., 2012).

Melaleuca alternifolia, commonly known as tea tree, is a small tree or tall shrub of the Myrtle family. It is native to Southeast Queensland and the northeast coast of New South Wales, Australia, and is also grown in Europe and North America (Carson et al., 2006). The leaves have alternate or scattered arrangement and are rich in oil, known as tea tree oil (TTO) or melaleuca oil. TTO is an EO of fresh camphoraceous odor and a color ranging from pale yellow to nearly colorless and clear. It is extracted by steam distillation of the leaves and terminal branches of the *M. alternifolia* plant (Carson et al., 2006). TTO contains diverse classes of secondary metabolites, with the most prevalent ones being terpinen-4-ol, γ-terpinene, α-terpinene, and 1,8-cineole. The gas chromatography/mass spectrometry (GC/MS) characterization of major chemical constituents of TTO from 97 commercial samples are summarized in Table 1 (Hart et al., 2000).

TTO is notable for its antifungal, antibiotic, and topical applications for treating dandruff, acne, lice, scabies, insect bites, herpes, and skin infections. It has

Table 1 Physical and chemical properties of *Melaleuca aternifolia* leaf extract, tea tree oil, and leaf oil

Property	Description	Reference
Tea tree leaf extract		
Physical characteristics	Translucent yellow to brown mobile liquid with a characteristic odor	Native Extracts, 2020
Solubility	Soluble in water	Native Extracts, 2020
Specific gravity (at 20 °C)	1.130–1.280	Native Extracts, 2020
Tea tree oil		
Physical characteristics	Colorless to pale yellow, clear, mobile liquid with a “characteristic” odor;	ATTIA, 2020
	Colorless to pale yellow, clear, mobile liquid that has a “terpeny,” coniferous and “minty-camphoraceus” odor;	WHO, 2012
	Colorless to pale yellow liquid with a myristic odor;	RIRDC, 2007
	Clear colorless liquid with a green/yellow tinge and “antiseptic” odor	ECHA, 2021
Solubility	Insoluble in water; soluble in two volumes of 85% ethanol (20 °C); Sparingly soluble in water; miscible with non-polar solvents	SCCP, 2008
Boiling point (°C)	97–220	ECHA, 2021
Freezing point (°C)	−22	ECHA, 2021
Optical rotation	+7° to +12°	ATTIA, 2020
Vapor pressure (Pa at 25 °C)	2100	SCCP, 2008
Tea tree leaf oil		
Physical characteristics	Pale yellow to yellow clear mobile liquid with a myristic, characteristic odor	Native Extracts, 2020
Solubility	Insoluble in water 332.1 mg/L at 25 °C (estimated); One part miscible with two parts of ethanol (85%, volume fraction) at 20 °C; Soluble in alcohol, fixed oil, paraffin oil; insoluble in glycerin; Miscible in non-polar solvents	Native Extracts, 2020
Boiling point (°C)	97–220	Native Extracts, 2020
Freezing point (°C)	−22	Native Extracts, 2020
Optical rotation	+7° to +12°	Native Extracts, 2020
	+5° to +15°	TGSC Information System, 2015
Relative density	0.885–0.906	TGSC Information System, 2015
Refractive index (at 20 °C)	1.475–1.482	Native Extracts, 2020

been proposed as a good alternative for treating microbial infections in combination with other drugs because of its efficacy in case of resistant microorganisms. In addition to killing insects, TTO has been shown to alter the expression of various genes. It also has a potent antiviral effect both in vaporized and aerosolized forms, indicating its potential in disinfecting applications. The above effects have been ascertained by the Australian tea tree industry, which released the data for using TTO as sanitizers, vaporisers, or heating, ventilation, and air conditioning (HVAC) inserts and as a surface cleaning product (Usachev et al., 2013). Another study proposed that, based on its virucidal effectiveness against feline coronavirus type II (FCoVII) and human coronavirus OC43 (HCoV-OC43) as well as alterations in the physical features and structural organization of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) envelope, TTO might be a potential disinfectant to stop the transmission of SARS-CoV-2 virus (Romeo et al., 2022). The components of TTO, including terpinen-4-ol and α-terpineol, are thought to be crucial in immunomodulation via inhibiting the synthesis of interleukin (IL)-1β, IL-6, and IL-10 in human macrophages (Nogueira et al., 2014). The antiseptic and anti-inflammatory uses of TTO have been historically capitalized and well documented (Carson et al., 2006). Despite a lot of beneficial uses of TTO, some adverse reactions and safety concerns such as skin irritation, dermatitis, and allergic reactions warrant its advanced applications (Lin et al., 2018). An optimum dose of TTO (100 mg/kg) was reported to enhance antioxidant activity and autophagy intensity through the *Relish-Imd* pathway by increasing lipid droplet breakdown (Liu et al., 2022). Some of the compounds of TTO have been found to be potential neurotherapeutic drugs, but few studies have formulated hypotheses to postulate its neuroprotective effect. Therefore, we conduct a systematic review to fill the research gap between existing knowledge and the prospective use of TTO, to provide an insight into its use as a neuroprotective agent, focusing on its anti-inflammatory, immunomodulatory, and antioxidative actions. We provide a broad discussion of the phytochemical, biological, and medicinal values of TTO, especially regarding its neuronal advantages for prospective therapeutic developments.

2 Inclusion and exclusion criteria

Our investigation targeted the direct and indirect uses of TTO and its benefits leading to the neuroprotective effects of TTO. We included the phytoconstituents of TTO and their biological functions, especially antioxidant, anti-inflammatory, growth regulatory, neuroprotective, and other relevant effects in various in vitro, in vivo, and ex vivo models. On the other hand, the effects of TTO revealed by in silico models and the use of chemically synthesized derivatives of TTO have been excluded.

3 Methods and search for the study

This systematic review was designed and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2020, while incorporating the updated scientific databases of TTO. To retrieve the data on TTO, the major keyword combinations for the search were as follows: tea tree oil, *Melaleuca alternifolia*, anti-inflammatory and antioxidative effects of TTO, pharmacological and biological potentials of *Melaleuca alternifolia*, industrial use of tea tree oil, and phytochemicals of tea tree oil. Google was used as the search engine to gather information for the extensive literature review involving the Web of Science, Google Scholar, PubMed, ScienceDirect, and Scopus databases. Articles published by esteemed publishers, such as Elsevier, Springer, Frontiers, Taylors and Francis, were prioritized for citation.

4 Data curation

4.1 Chemical composition of TTO

TTO is a volatile aromatic oil extracted primarily from *M. alternifolia*. Volatile aromatic oils mainly contain terpenes as the primary phytochemical class of TTO, such as monoterpenes, sesquiterpenes, and their associated alcohols (Thosar et al., 2013) (Table 2). Early reports on the composition of TTO showed that it contains over 100 components, the majority being monoterpene and sesquiterpene hydrocarbons and their alcohols. About 1.0%–1.8% (yield value) of EOs from the leaves and terminal branches of *M. alternifolia*

have been isolated (Hammer et al., 1996; de Groot and Schmidt, 2016). By using GC and CG-MS to analyze more than 800 TTO samples, Brophy et al. (1989) revealed the presence of about 100 components and the concentration ranges for each (Table 3), although early reports on the TTO composition described twelve (Christoph et al., 2000), twenty (Choi and Kang, 2017), or forty-eight (D'Auria et al., 2001) components. Advanced studies on the GC/MS profile of TTO showed that 4-terpineol (48.7%) was present as a main constituent, followed by terpinene (12.7%), γ-terpinene (10.4%), cineol (7.3%), *p*-cymene (4.1%), α-pinene (2.5%), α-terpineol (2.0%), α-terpinolene (1.0%), and α-*p*-cyeme-8-ol (0.4%) (Ramage et al., 2012). Instead of the species of *Melaleuca*, the ingredients and their percentage lay forth the physical and chemical requirements for the desired chemotype. Six varieties of *M. alternifolia* have been described, each producing oil with a distinct chemical composition, namely the terpinen-4-ol chemotype, a terpinolene chemotype, and four 1,8-cineole chemotypes. The terpinen-4-ol chemotype is used for producing commercial TTO, which has a terpinen-4-ol content between 30% and 40% (Homer et al., 2000). The composition of TTO changes depending on the location, manufacturing process, age of oil, and whether oxidation has taken place. For instance, the age of leaves, method of production (such as commercial steam distillation or laboratory hydrodistillation), time of year, leaf maceration, biomass used (such as wild or domesticated trees, leaves only, or leaves and branchlets), and the duration of distillation can all significantly affect the natural content of the various constituents of TTO (Brophy et al., 1989; de Groot and Weyland, 1992). As mentioned above, the age of the oil can also affect its composition. A study that analyzed new and old TTOs using GC/MS discovered that the quantities of α-terpinene were 10%–11% in recently obtained oil, 5% in oil that was 10 years old, and 8% in oil that was older than 10 years. Over fifty oxidation byproducts of α-terpinene were found in the samples, including *p*-cymene, 1,2-epoxide, diol, and (E)-3-isopropyl-6-oxohept-2-enal; however, the authors could not rule out the possibility that these byproducts originated from another compound found in TTO. Table 4 compares the levels of *M. alternifolia* monoterpenoid compounds found in aged oils with varied rates of deterioration (Brophy et al., 1989).

4.2 Neuroprotective effects of TTO

The neuroprotective effects of TTO have been defined in the context of a spectrum of biological events that appeared to be influenced by *M. alternifolia* (Fig. 1), as described below.

Table 2 Chemical constituents of tea tree oil (identified from 97 commercial tea tree oil samples[*]) identified by CG-MS

Constituent	Concentration (%)	Constituent	Concentration (%)
Terpinen-4-ol	6.2–44.9	α-Gurjunene	0.2–1.0
1,8-Cineole	0.5–18.3	α-Eudesmol	0.03–0.50
α-Terpinene	2.3–11.7	*cis*-3-Hexenyl acetate	0–0.02
Terpinolene	0.04–45.70	*cis*-3-Hexen-1-ol	0.01–0.07
γ-Terpinene	3.1–23.0	α-Humulene	Trace–0.2
Limonene	0.5–3.0	Linalool	0.06–0.80
α-Terpineol	1.9–4.2	Ledol	0.02–0.30
Sabinene	0.03–1.30	*p*-Menth-2-en-1-ol	0.04–0.70
Aromadendrene	0.1–0.2	Methyleugenol	0.01–0.40
δ-Cadinene	0.1–1.9	γ-Muurolene	0–0.3
Globulol	0.02–0.60	Myrcene	0.2–4.1
Viridiflorol	0.08–0.80	α-Phellandrene	0.2–0.6
α-Pinene	1.8–9.2	β-Phellandrene	Trace–5.2
p-Cymene	0.3–19.4	β-Pinene	0.3–1.7
Ledene	0.3–2.1	Piperitol	0.05–0.30

[*] Samples were collected from Australia, Vietnam, and China. CG-MS: gas chromatography-mass spectrometry.

Table 3 Variation in the chemical constituents of tea tree oil based on its nature and collection method

Method	Aromadendrene (%)	Limonene (%)	1,8-Cineole (%)	Globulol (%)	α-Terpineol (%)
Steam distillation (WHO, 2012)	NR	1.0–5.0	4.5–16.5	NR	NR
Supplier information (GC) (EODL, 2011)	Trace–3.0	0.5–1.5	Trace–15.0	Trace–1.0	1.5–8.0
Test samples (steam-distilled; GC or GC/MS) (Brophy et al., 1989)	1.5	1.0	5.1	0.2	2.4
Test sample (GC/MS) (Hammer et al., 2016)	1.0	0.9	2.1	0.6	2.9
Test sample (steam-distilled from leaves; GC/MS) (Lee KAYR et al., 2020)	<0.1	0.5	1.7	0.3	3.0
Essential oil (from leaves) (Tisserand and Young, 2014)	2.1	1.1	3.1	NR	2.8

Method	α-Terpinene (%)	Terpinen-4-ol (%)	Ledene (%)	δ-Cadinene (%)	*p*-Cymene (%)
Steam distillation (WHO, 2012)	2.7–13.0	29.0–45.0	NR	NR	1.0–5.0
Supplier information (GC) (EODL, 2011)	5.0–13.0	30.0–48.0	Trace–3.0	Trace–3.0	0.5–8.0
Test samples (steam-distilled; GC or GC/MS) (Brophy et al., 1989)	10.4	40.0	NR	1.3	2.9
Test sample (GC/MS) (Hammer et al., 2016)	10.2	41.5	NR	1.0	1.5
Test sample (steam-distilled from leaves; GC/MS) (Lee KAYR et al., 2020)	9.6	47.3	NR	NR	1.5
Essential oil (from leaves) (Tisserand and Young, 2014)	9.6	39.8	1.8	1.6	2.7

Method	γ-Terpinene (%)	α-Pinene (%)	Sabinene (%)	Terpinolene (%)	Viridiflorol (%)
Steam distillation (WHO, 2012)	10.0–28.0	1.0–5.0	NR	1.0–5.0	NR
Supplier information (GC) (EODL, 2011)	10.0–28.0	1.0–6.0	Trace–3.5	1.5–5.0	Trace–1.0
Test samples (steam-distilled; GC or GC/MS) (Brophy et al., 1989)	23.0	2.6	0.2	3.1	0.1
Test sample (GC/MS) (Hammer et al., 2016)	21.2	2.5	0.4	3.5	0.3
Test sample (steam-distilled from leaves; GC/MS) (Lee KAYR et al., 2020)	20.6	2.0	1.6	3.0	NR
Essential oil (from leaves) (Tisserand and Young, 2014)	20.1	2.4	NR	3.5	NR

NR: not reported; GC/MS: gas chromatography/mass spectrometry.

4.2.1 Neuroprotection via metabolic upregulation

A variety of natural compounds, especially plant extracts from *G. biloba*, *C. longa*, *P. ginseng*, *B. monnieri*, and *S. officinalis*, have been utilized in traditional medicine for neuroprotective, memory-improving, and anti-aging purposes (Kumar et al., 2012). Neurodegenerative diseases of the human brain include a wide range of disorders that affect an increasing proportion of the population. Abnormal metabolic processes may influence the deleterious neuronal effects to cause neurodegenerative diseases. TTO exerts impacts over some of those metabolic processes including the sphingolipid metabolism, which opens a new therapeutic opportunity for brain degenerative disorders. Sphingolipids, long thought to be merely ubiquitous cell membrane components, play a crucial role in controlling essential cell processes and the development of membrane microdomains known as "lipid rafts" that coordinate cell signaling. They support the early growth and development of neuronal cells, and at low levels, promote cell survival and division (Mullen et al., 2012; Czubowicz and Strosznajder, 2014). TTO has been reported to upregulate the sphingolipid metabolism to maintain cellular concentrations, thereby affecting the mitochondrial metabolic process and assisting with neuronal protection (Fig. 2).

4.2.2 Neuroprotection via anti-inflammation and immunomodulation

Inflammation and oxidative stress are important components of the pathology of chronic neurodegenerative conditions, including Alzheimer's disease (AD),

Table 4 Comparison of monoterpenoid composition of aged oils of *M. alternifolia*

Age of sample (year)	Relative deterioration rate	α-Pinene (%)	Sabinene (%)	α-Terpinene (%)	Limonene (%)	*p*-Cymene (%)	1,8-Cineole (%)	γ-Terpinene (%)	Terpinolene (%)
Unaged sample		2.60	0.20	10.40	1.00	2.90	5.10	23.00	3.10
1	Moderate	2.50	Trace	6.60	NR	8.00	NR	17.60	3.10
2	Rapid	2.00	Trace	0.10	NR	35.30	NR	Trace	Trace
5	Rapid	Trace	NR	NR	NR	21.70	NR	Trace	Trace
10	Rapid	3.20	0.10	0.20	NR	32.00	NR	Trace	Trace
10	Slow	2.20	NR	5.80	NR	4.30	NR	15.90	2.70

Age of sample (year)	Relative deterioration rate	Terpinen-4-ol (%)	α-Terpineol (%)	Limonene/ β-phellandrene/ 1,8-cineolea (%)	α-Thujenea (%)	β-Pinenea (%)	Myrcenea (%)	α-Phellandrenea (%)	1,2,4-Trihydroxymenthanea (%)
Unaged sample		40.00	2.40	NR	0.90	0.30	0.50	0.30	Trace
1	Moderate	37.30	2.90	8.00	0.80	0.70	0.70	0.40	Trace
2	Rapid	23.80	8.20	35.30	0.20	0.40	0.10	Trace	3.60
5	Rapid	45.90	9.60	21.70	NR	Trace	Trace	NR	2.50
10	Rapid	31.50	6.40	32.00	NR	0.30	0.20	Trace	4.60
10	Slow	41.60	3.70	4.30	0.60	0.60	0.50	0.20	Trace

NR: not reported.

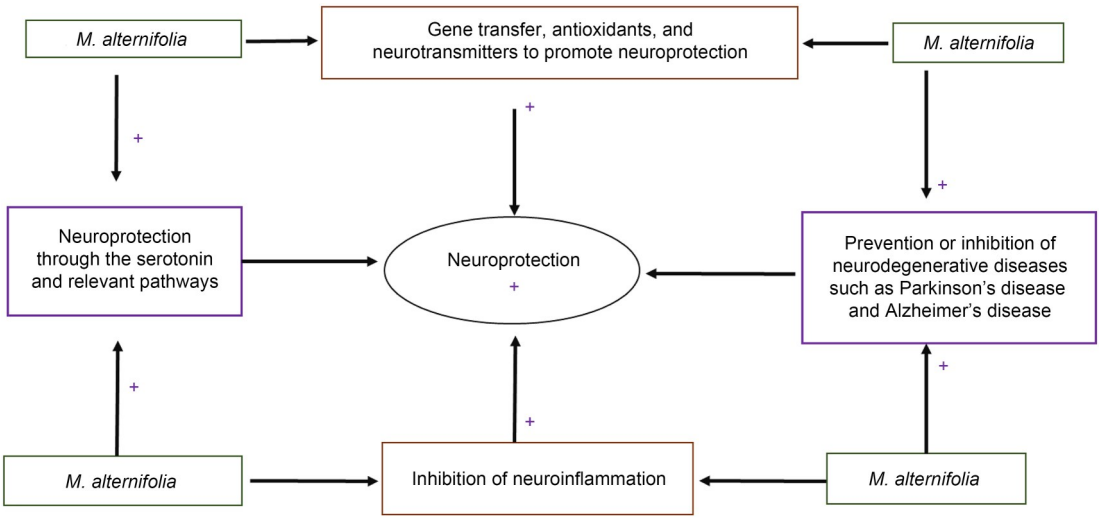

Fig. 1 Possible ways of neuroprotection by *Melaleuca alternifolia*. The strong antioxidative and anti-inflammatory potential of *M. alternifolia* tea tree oil (TTO) is evident, which affects several pathways and modulators delineated into other figures.

Down syndrome, and multiple sclerosis (Aruoma et al., 2003). One of the major neurodegenerative conditions, AD, is characterized by neuroinflammation, cognitive loss, oxidative stress, the accumulation of amyloid-beta (Aβ) plaques, the hyperphosphorylation of tau proteins, and the formation of neurofibrillary tangles from these proteins (Lecomte et al., 2010). Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes associated with the building of Aβ plaques and excessive lipoxidase (LOX) activity cause neuroinflammation and synaptic malfunction in AD patients via the generation of inflammatory and immune response mediators (Joshi and Praticò, 2015; AlFadly et al., 2019; Rojas-García et al., 2023). In addition, AD patients also have decreased levels of glutathione peroxidase (GPx) and superoxide dismutase (SOD) enzymes, which accelerate oxidative stress and the build-up of free radicals like reactive oxygen species

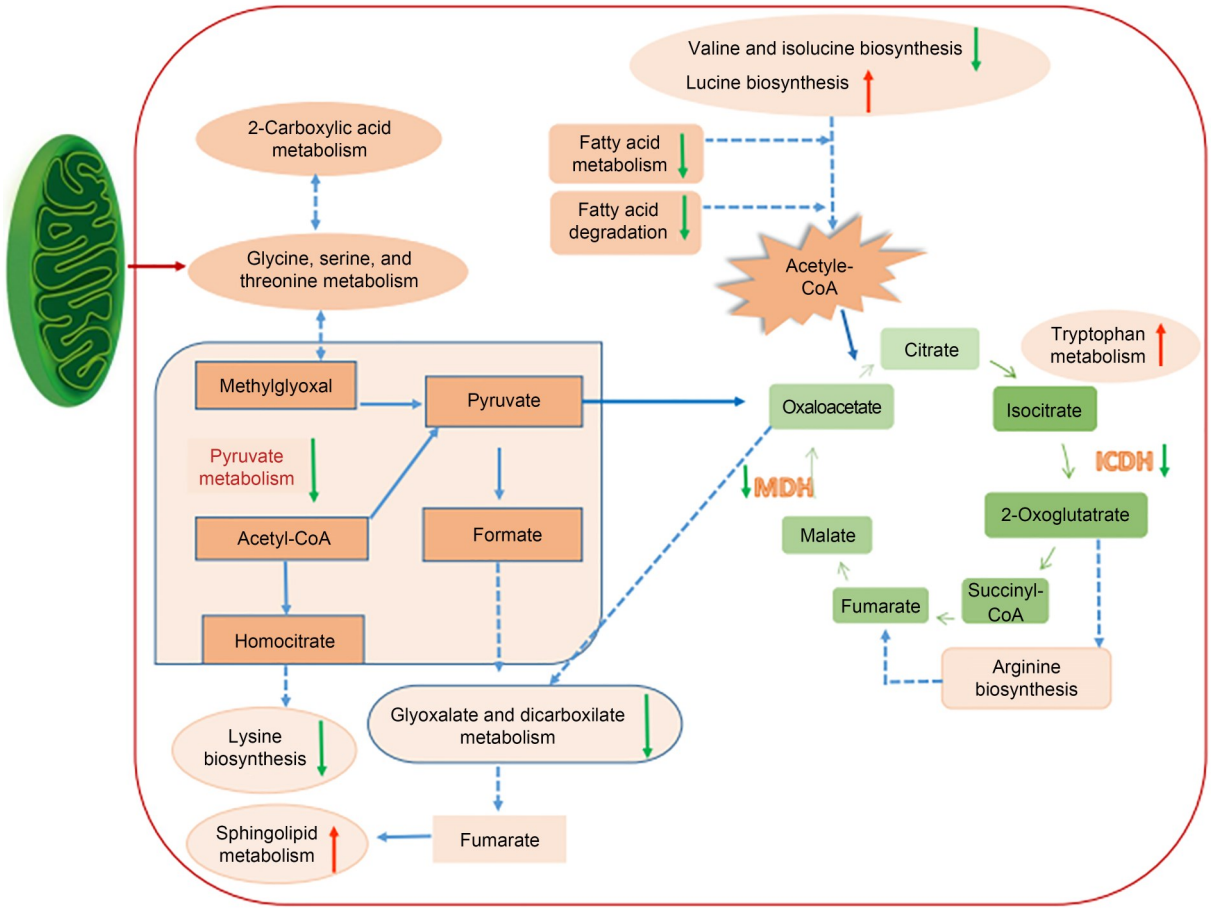

Fig. 2 Roles of tea tree oil (TTO) in the metabolic processes. Decreases in malonaldehyde (MDH), isocitrate dehydrogenase (ICDH), fatty acid metabolism, and pyruvate metabolism, while an increase in sphingolipid, are caused by TTO to foster its neuroprotective effect. CoA: coenzyme A.

(ROS) and reactive nitrogenous species (RNS). As a result, neuronal cell death occurs in the last step due to mitochondrial alteration and changes in the permeability of the cellular membrane (Pizzino et al., 2017).

Therefore, the optimization of oxidative stress by antioxidant properties, the optimization of neuroinflammation through anti-inflammatory action, and inhibition of AChE, BChE, and LOX, as a whole, can be effective strategies in preventing neuronal cell death (Hatami et al., 2023) (Fig. 3). However, the synthetic neuroprotective agents available in clinical practice are not effective in all cases.

Moreover, side effects and drug interactions are major limitations for their clinical utility. Therefore, phytopharmaceuticals have become an alternative approach worldwide, as they are safer, more economical, and more effective, and achieve more rational results (Hussain et al., 2021; Mohamed et al., 2021).

TTO was previously described to possess anti-inflammatory properties (Hart et al., 2000). Apart from *M. alternifolia*, large amounts of terpenes or terpene derivatives from natural sources have been reported to exhibit antioxidant, anti-inflammatory, and anticholinesterase bioactivity (Min et al., 2022). TTO and its components (terpinen-4-ol and α-terpineol) were noticed to exert a significant immunomodulatory role via reducing the production of tumor necrosis factor-α (TNF-α), IL-1β, IL-6, IL-10, and prostaglandin E2 (PGE2) in lipopolysaccharide (LPS)-stimulated macrophages, implying its effectiveness in preventing neuroinflammation (Hart et al., 2000) (Fig. 3). In an Australian study, 100% TTO was applied topically on 21 volunteers at the dose of 25 μL, and its effect on histamine-induced weal and flare was analyzed. It was found to significantly decrease the flare after ten minutes of the administration of the doses. The study concluded that TTO could reduce histamine-induced

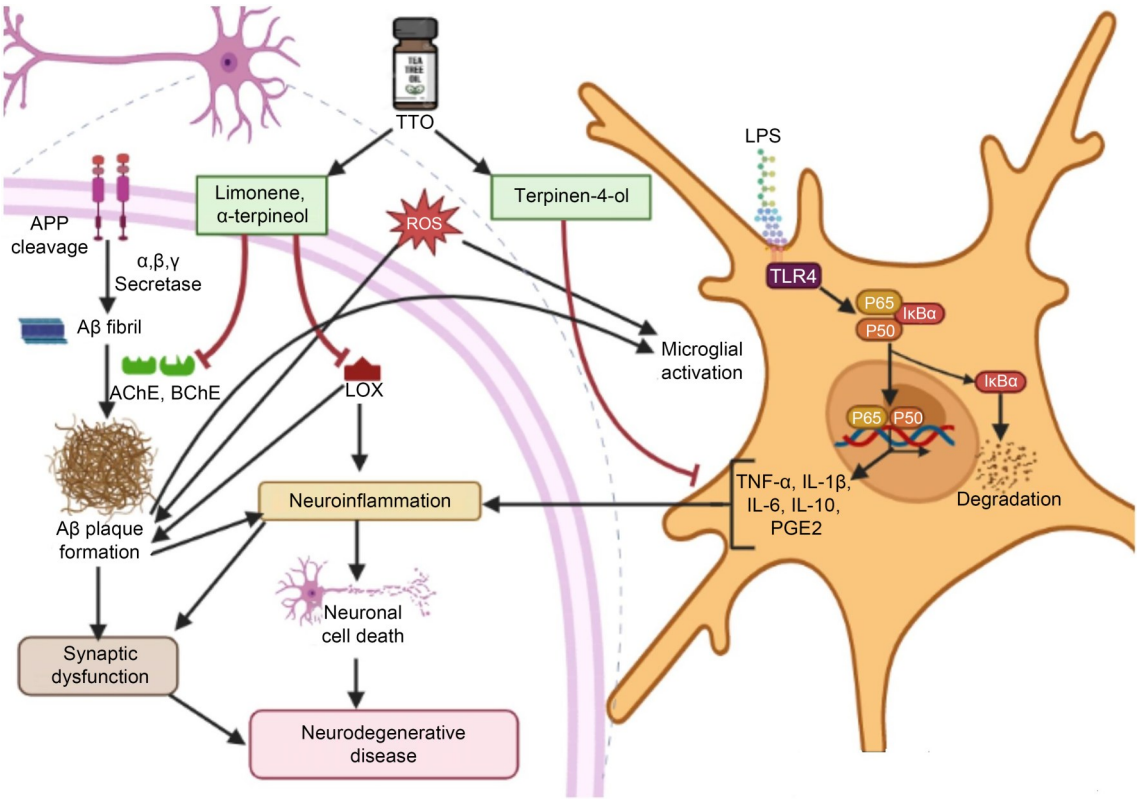

Fig. 3 Effects of TTO on the neuroprotective molecules. Three major compounds of TTO, limonene, α-terpineol, and terpinen-4-ol, inhibit the enzymes acetyl choline esterase, butyl choline esterase, and lipoxygenase, which ultimately arrest neuroinflammation and inhibit neuronal death. TLR-induced anti-inflammatory interleukins (triggered by microglial activation trough Aβ plaque formation) are also inhibited by terpinen-4-ol. TTO: tea tree oil; APP: amyloid precursor protein; AChE: acetylcholinesterase; BChE: butyrylcholinesterase; LOX: lipoxigenase; LPS: lipopolysaccharide; TLR: Toll-like receptor; IκB: inhibitor of NF-κB; TNF-α: tumor necrosis factor-α; PGE2: prostaglandin E2; ROS: reactive oxygen species.

inflammation (Koh et al., 2002). In another study, TTO at the dose of 0.125% was evaluated in vitro for the examination of human peripheral blood monocytes through the LPS-induced production of TNF-α, IL-1β, IL-8, IL-10, and PGE2 (Hart et al., 2000). The demonstrated dose of TTO significantly suppressed the LPS-induced production of these cytokines. However, the same study also evaluated the effects of the water-soluble components of TTO, namely, terpinen-4-ol, α-terpineol, and 1,8-cineole. Terpinen-4-ol significantly suppressed the production of TNF-α, IL-1β, IL-8, IL-10, and PGE2 by LPS-activated monocytes after 40 h from the administration of test dose (Hart et al., 2000). Several monoterpenes and sesquiterpenes, such as limonene, α-terpineol, and β-caryophyllene, have been reported as cholinesterase (AChE and BChE) inhibitors as well as effective LOX inhibitors (Hung et al., 2022). Moreover, mono- and sesquiterpenoid hydrocarbons like limonene or valencene have been found to show high blood-brain barrier (BBB) permeability (Sánchez-Martínez et al., 2021).

TTO significantly contributes to lipid metabolism, alleviating the inflammatory responses. As is known, fatty liver is associated with lipid accumulation in hepatocytes, leading to inflammation. Using a palmitic acid-induced lipid accumulation assay, Yang et al. (2022a) showed that TTO reduces triglyceride (TG) content by inhibiting the expression of sterol regulatory element-binding protein 1C (SREBP1C) and its target genes involved in fatty acid synthesis. SREBPs are the transcription factors that promote the gene expression of lipogenesis and fatty acid synthesis, while SREBP1C modulates the genes including acetyl-coenzyme A (CoA) carboxylase 1 (*ACC1*) and fatty acid synthesis (*FAS*), which are necessary for fatty acid synthesis and deposition (Lecomte et al., 2010). Furthermore, TTO upregulates the downstream targets (carnitine palmitoyl transferase 1A (CPT1A) and CPT2) of

peroxisome proliferator-activated receptor α (PPARα), an essential process controlling mitochondrial and fatty acid oxidation in ruminants (Deng et al., 2015) (Fig. 4).

These findings imply that the addition of TTO regulates the expression of important enzymes in palmitic acid-induced bovine hepatocytes, promoting lipid oxidation and inhibiting lipid synthesis. The

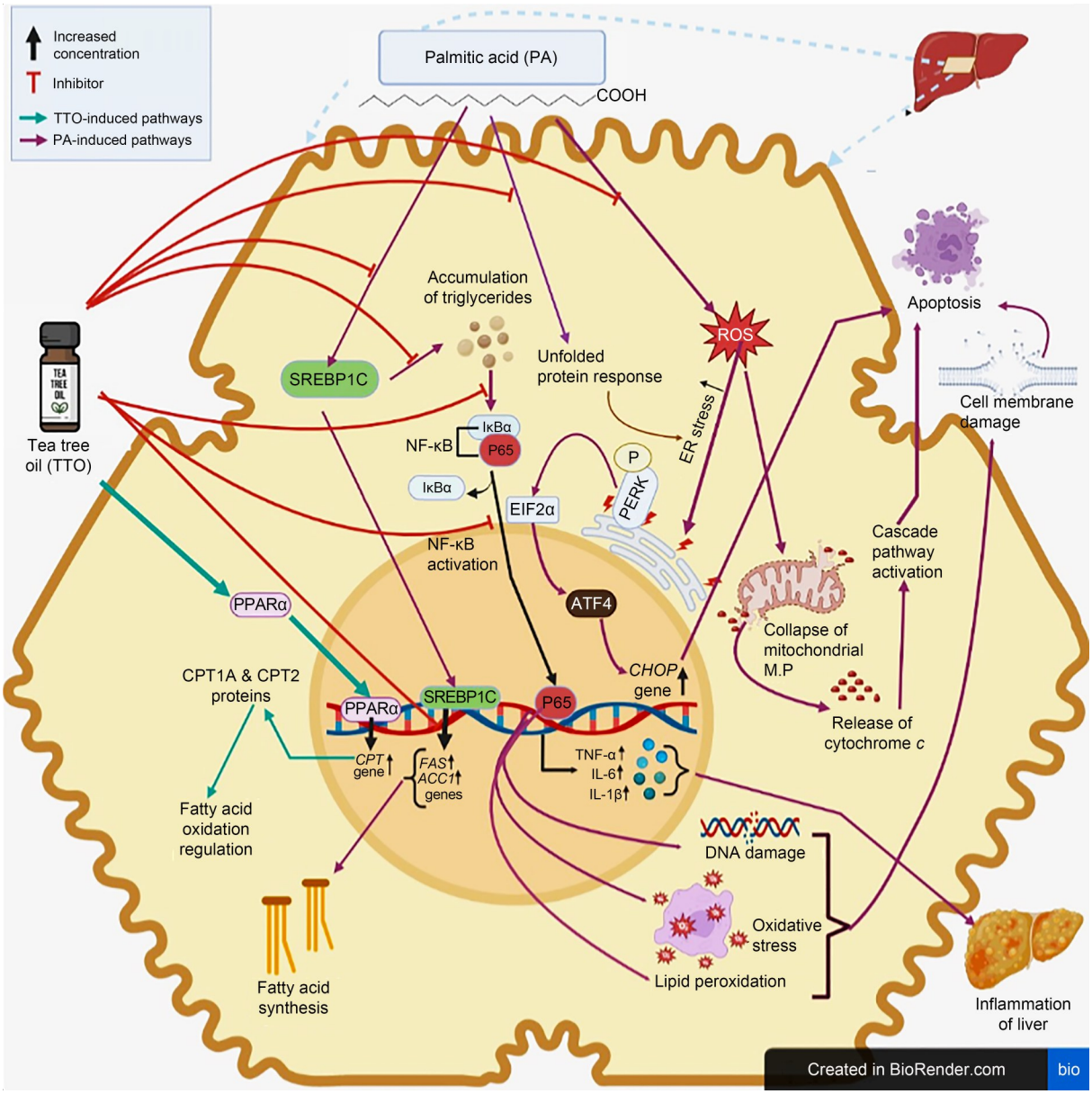

Fig. 4 Effects of tea tree oil (TTO) on palmitic acid (PA)-induced inflammation. PA activates the SREBP1C, the accumulation of triglycerides, and ROS production. TTO inhibits NF-κB activation, which eventually deactivates TNF-α, IL-6, and IL-1β that are responsible for liver inflammation. The activation of PPARα promotes the uptake, utilization, and catabolism of fatty acids by upregulating genes involved in fatty acid transport, fatty acid binding and activation, and peroxisomal mitochondrial fatty acid β-oxidation, thus substantially regulating fatty acid oxidation. ROS: reactive oxygen species; NF-κB: nuclear factor-κB; TNF-α: tumor necrosis factor-α; IL: interleukin; PPARα: peroxisome proliferator-activated receptor α; CPT: carnitine palmitoyl transferase; ACC1: acetyl-coenzyme A (CoA) carboxylase 1; FAS: fatty acid synthesis; IκB: inhibitor of NF-κB; SREBP1C: sterol regulatory element-binding protein 1C; EIF2α: eukaryotic initiation factor-2α; PERK: protein kinase R-like endoplasmic reticulum kinase; ER: endoplasmic reticulum; M.P: membrane potential; ATF4: activating transcription factor 4; CHOP: C/EBP-homologous protein; P: phosphorylation.

accumulation of TG over time can activate the nuclear factor-κB (NF-κB) pathway and exacerbate inflammation, as demonstrated by Angulo (2002) and Yang et al. (2022a). Furthermore, TTO has been shown to exhibit anti-inflammatory and antioxidative properties by inhibiting NF-κB, which plays a crucial role in the intracellular regulation of inflammation. (Yang et al., 2022b). TTO also prevents NF-κB and inhibitor of NF-κB (IκB) phosphorylation, which is important for NF-κB activation and the expression of inflammatory cytokines, including TNF-α and IL-6 (Barnes and Karin, 1997). According to Blaser et al. (2016), the activation of NF-κB can directly or indirectly damage cells by causing oxidative stress, DNA damage, and lipid peroxidation, thus destroying cell membranes, promoting mitochondrial fission, and ultimately resulting in cell death.

Terpinen-4-ol, the major bioactive compound found in TTO, has demonstrated its remarkable role in other experimental models of inflammation and immunomodulation. Ninomiya et al. (2013) used a murine oral candidiasis model to indicate the anti-inflammatory role of terpinen-4-ol, where 50 μL (40 mg/mL) of terpinen-4-ol significantly removed the inflammation produced in *Candida albicans*-induced inflammation in immunosuppressed mice. Terpinen-4-ol also clearly inhibited cytokine production by macrophages cultured in the presence of heat-killed *C. albicans* cells in vitro. Moreover, TTO was found to decrease the sensory neuropeptide-mediated histamine-induced vascular changes in human and rat inflammatory microvascular events (Khalil et al., 2004). An in vitro study of TTO showed a significant reduction in superoxide production by neutrophils induced by *N*-formyl-methionyl-leucyl-phenylalanine (fMLP) and LPS, suggesting the ability of the bioactive ingredients of TTO to act via selective cellular responses during inflammation (Brand et al., 2001). A study demonstrated that TTO and terpinen-4-ol reduced IL-8 levels by transcript and protein analysis (Ramage et al., 2012). Altogether, the anti-inflammatory and immunomodulatory properties of terpenes and their analogues in TTO were shown to function against neurodegeneration by acting as AChE, BChE, and LOX inhibitors (Wojtunik-Kulesza et al., 2019), indicating the promising therapeutic potential of TTO as a neuroprotective agent. The anti-inflammatory and immunomodulatory functions of different TTO components are summarized in Table 5. Nonetheless, the comprehensive research accompanying several specific cellular pathways associated with inflammation and immune responses needs to be more focused; the active constituents have been isolated so far but very few components have been screened for their anti-inflammatory potential. Advanced studies need to be conducted to figure out the core mechanism of action for TTO. Additionally, preclinical evidence needs to be verified using well-structured clinical trials. The evaluation of potential pharmacokinetic and pharmacodynamic characteristics is warranted to provide a final estimate of the immunomodulatory action of TTO.

4.2.3 Neuroprotective effects via growth factor regulation

The modulation of growth regulatory elements may allow TTO to exhibit neuroprotective effects; evidence on growth regulation by TTO has been corroborated by many recent studies. Yang et al. (2022a) demonstrated the effect of TTO on improving the growth performance factors of finishing pigs. They discovered that TTO supplementation escalated the messenger RNA (mRNA) expression of growth hormone (*GH*), insulin-like growth factor-I (*IGF-I*), and heart fatty acid-binding protein (*H-FABP*), while the mRNA expression of calpastatin (*CAST*) and myostatin (*MSTN*) was decreased by TTO supplementation (Cuttle et al., 2008; Yang et al., 2022b). Although relevant observations have been made in pigs, GH-IGF components were shown to have significant functions in controlling growth and development. *GH* is an essential gene in this regard, and *IGF-I* can promote cell division, proliferation, and other cellular processes in various tissues (Slifierz et al., 2013). The relationship between *IGF-I* expression in the liver and growth efficiency was reported as favorable (Montserrat et al., 2007), suggesting that TTO supplementation enhances *GH* and *IGF-I* mRNA expression in the liver and longissimus dorsi (LD) muscle, that is, it may have a beneficial effect on protein metabolism (Yang et al., 2022b). Additionally, IGF-I and IGF-II share features that can help with growth performance. The transforming growth factor-β (TGF-β) superfamily member MSTN, which is a negative regulator of muscle growth, has been shown to be downregulated by TTO. Interestingly, IGF-II, a naturally occurring hormone, has neurotrophic and neuroprotective effects on a variety of neurodegenerative

Table 5 Anti-inflammatory action of TTO demonstrated in various in vitro and in vivo models

Extracts/ fractions/ compounds	Screening model	Types of study	Dose	Key findings/mode of action or biochemical and histopathological parameters studied	References
TTO	Histamine-induced weal and flare	In vivo	25 μL	↓ Histamine-induced skin inflammation	Koh et al., 2002; Saikia et al., 2018
TTO	LPS-activated human peripheral blood monocytes	In vitro	0.125% (volume fraction)	↓ TNF-α, IL-1β, IL-8, IL-10, and PGE2 production	Hart et al., 2000
Terpinen-4-ol	LPS-activated monocytes	In vitro		↓ TNF-α, IL-1β, IL-8, IL-10, and PGE2 production	Hart et al., 2000
TTO	Skin infection		10% (mass fraction)	↑ Clinical condition of scaling, inflammation, itching, and burning	Tong et al., 1992
Terpinen-4-ol	Cytokine production of the macrophages	In vitro	800 μg/mL	↓ Cytokine production of the macrophages	Ninomiya et al., 2013
TTO	ROS production on the human blood leukocytes		0.1% (volume fraction)	↓ Reduced intracellular ROS production	Caldefie-Chézet et al., 2004; Khalil et al., 2004
Terpinen-4-ol and α-terpineol	Histamine-induced forearm skin		40% and 3% (volume fraction) TTO	↓ Reduced microvascular changes	Brand et al., 2001; Khalil et al., 2004
TTO	fMLP- and LPS-induced neutrophils	In vitro		↓ Reduced superoxide production by neutrophils	
TTO and terpinen-4-ol	IL-8	In vitro		↓ Reduced IL-8 in cell	Ramage et al., 2012

TTO: tea tree oil; fMLP: *N*-formyl-methionyl-leucyl-phenylalanine; LPS: lipopolysaccharide; TNF-α: tumor necrosis factor-α; IL: interleukin; PGE2: prostaglandin E2; ROS: reactive oxygen species.

disorders and aging processes. According to mounting evidence, the effects of IGF-II on the brain may be explained by its binding ability to the particular transmembrane receptor, IGF-II/mannose-6-phosphate (M6P) receptor (IGF-IIR). Unfortunately, the function of IGF-II via IGF-IIR in neuroprotection has not yet been elucidated (Martín-Montañez et al., 2017).

4.2.4 Neuroprotection via antioxidative action

Terpinen-4-ol has demonstrated excellent antioxidant properties in some in vitro and in vivo investigations. The effect of TTO on human blood leukocytes was evaluated by assessing the development of ROS by flow cytometry using phorbol ester (phorbol 12-myristate, 13-acetate, PMA), fMLP, and opsonized zymosan (OZ). In an in vitro study, the application of 0.1% (volume fraction) TTO to the ROS produced cells achieved a significantly reduction in intracellular ROS production. ROS are the main signaling substances that play a critical part in the development of chronic inflammation, leading to the damage of neuronal cells (Caldefie-Chézet et al., 2004). Another in vitro study on TTO showed a significant reduction in superoxide production by neutrophils that induced by fMLP and LPS, suggesting the ability of these kinds for selective cellular responses during inflammation (Brand et al., 2001).

ROS in high concentrations cause oxidative stress, which in turn leads to neurotoxicity and disrupts the BBB, and results in vasogenic edema (de Oliveira Manoel and Macdonald, 2018). ROS usually include free radicals (e.g., alkoxyl radicals, hydroxyl radicals, peroxyl, and superoxide anion) and oxygen species that can generate radicals in situ (hypohalous acids, hydrogen peroxide, and singlet oxygen). An imbalance between antioxidant defense systems and ROS causes oxidative stress (Duan et al., 2016; Zheng et al., 2018). Once initiated, it induces the damage of membrane lipids and DNA and the decline of cellular protein function, leading to neuronal cell damage via a membrane directly and DNA damage, as well as the initiation of apoptosis (Toda et al., 2009). The neuroprotective effect of numerous antioxidant enzymes, including SOD and GPx, has been reported since they are postulated

to be highly protective against free radicals (Lee KH et al., 2020). Reduced glutathione (GSH) is a non-enzymatic antioxidant and an oligopeptide capable of reducing and inactivating oxidized proteins and pro-oxidant xenobiotic agents. GPx is believed to play a neuroprotective role by reducing phospholipid hydroxide and lipid peroxidation (Demir et al., 2013; Lee KH et al., 2020; Tekeli et al., 2023). Therefore, the cellular GSH level is crucial for a number of important biological processes, such as the control of redox-sensitive signal transmission and the transcriptional activation of particular genes (Espinosa-Diez et al., 2015). Interestingly, TTO is assumed to positively influence the activity of the enzymes SOD and GPx, suggesting a link between the functions of TTO and increased neuroprotection.

5 Other activity of TTO

5.1 Anticancer activity of TTO

To date, TTO has been reported to have anti-cancer activity by several anticancer tests using a variety of cell lines in vitro. Hayes et al. (1997) conducted experiments with TTO using five cell lines, including HeLa (epithelioid carcinomic cell line), HepG2 (hepatocellular carcinomic human cell line), MOLT-4 (human lymphoblastic leukemia T-cell line), CTVR-1 (B-cell line), and K-562 (human chronic myelogenous leukemia cell line) collected from bone marrow cells of cancer patients. Their aim was to observe the cytotoxicity of TTO and its components, α-terpineol, terpinen-4-ol, and 1,8-cineole. The cytotoxicity in the affected cells was significantly reduced (Hayes et al., 1997). A study examined the effect of terpinen-4-ol on human HL-60 cells, which showed a 1000-fold higher toxicity to trypanosomes rather than human cells and was able to stop cancer-associated cells (Mikus et al., 2000). Another in vitro study demonstrated that TTO showed a positive effect in inhibiting human melanoma cells (Calcabrini et al., 2004). In the same study, terpinen-4-ol was able to induce the caspase-dependent apoptosis of melanoma cells. Correspondingly, TTO and terpinen-4-ol were found to markedly inhibit the growth of tumor cell line and fibroblast cell lines in a time-dependent manner, as observed by the rates of apoptotic and necrotic cell death; TTO and its component terpene-4-ol inhibited the growth of two cell lines. Compared to fibroblast cell lines, TTO was shown to be more effective against tumor cell lines. This was discovered using transmission electron microscopy and video time-lapse microscopy, which demonstrated that TTO and its components were responsible for both necrotic cell death and apoptotic cell death (Greay et al., 2010). Subsequently, an in vivo study investigated the effect of topically applied TTO on the incidence of skin cancer in similar cell lines. Topically applied TTO was observed to directly exert anti-cancer cytotoxicity in subcutaneous tumor bearing mice (Ireland et al., 2012).

In addition, the potential role of TTO in the management of oral candidosis in cancer patients was studied using OKF6-TERT2 epithelial cells. The findings demonstrated that TTO and terpinen-4-ol were cytotoxic at 1×MIC_{50} (minimum inhibitory concentration at which 50% of the isolates were inhibited), whereas 0.5× MIC_{50} terpinen-4-ol showed no significant toxicity by scanning electron microscopy (Ramage et al., 2012). Recently, the anticancer properties of TTO in leukemia cell line K562 were investigated, and cytotoxicity was observed at the concentration of 3.125 μg/mL (Byahatti et al., 2018). A similar in vitro assay in human glioblastoma cells U87MG showed the cellular growth hindrance by a synergistic approach of necrosis, low-level apoptosis, and cell cycle arrest (Arcella et al., 2019).

5.2 Antimicrobial activity

5.2.1 Antifungal effect of TTO

According to more recent data, TTO has fungicidal and fungistatic properties. It has been tested for its in vitro antifungal activity against 26 strains of different dermatophyte species, 54 yeasts, including 32 strains of *C. albicans* and other *Candida* spp., as well as 22 different *Malassezia furfur* strains. TTO was found to be capable of inhibiting the growth of all clinical fungal isolates, and all strains were susceptible to higher TTO concentrations than the usual susceptibility determination concentration of 0.025–100 μg/mL (Nenoff et al., 1996). In an antifungal study, which used the hydrogel formulation of antifungal gel with the combination of ketoconazole (KTZ) and TTO, the presence of TTO improved the penetration and retention of KTZ through the artificial skin membrane, implying the favorable role of TTO in drug release and antifungal activity. Furthermore, the bioadhesive properties of the formulation were attributed to TTO

(Wróblewska et al., 2021). Hammer et al. (2003) showed that TTO and its components exert antifungal actions on *Candida glabrata*, *C. albicans*, and *Saccharomyces cerevisiae* by altering the membrane properties and compromising membrane-associated functions. To combat the most common causes of tinea and onychomycosis, *Trichophyton mentagrophytes* var. *interdigitale* and *Trichophyton rubrum*, TTO and lavender EOs were tested individually and in combination. The results showed that the two EOs that are frequently used together had a synergistic effect on antifungal activity (Casella et al., 2023). An in vitro study has been conducted on three species of yeasts (*Candida* spp., *Debaryomyces hansenii*, *Schizosaccharomyces pombe*) and dermatophytes (*Tricophyton* spp. and *Microsporum* spp.) to assess their antifungal properties. TTO hindered the conversion of *C. albicans* from yeast to mycelial form at a concentration of 0.16% (volume fraction). The MIC ranged from 0.12% to 0.50% (volume fraction) for yeasts and 0.12% to 1.00% (volume fraction) for dermatophytes; however, the cytocidal potential was revealed at a similar concentration (D'Auria et al., 2001). Likewise, one study selected five different EOs along with TTO to assess their in vitro antifungal activity using the broth dilution method (Christoph et al., 2000). Among them, TTO was found to have a significant MIC of antimicrobial potential. Ramage et al. (2012) examined the antifungal activity of TTO and its component terpinen-4-ol against oral biofilm formation by *C. albicans*. The in vitro evidence showed the strong antimicrobial potential of these substances against fungal biofilms.

5.2.2 Antibacterial activity of TTO

An antibacterial susceptibility test of TTO was conducted against some bacterial strains, where the MIC and minimum bactericidal concentration (MBC) of TTO were found to be 0.25% for *Serratia marcescens* and 3% for *Pseudomonas aeruginosa. S. marcescens* and *Klebsiella pneumoniae* showed a lower (0.25%) MIC, while the highest MIC was 8% for *Staphylococcus capitis* (Hammer et al., 1996). A study observed that TTO was remarkably effective against halitosis-associated bacterium *Solobacterium moorei* through a direct exposure test (Forrer et al., 2013). Choi and Kang (2017) investigated and established the antibacterial potential of TTO against *Streptococcus mutans*. An in vitro research demonstrated that TTO prevents biofilm formation in the tympanostomy tube, and highlighted the efficacy of TTO against methicilline-resistant *Staphylococcus aureus* (MRSA) (Park et al., 2007). The antibacterial mode of TTO has been elucidated using bacterial strains of *Escherichia coli* and *S. aureus*, and concluded that the lethal activity at MIC levels was the propensity of TTO to decimate the permeability barrier of the cellular membrane system of bacteria (Cox et al., 2000).

5.2.3 Antiviral activity of TTO

The antiviral activity of TTO had been hardly explored until its anti-tobacco mosaic virus (anti-TMV) effect on *Nicotiana glutinosa* was reported by Lu et al. (2013), who noticed a minimization of random lesions on the tobacco leaf. Chao et al. (2000) investigated the antiviral activity of TTO against the T_7 phage of *E. coli* and the SA phage of *Streptococcus aureus* by incubating them for 24 h at 37 ℃, and reported the strong inhibitory action of TTO on both phages. Schnitzler et al. (2001) examined the in vitro antiviral activity of TTO against herpes simplex virus type-1 (HSV-1) and HSV-2 on RC-37 and identified the half maximal inhibitory concentration (IC_{50}) values of TTO against HSV-1 and HSV-2 as 0.0009% and 0.0008%, respectively, and reported a remarkable reduction in virus titers by TTO. Minami et al. (2003) presented promising results for the in vitro viral inhibitory action of TTO through an evaluation of HSV-1 replication. Furthermore, an in vitro study was conducted using time-killing assay and staging assay, and showed the promising anti-viral activity of TTO, especially in the earlier stages of viral replication (Schnitzler et al., 2001). Another in vivo study of TTO was performed on patients with recurrent herpes labialis (RHL), a cold sore in which instances of frequent or extensive attacks occur through considerable discomfort and cause lesions. The reported time to re-epithelialization in lesions was lessened in the TTO group (Schnitzler et al., 2001). Most recently, research has confirmed that TTO monoterpene compounds showed antiviral activity against HSV-1 and HSV-2 (Astani et al., 2010; Astani and Schnitzler, 2014) pragmatizing it as a potent antiviral oil. Garozzo et al. (2009) showed the antiviral effects of TTO constituents against airborne DNA and RNA influenza A/PR/8 virus subtype H1N1, enteric cytopathic human orphan virus (subtype, ECHO 9), Coxsackie B1, polio type 1, HSV-1 and HSV-2 viruses, and adeno type 2, in a 50% plaque reduction assay against Madin-Darby canine kidney

(MDCK) cells, although some of their results contradicted those of further assays (Li et al., 2013). Yet, this discovery brought up an intriguing point: TTO was found to impede the early phases of viral replication even at concentrations lower than the lethal dose (Garozzo et al., 2009). Subsequently, Pyankov et al. (2012) studied influenza virus captured onto the conventional HVAC filter surfaces and suggested the prospect of TTO against both enveloped and non-enveloped viruses. However, extensive and more advanced scientific and clinical trials are strongly recommended to confirm the aforesaid effect of TTO.

5.3 Topical use on the skin

The topical use of TTO started with controversies, including several cases of acne to major skin problems like psoriasis, whereas its safe use was later confirmed by several researchers (Hammer et al., 2006). Lee et al. (2013) tested components of TTO and concluded that it was safe to use, and 5% concentration proved the best to treat acne. Thus, it can be considered as a potential alternative to conventional acne treatment due to its weaker adverse effect (Bassett et al., 1990). The histamine-induced skin inflammation was diminished after using TTO, which could help in treating inflammation arising from acne (Koh et al., 2002) and the antimicrobial action could kill acne causing bacteria (Nenoff et al., 1996). Tinea pedis caused by *T. rubrum*, *T. mentagrophytes*, and *Epidermophyton floccosum* in sweaty toes was reported to be healed by TTO alone and its combination with 1% tolnaftate (10% (mass fraction) TTO cream) (Tong et al., 1992). Another skin disease, seborrhoeic dermatitis caused by *M. furfur* and other *Malassezia* species via immune function impairment (Gupta et al., 2004; Waldroup and Scheinfeld, 2008), was demonstrated to be healed using an antifungal product containing at least 5% (mass fraction) TTO (Champion et al., 1992; Waldroup and Scheinfeld, 2008). Researchers suggested that psoriasis, an inflammatory condition of patchy, scaly skin, and red crusts in different skin areas, could be improved by TTO, especially by its main component terpinen-4-ol that had an inhibitory activity on TNF-α, IL-1, IL-8, PGE2, and vasodilatation (Mondello et al., 2006; Pazyar and Yaghoobi, 2012). However, further mechanistic studies are strongly recommended alongside clinical investigation for the development of new tropical products.

6 Safety and toxicity of TTO

Despite numerous global uses of TTO mainly as a cosmetic product, some minor yet concerning side effects have been reported over the years.

Higher concentrations of TTO applied topically can have adverse effects. These include allergic contact dermatitis, skin irritation, linear immunoglobulin A disease, systemic contact dermatitis, erythema-like reactions, and systemic hypertension reactions. Meanwhile, no toxicity was found by other scholars (Veien et al., 2004). Since irritating reactions can be effectively prevented using lower concentrations of the oil, the use of well formulated products rather than the neat oil is encouraged. Nonetheless, most of the reported allergic reactions (de Groot and Weyland, 1992; van der Valk et al., 1994) were caused mainly by the oxidation products that occur in aged or improperly stored oil (Hausen et al., 1999). Young boys and girls who have not yet reached puberty are suggested not to apply TTO and lavender oil containing lotions on their skin because of speculated hormonal effects. For instance, idiopathic male pubertal gynecomastia has been reported in parallel with increased use of TTO (Henley et al., 2007). When consumed orally, TTO can also be dangerous. Oral poisoning has been reported to induce disorientation, inability to walk, unsteadiness, rash, and in rare cases, coma in both infants (Jacobs and Hornfeldt, 1994; del Beccaro, 1995; Morris et al., 2003) and adults (Carson et al., 1995; Bischoff and Guale, 1998). Therefore, without dilution, no concentrated EO should be used orally. No human deaths caused by TTO have been reported in the literature (Hammer et al., 2003). The usual justification for continuing to use the oil is partly based on its nearly 80-year history of allegedly safe use; anecdotal data indicate that topical use is safe and that adverse reactions are often small, self-limiting, and infrequent.

7 Critical insights, future prospects, and concluding remarks

Plant resources in the form of extracts, volatile oils, or supplements have been used as natural remedies since ancient times. Advanced molecular studies have added new values and approaches for the prospective use of such products; however, numerous plant materials are yet to be explored in the context of their

mode of action, while known works are helping to unravel unsolved mysteries in many cases. Likewise, this review aimed to analyze the pharmacological and biological functions of TTO to figure out its neuroprotective prospects through antioxidative, anti-inflammatory, immunomodulatory, antimicrobial, and other activities. It is evident from existing research that active bioactive compounds found in *M. alternifolia* have a broad range of pharmacological properties, including ROS deactivation, neutralizing inflammatory molecules, biological SOD and reduced GPx activation, or growth factor stimulating activities. Neuroprotection is indeed defined in terms of the combination of all or some of these effects, as postulated through extensive research. However, the active compounds of TTO are yet to be explored for all their possible bioactivity; therefore, studies on the neuropharmacological effects of the active constituents of TTO should be conducted together with qualitative and quantitative analyses to validate the above postulation. Especially, given the amount of experimental evidence obtained to date, TTO and its constituents might be a remarkable source for neuroprotective therapies. Nonetheless, based on the current research flow, it can be predicted that TTO itself or its components, either individually or in combination, may serve as dietary supplements, pharmaceutical products, or nutritional supplements for the treatment of chronic neuro-related diseases. To achieve this goal, extensive research should be conducted along with proper molecular pharmacology and network pharmacology, as well as cellular in vitro and in vivo mechanistic studies, including pharmacodynamics, pharmacokinetics, bioavailability, and toxicological research, in order to gather sufficient preclinical data prior to clinical trials.

Data availability

Data will be available on request.

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Author contributions

Md Atiar RAHMAN: conceptualization, project administration, supervision, resources, reviewing, and editing; Abida SULTANA: data curation, formal analysis, software, and methodology; Mohammad Forhad KHAN: draft preparation, data curation, and methodology; Rachasak BOONHOK: reviewing, editing, and validation; Sharmin AFROZE: methodology and draft preparation. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Md Atiar RAHMAN, Abida SULTANA, Mohammad Forhad KHAN, Rachasak BOONHOK, and Sharmin AFROZ declare that they have no conflict of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

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