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Review Article

The biological effects of *Teucrium polium*: an updated literature review

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Abstract

Objective: *Teucrium polium* (TP) is a medicinal plant extensively used in traditional medicine. This review aimed to provide an updated and critical synthesis of the phytochemical composition, biological activities, underlying mechanisms of action, and therapeutic potential of TP.

Materials and Methods: A comprehensive literature search was conducted in PubMed, Web of Science, and Scopus for studies published between 2004 and 2025 using predefined keywords related to TP and its pharmacological effects. After screening according to eligibility criteria, relevant studies, including *in vitro*, animal, and clinical investigations, were included in the review.

Results: Accumulating evidence indicates that TP exerts antioxidant, anti-inflammatory, antimicrobial, antidiabetic, neuroprotective, cardioprotective, and anticancer activities through modulation of oxidative stress, inflammatory signaling pathways, mitochondrial function, neurotransmitter systems, and cellular apoptosis. Hepatoprotective effects were observed at moderate doses; however, several studies reported hepatotoxicity at higher doses or with specific extracts, highlighting a dose-dependent safety concern. Despite promising preclinical findings, clinical evidence remains limited, and substantial heterogeneity exists regarding plant origin, extraction methods, phytochemical composition, dosage regimens, and experimental designs.

Conclusion: TP demonstrates considerable therapeutic potential across multiple biological systems; however, its clinical application is currently limited by insufficient human evidence, lack of phytochemical standardization, and unresolved toxicological concerns.

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Introduction

Historically, medical plants and their products have been used to fight diseases from the dawn of civilization. According to the World Health Organization (WHO), up to 80% of the population in some developing countries relies on traditional medicine, largely plant-based, for primary health care (Kumar et al. 2025; Organization 2020) . Herbal medicines have received special attention in both developing and developed countries due to their high biological and medical value, low side effects and cost-effectiveness. The amount of research on secondary metabolites, structural diversity and biological importance of medical plants is rising rapidly (Rajizadeh et al. 2025; Rajizadeh et al. 2024).

The genus *Teucrium* belongs to the family Lamiaceae (subfamily Ajugoideae). The genus comprises species distributed on all continents, but more concentrated in the Mediterranean region and the Middle East. Twelve species are found in southwestern Asia(Bahramikia et al. 2022a).

The most important compounds of these species are flavonoids, monoterpenoids, phenolic acids, and steroids. *Teucrium polium* (TP) is one of these species and is mainly distributed in the Mediterranean region and southwestern Asia. The aerial parts of the plant have an aromatic odor and a bitter taste (Figure 1).The morphological polymorphism in flower colors may be related to environmental parameters and the pH of soil (Djabou et al. 2012). Previous reviews have summarized the traditional uses, phytochemical constituents, and biological activities of TP. However, the available literature has continued to expand, with numerous studies investigating its pharmacological activities, mechanisms of action, and potential toxic effects in recent years. Therefore, the present review aims to provide an updated and comprehensive synthesis of the available evidence published from 2004 to 2025. In addition to summarizing the established phytochemical and biological properties of TP, this review incorporates recent findings on its diverse biological activities and toxicological effects, including hepatotoxicity. By covering a broader and more recent body of literature, this review provides an updated perspective on the biological effects and potential therapeutic and safety implications of TP.

Materials and Methods

A comprehensive literature search was performed in PubMed, Scopus, and Web of Science to identify studies investigating the biological effects of TP. The search covered publications from 2004 to 2025 using combinations of the keywords "*Teucrium polium*", "biological effects", "mechanisms of action", "inflammation", "oxidative stress", "clinical", "animal", "*in vitro*", "cell line", and "phytochemical constituents". Studies were included if they reported biological or pharmacological effects of TP in *in vitro*, *in vivo*, or clinical settings. Review articles, non-English publications, duplicate records, and studies lacking relevant biological outcome data were excluded from the analysis.

Results

Traditional uses

In traditional medicine, TP has been used as an antispasmodic, diuretic, and diaphoretic for about 2000 years. It has also been reported to have hypoglycemic and insulinotropic effects. It has been used for digestive tract disorders such as indigestion, gastric ailments, intestinal motility disorders, and liver diseases. TP has also been used as an antipyretic and to alleviate rheumatism and kidney stones and to reduce tumors. Anti-inflammatory, analgesic, and antioxidant effects have also been attributed to it, and its antioxidant effect is related to its phenolic and flavonoid compounds. Furthermore, antibacterial and antiviral activities have been demonstrated in various studies (Bezić

et al. 2011; Setif 2011). In vitro, TP has been reported to reduce fatty acid levels, and its administration to hypercholesterolemic animals reduced triglyceride, low-density lipoprotein cholesterol (LDL-C), and total cholesterol and increased high-density lipoprotein cholesterol (HDL-C)(Amraei et al. 2018a). TP has also been reported to inhibit red blood cell lipid peroxidation (Suboh et al. 2004) and angiogenesis in cancer (Askari et al. 2019). In addition, anti-proliferative, cytotoxic, and pro-apoptotic activities of TP on some cancer cell lines have been demonstrated (Nikodijević et al. 2016) activities of TP on some cancer cell lines have been demonstrated in different studies .

Phytochemical compounds

Major phytochemical compounds extracted from different parts of TP include: (I) essential oil constituents (germacrene D, β-caryophyllene, α-pinene, β-pinene, elemol, cubenol, limonene, and α-phellandrene)(Kovacevic et al. 2001; Perez-Alonso et al. 1993), (II) aerial-part constituents, including three isoprenoids, four diterpenes, and the flavones cirsiliol and apigenin(Carreiras et al. 1989), (III) aqueous-phase components (raffinose, glucose, and rhamnose) (Capasso et al. 1983), and (IV) flavonoids such as apigenin, rutin, cirsiliol, luteolin, eupatorin, and salvigenin (Table 1).

Table 1. Major phytochemical compounds identified in *Teucrium polium*, their chemical classes, reported concentrations, and plant parts or extracts.

Compound / compound group	Chemical class	Reported concentration/content	Plant part / extract
α-Pinene	Monoterpene hydrocarbon	18.2%	Fruit essential oil
β-Pinene	Monoterpene hydrocarbon	10.1%	Fruit essential oil
Elemol	Sesquiterpene	14.5%	Fruit essential oil
Cubenol	Sesquiterpene	10.0%	Fruit essential oil
Limonene	Monoterpene hydrocarbon	5.0%	Fruit essential oil
Caryophyllene	Sesquiterpene	NR	Aerial parts / essential oil
Germacrene D	Sesquiterpene hydrocarbon	NR	Essential oil
α-Pinene	Monoterpene hydrocarbon	NR	Essential oil
β-Pinene	Monoterpene hydrocarbon	NR	Essential oil
Spathulenol	Oxygenated sesquiterpene	NR	Essential oil
Myrcene	Monoterpene hydrocarbon	NR	Essential oil
Bicyclogermacrene	Sesquiterpene	NR	Essential oil
Carvacrol	Phenolic compound	NR	Aerial parts
Torreyol	Oxygenated sesquiterpene	NR	Aerial parts
Terpinen-4-ol	Oxygenated monoterpene	NR	essential oil
α-Thujene	Monoterpene hydrocarbon	NR	essential oil
p-Cymene	Monoterpene hydrocarbon	NR	essential oil
Sabinene	Monoterpene hydrocarbon	NR	essential oil
Cirsiliol	Flavonoid	NR	Aerial parts
Apigenin	Flavone	NR	Aerial parts
Rutin	Flavonoid	NR	Extract
Luteolin	Flavonoid	NR	Extract
Eupatorin	Flavonoid	NR	Extract
Salvigenin	Flavonoid	NR	Extract
Raffinose	Carbohydrate	NR	Aqueous phase
Glucose	Carbohydrate	NR	Aqueous phase
Rhamnose	Carbohydrate	NR	Aqueous phase
Monoterpene hydrocarbons	—	1.2%	Essential oil
Oxygenated monoterpenes	—	15.0%	Essential oil
Sesquiterpene hydrocarbons	—	33.9%	Essential oil
Oxygenated sesquiterpenes	—	21.3%	Essential oil
Phenolic compounds	—	10.3%	Essential oil
Hydrocarbons	—	6.5%	Essential oil
Fatty acids	—	0.6%	Essential oil
Carbonyl compounds	—	2.6%	Essential oil

NR = not reported

Analysis of the essential oil of Iranian TP fruits revealed 45 constituents, mainly α- and β-pinene (18.2% and 10.1%, respectively), elemol (14.5%), cubenol (10.0%), and limonene (5.0%), with small amounts of caryophyllene and germacrene D(Sabzeghabaie and Asgarpanah 2016). The composition of fruit essential oils varies between regions, and the stage of the vegetative cycle and differences between plant organs have been suggested as possible causes (Thomas 2013). Another study identified 10 constituents in the aerial parts, mainly caryophyllene, carvacrol, and torreyol (Bsharat et al. 2025). Martino et al. reported the following essential oil fractions: monoterpene hydrocarbons (1.2%), oxygenated monoterpenes (15%), sesquiterpene hydrocarbons (33.9%), oxygenated sesquiterpenes (21.3%), phenolic compounds (10.3%), hydrocarbons (6.5%), fatty acids (0.6%), and carbonyl compounds (2.6%). A study comparing TP essential oils from western Algeria and Corsica reported α-pinene, β-pinene, germacrene D, limonene, spathulenol, myrcene, and bicyclogermacrene as the main constituents of the Algerian oil (Martino et al. 2010).

The great polymorphism in the essential oil components of different regions can be attributed mainly to genetic background, growth stage at collection, and the ecological features of the collection area(Menichini et al. 2009). Furthermore, many phenolic and flavonoid compounds have been reported in the essential oils of the aerial parts and in acetone extracts of this plant(DJORDJEVIC et al. 2018; Guetata and Al-ghamdia 2014). The antioxidant effects of TP can be attributed to these compounds (Tables 1 and 2).

Pharmacological properties

Several pharmacological activities, especially in the digestive tract, have been reported for TP, including hepatoprotective, anti-ulcer, antioxidant, and anti-inflammatory effects.

Table 2. Phenolic and flavonoid compounds of TP

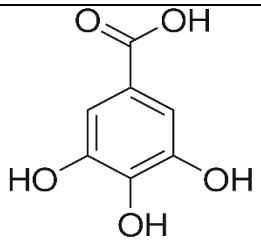
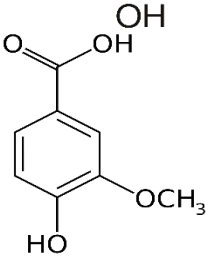
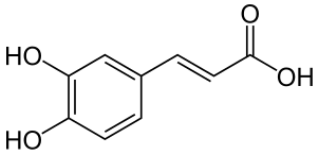
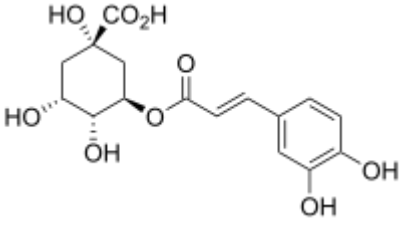
Gallic acid	**C7H6O5**	
Vanillic acid	**C8H8O4**	
Caffeic acid	**C9H8O4**	
Chlorogenic acid	**C16H18O9**	

Table 2. Continued

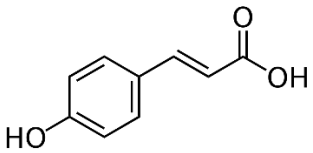
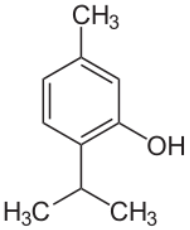
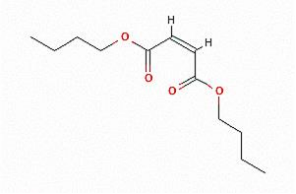
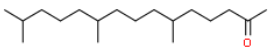
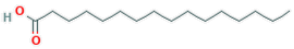
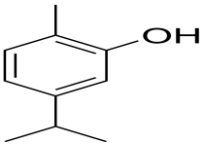
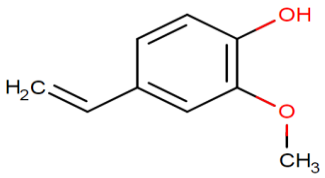
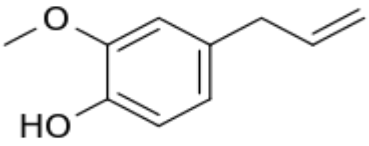
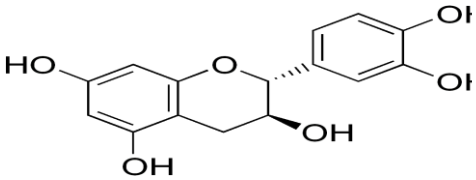
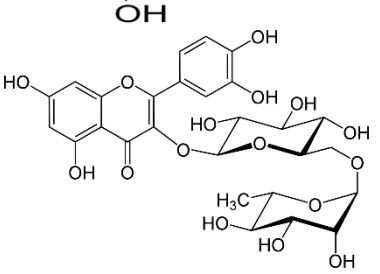
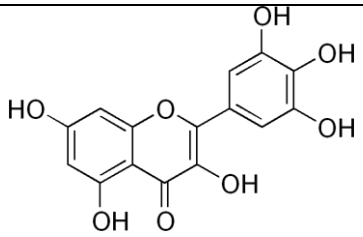
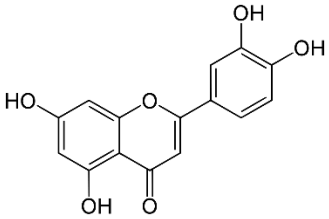
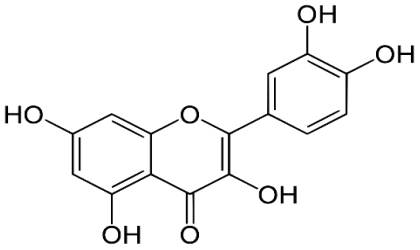
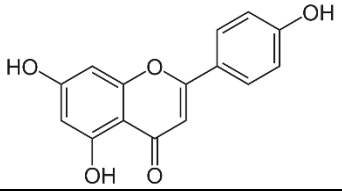
p-coumaric acid	**C9H8O3**	
Thymol	**C10H14O**	
Dibutyl ester	**C12H20O4**	
Hexahydrofarnesyl acetone	**C18H36O**	
Palmitic acid	**C16H32O2**	
Carvacrol	**C10H14O**	
Vinyl guaiacol	**$C_9H_{10}O_2$**	
Eugenol	**C10H12O2**	
Catechin	**C15H14O6**	
Rutin	**C27H30O16**	

Table 2. Continued

Myricetin	**C15H10O8**	
Luteolin	**C15H10O6**	
Quercetin	**C15H10O7**	
Apigenin	**C15H10O5**	

TP and liver

In male ICR mice with acetaminophen-induced hepatotoxicity, pretreatment with the hydroalcoholic extract (80% aqueous ethanol) of the whole TP plant (125, 250, and 500 mg/kg, p.o., for 5 days) significantly reduced serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), with the strongest protection at 250 and 500 mg/kg (Forouzandeh et al. 2013). A polyphenol-rich extract of the aerial parts of *TP* subsp. *geyrii* (300 mg/kg, p.o., for 10 days) prior to a single acetaminophen dose (1 g/kg) in rats suppressed hepatic

cytochrome P450 2E1 (CYP2E1)

, glutathione S-transferase pi (GSTpi), and tumor necrosis factor alpha (TNF-α) expression, together with improvement of mitochondrial bioenergetics (Bahramikia et al. 2009; Bahramikia and Yazdanparast 2012b). Similarly, the ethyl acetate extract of whole plant of *TP* exhibited hepatoprotective activity against carbon tetrachloride-induced liver injury through attenuation of oxidative stress and enhancement of antioxidant defense systems (Panovska et al. 2007).

Further evidence showed that the ethyl acetate fraction of *TP leaves* (0.5 g/kg leaf powder equivalent) protected against methionine- and choline-deficient diet-induced liver injury. Treatment reduced hepatic TNF-α, transforming growth factor beta (TGF-β), caspase-3, and phosphorylated c-Jun N-terminal kinase (JNK) levels while increasing phosphorylated extracellular signal-regulated kinase 1/2 (ERK1/2) and improving serum lipoprotein profiles. In addition, liver enzyme activities (ALT, AST, and ALP) were significantly decreased (Amini et al. 2009a). Across different experimental models, whole plant of *TP* consistently enhanced antioxidant status by increasing endogenous

antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), and reduced glutathione (GSH), while reducing lipid peroxidation markers. These findings suggest that attenuation of oxidative stress and inflammation constitutes a major mechanism underlying the hepatoprotective action of TP (Amini et al. 2009a; Panovska et al. 2007).

Despite these beneficial effects, evidence also indicates the potential hepatotoxicity of TP. The petroleum ether fraction was associated with increased apoptosis and vacuole formation in liver tissue compared with the crude extract (Mazokopakis et al. 2004; Polymeros et al. 2002). Weekly IP administration of the petroleum ether fraction of aerial parts of *TP* (50–400 mg/kg, for 3 weeks) reduced weight gain at 400 mg/kg and altered GGT and ALP, while ALT, AST, glucose, cholesterol, and triglycerides were unchanged and no histopathological changes were observed (Shahraki et al. 2007). Liver necrosis was also observed following administration of very high doses of ethanol extract of whole plant of *TP* (4 g/kg) (Nematollahi-Mahani et al. 2007).

The hypoglycemic effects of whole plant of TP are attributed to bioactive constituents such as iridoids, flavonoids, and cirsiliol (Shakhanbeh and Adigüzel 2001). Although TP can reduce serum glucose levels, its potential hepatotoxicity limits its suitability as an antidiabetic agent.

Taken together, the hepatic effects of TP appear to be dose- and fraction-dependent. While moderate doses of hydroalcoholic and ethyl acetate extracts demonstrated hepatoprotective properties through antioxidant and anti-inflammatory mechanisms, the petroleum ether fraction and high doses (4 g/kg) were associated with hepatotoxicity, liver necrosis, and elevated liver enzymes. This dose-dependent duality suggests a narrow therapeutic window and warrants caution in clinical application.

The available evidence suggests that the hepatic effects of TP are strongly dependent on dose, extract type, fraction, and duration of exposure. In experimental models, hydroalcoholic extracts administered at 125–500 mg/kg demonstrated hepatoprotective effects, with more pronounced protection reported at 250 and 500 mg/kg. An ethyl acetate fraction administered at approximately 500 mg/kg also showed hepatoprotective effects. In contrast, administration of the petroleum ether fraction at 50–400 mg/kg was associated with weight loss and elevations in GGT and ALP, while a very high dose of TP leave extract (4 g/kg) was associated with liver necrosis. Therefore, the available evidence does not support a single safe dose range applicable to all TP preparations. Rather, the reviewed studies suggest that approximately 125–500 mg/kg may represent a potentially effective experimental range for certain hydroalcoholic preparations, whereas the safety of other fractions cannot be inferred from these findings. Importantly, these doses are derived from animal studies and should not be interpreted as clinically safe doses for humans. Differences in extraction method, phytochemical composition, animal model, route of administration, and treatment duration further limit direct dose extrapolation. Consequently, a definitive therapeutic window for clinical use cannot currently be established, and standardized dose–response and toxicity studies are required before a safe human dose can be proposed (Figure 1 and Table 3).

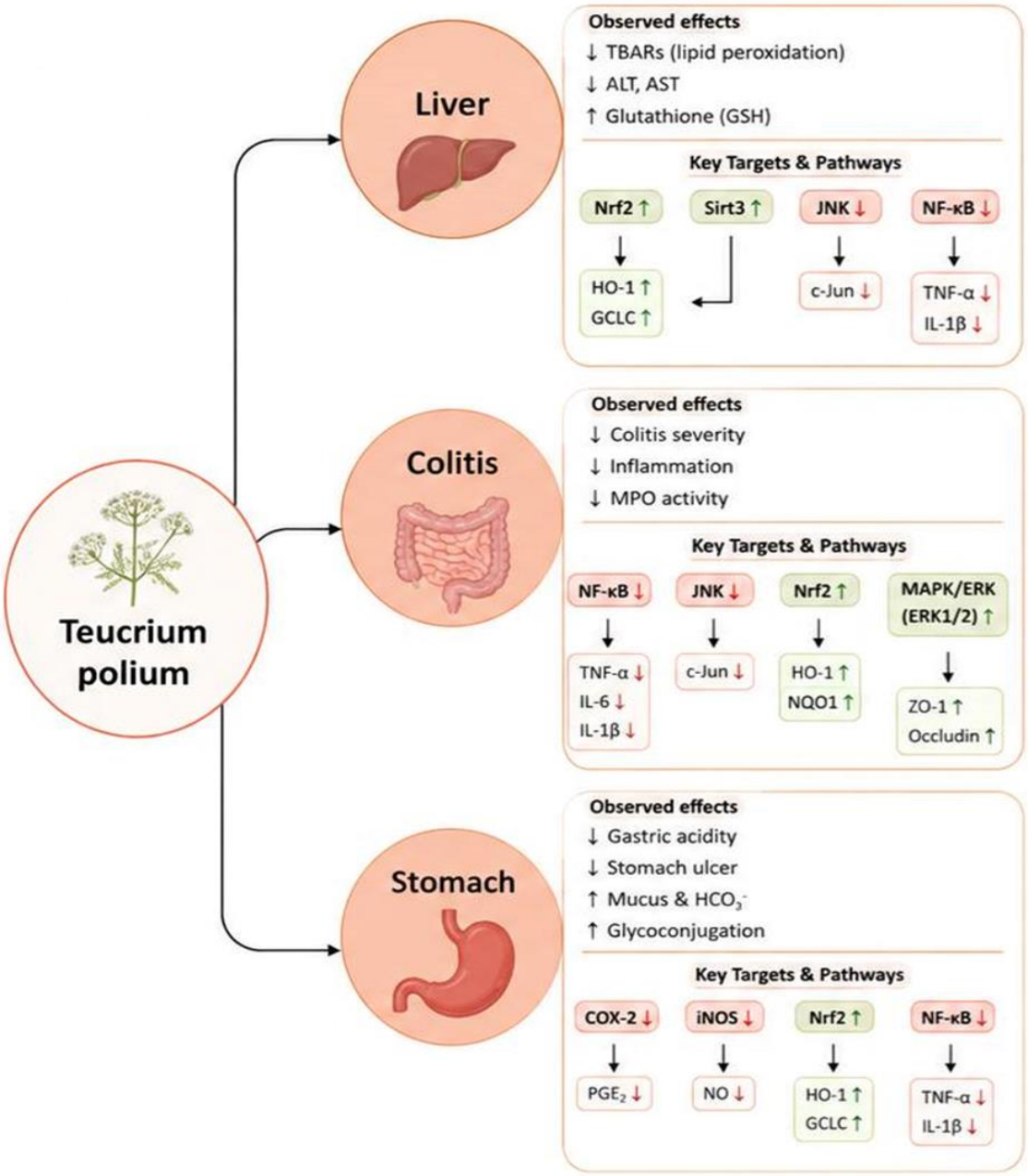


Figure 1. Organ-specific protective effects and underlying molecular mechanisms of TP. ALT, alanine aminotransferase; AST, aspartate aminotransferase; COX-2, cyclooxygenase-2; ERK1/2, extracellular signal-regulated kinase 1/2; GCLC, glutamate-cysteine ligase catalytic subunit; GSH, reduced glutathione; HCO_3^-, bicarbonate; HO-1, heme oxygenase-1; IL-1β, interleukin-1 beta; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MPO, myeloperoxidase; NF-κB, nuclear factor kappa B; NO, nitric oxide; NQO1, NAD(P)H quinone dehydrogenase 1; Nrf2, nuclear factor erythroid 2-related factor 2; PGE_2, prostaglandin E2; Sirt3, sirtuin 3; TBARS, thiobarbituric acid reactive substances; TNF-α, tumor necrosis factor alpha; ZO-1, zonula occludens-1. ↑, increase; ↓, decrease.

Table 3. Dose and the model of the included studies done on *T. polium*

Dose	Experimental model	Effect	Reference
125, 250 and 500 mg/Kg, orally	Acetaminophen-Induced Hepatotoxicity in Mice	Reduced the AST, ALT and ALP levels Decreased the direct and total bilirubin concentration	(Forouzandeh et al. 2013)
300 mg/kg, orally	Acetaminophen-Induced Hepatotoxicity in Rats	Improving transaminases leakage and liver histology inhibition of liver CYP2E1, GSTpi and TNF-_ mRNA levels improvement of mitochondrial activity	(Baali et al. 2016a)
0.25 mg/mL, IP	Hepatic injury induced by Carbontetrachloride in rats	SOD levels increased, TAS and TBARS decreased	(Amini et al. 2011)
0.01–1 mg/mL, in vitro	HepG2 cells	Increased the total and reduced glutathione levels	(Shtukmaster et al. 2010)
0.5 g of plant leaves powder/kg, orally	liver injury induced by MCD diet in rats	Reduced the TNF-a and TGF-β Increased MDA, SOD and GPx activity	(Aghazadeh and Yazdanparast 2010)
50, 100, 200 and 400 mg/kg, IP	CCl4- induced liver toxicity in rats	Decreased caspase-3 and JNK levels and increased ERK1/2 level	(KADIFKOVA PANOVSKA et al. 2007)
1- 4 g/Kg, orally	pregnant women	Reduced the weight of rats GGT and ALP increased	(Dağ et al. 2014)
400 mg/kg, orally and transrectally	Gastric ulcer induced by Indomethacin- in rats	Liver necrosis Increased the mast cells numbers	(Mehrabani et al. 2009)
0.5 g/kg, orally	Ulcerative Colitis Induced in the Dog	Increased the number of healthy cells and reduced inflammatory cells	(Mehrabani et al. 2012)
47, 94, 188, 376 and 470 mg/l, in vitro	Intestinal damage induced by radiation	Reduced the intestinal MPO levels and inflammation scores Decreased the ileum contraction	(Demirel et al. 2011a)

TP and stomach

Mansour et al. (2025) reported that pretreatment with hydroalcoholic extract of TP leaves significantly reduced gastric ulcer formation in rat models at both tested doses. The authors also showed that pretreatment improved antioxidant defenses, reduced gastric acid secretion and lipid peroxidation, and consequently improved gastric mucosal architecture in ulcerated rats. These effects were attributed to phenolic acids (p-coumaric, ferulic, and syringic acids) and flavonoids (myristicin, luteolin-7-O-glucoside, and hyperoside) identified by HPLC analysis (Mansour et al. 2025).

TP leaves hydroalcoholic extract (300 mg/kg) exhibited healing effects in indomethacin-induced gastric ulcers in rats, including mucosal hyperplasia, enhanced re-epithelialization, increased epithelial cell proliferation and migration, and reduced inflammatory cell infiltration. The 80% ethanol extract of TP, given orally 24 h after indomethacin (25 mg/kg), reduced ulcer indices by >50%, >80%, and >90% after 1, 2, and 4 weeks in male Sprague-Dawley rats (Mansour et al. 2025). Furthermore, administration of a high dose of TP leaves hydroalcoholic extract (4 g/kg) increased acidic glycoconjugates and decreased neutral glycoconjugates in the gastric mucosa. Mast cell numbers also increased in the serosa and muscularis externa layers of the stomach. However, no histopathological alterations were observed in gastric tissue (Nematollahi et al. 2022; Sheikhbahaei et al. 2021)(Figure 2).

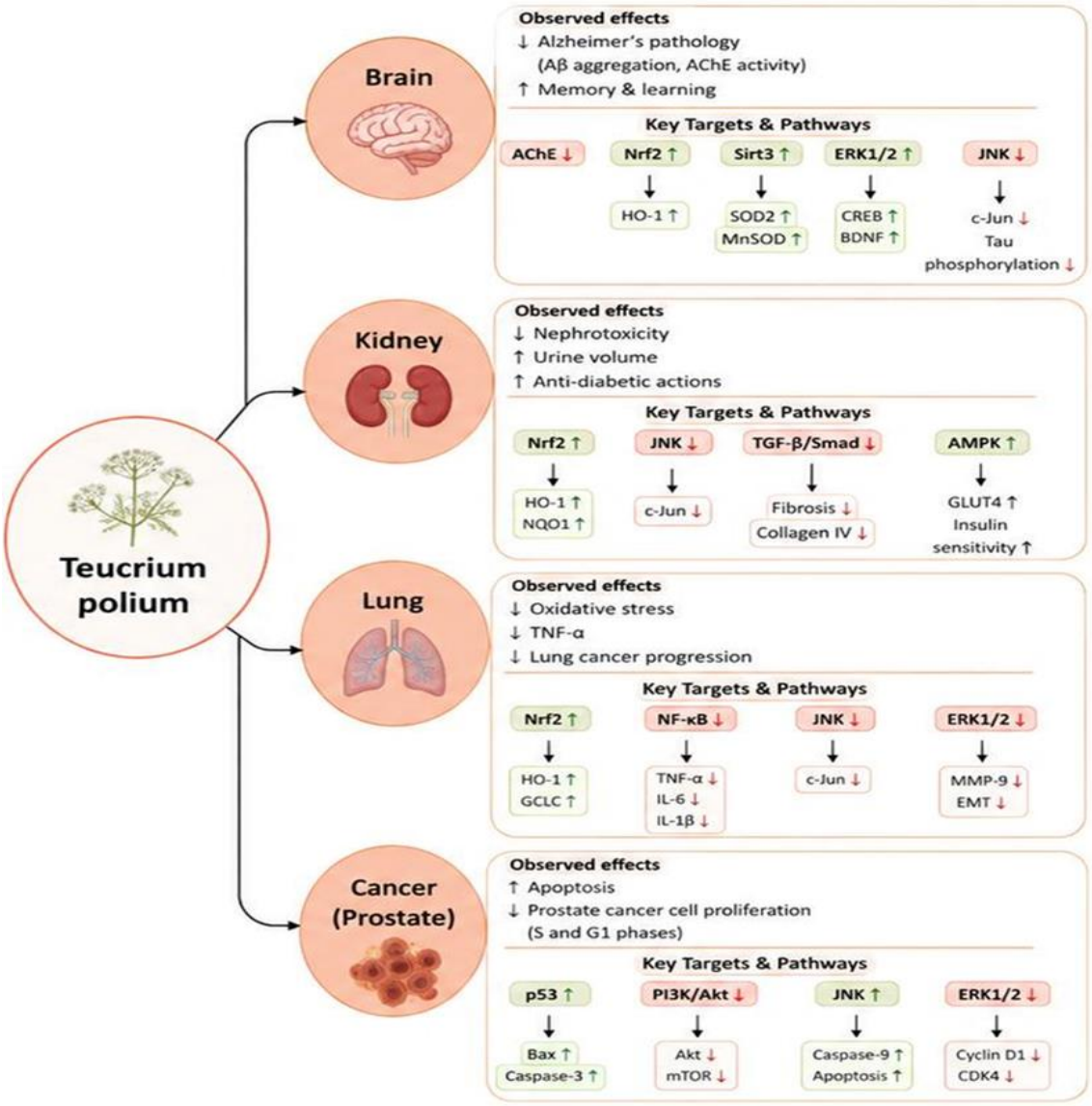


Figure 2.Therapeutics effects of TP on the brain, kidney, lung and prostate cancer with associated molecular targets and signaling pathways.Aβ, amyloid-beta; AChE, acetylcholinesterase; Akt, protein kinase B; AMPK, AMP-activated protein kinase; Bax, Bcl-2-associated X protein; BDNF, brain-derived neurotrophic factor; CDK4, cyclin-dependent kinase 4; CREB, cAMP response element-binding protein; EMT, epithelial–mesenchymal transition; ERK1/2, extracellular signal-regulated kinase 1/2; GCLC, glutamate-cysteine ligase catalytic subunit; GLUT4, glucose transporter type 4; HO-1, heme oxygenase-1; IL-1β, interleukin-1 beta; IL-6, interleukin-6; JNK, c-Jun N-terminal kinase; MMP-9, matrix metalloproteinase-9; MnSOD, manganese superoxide dismutase; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappa B; NQO1, NAD(P)H quinone dehydrogenase 1; Nrf2, nuclear factor erythroid 2-related factor 2; p53, tumor protein p53; PI3K, phosphoinositide 3-kinase; Sirt3, sirtuin 3; SOD2, superoxide dismutase 2; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha. ↑, increase; ↓, decrease.

TP and ulcerative colitis

Mehrabani et al. (2012) used 6% acetic acid administered by enema to induce ulcerative colitis in dogs, resulting in severe colonic ulceration and inflammation, weight loss, diarrhea, and hematochezia. Following induction of colitis, rectal administration of TP (80% ethanol extract of the dried whole plant; 400 mg/kg/day, transrectally [and orally per the abstract]) (400 mg/kg/day) for one month produced significant clinical and histological improvement (Mehrabani et al. 2012).

Some studies reported that the aqueous extract of TP whole plant was not toxic to

cultured hepatocytes, as it preserved mitochondrial respiration and maintained cell membrane integrity (Panovska et al. 2007).

Mehrabani et al. further reported that TP whole ethanol extract treatment (400 mg/kg/day) significantly reduced colonic damage in dogs with ulcerative colitis. Following treatment, colonic architecture was completely restored, the number of healthy cells increased, and inflammatory cell infiltration was reduced. In addition, the surface epithelium and mucosal layer of the colon recovered following TP administration (Mehrabani et al. 2012).

TP whole hydroalcoholic extract also reduced intestinal myeloperoxidase (MPO) levels and inflammation scores in radiation-induced intestinal injury. However, intestinal TBARS levels, GSH content, and other histological parameters did not change significantly (Demirel et al. 2011b). Parsaee et al. also reported an antispasmodic effect of TP *in vitro*. Treatment with whole TP aqueous extract (47, 94, 188, 376, and 470 mg/L) significantly reduced ileal contractions induced by acetylcholine administration (Parsaee and Shafiee-Nick 2006) (Figure 2).

TP and brain

The brain is a highly specialized organ controlling cognition, movement, and physiology. Synaptic dysfunction in specific cholinergic networks has been implicated in β-amyloid-induced neurodegeneration investigated the neuroprotective effects of TP using *in vivo* single-unit extracellular recordings in rats. Following 12 weeks of intraventricular administration of Aβ (25–35), excitatory responses decreased while inhibitory synaptic activity increased in the nucleus basalis magnocellularis (NBM)-hippocampus and NBM-basolateral amygdala cholinergic circuits. TP whole plant ethyl alcohol-soluble extracts treatment restored the balance between excitatory and inhibitory responses by modulating synaptic transmission and improving short-term plasticity, suggesting a protective effect against β-amyloid-induced neuronal dysfunction (Simonyan et al. 2025).

Experimental studies have shown that appropriate doses of hydroalcoholic extract of aerial part of TP improve learning and memory performance in diabetic rats (Mousavi et al. 2015). The neuroprotective effects of ethyl alcohol soluble extract of TP whole plant may also be attributed to its bioactive flavonoids. Luteolin enhances long-term potentiation (LTP) and memory through activation of cAMP response element-binding protein (CREB), whereas apigenin modulates GABAergic and glutamatergic neurotransmission and protects hippocampal neurons against excitotoxicity (Jayawickreme et al. 2024; Simonyan and Chavushyan 2016).

TP hydroalcoholic extracts is considered a promising candidate for the prevention and management of Alzheimer's disease and related neurodegenerative disorders because of its antioxidant activity and its ability to inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), thereby enhancing cholinergic neurotransmission (Bahramikia et al. 2009; Bahramikia and Yazdanparast 2012a; Hano et al. 2026) . These effects may be associated with the high polyphenol content of TP, as phenolic compounds are major contributors to the neuroprotective properties of plants belonging to the Lamiaceae family.

Despite these beneficial effects, potential neurotoxicity has also been reported that treatment with crude aerial part of TP ethanolic extract induced apoptosis, neuronal degeneration, vacuolation, foam cell formation, and reduced cell proliferation in brain tissue, indicating that the neurological effects of TP may depend on dose, extract type, and duration of administration (Nematollahi-Mahani et al. 2007; Nematollahi et al. 2022).

TP and renal system

The kidneys play a central role in maintaining homeostasis through filtration of metabolic waste, regulation of electrolyte balance, and control of plasma osmolarity. Their susceptibility to drug-induced injury has prompted investigation of the nephrotoxic and nephroprotective potential of herbal compounds, including TP.

One study investigated the nephrotoxic effects of TP whole plant hydroalcoholic extract in Wistar rats receiving intraperitoneal doses of 50, 100, 150, or 200 mg/kg for 28 days. The authors reported that no significant renal damage was observed during the treatment period; however, following a 28-day withdrawal period, renal lesions including degeneration, destruction, and vacuolization became evident. Based on these findings, the authors suggested that TP may be associated with renal tubular injury and should therefore be used with caution(Baradaran et al. 2013).

Although the exact mechanism remains unclear, oxidative injury has been proposed as a possible contributing factor. The authors suggested that renal failure was likely secondary to intravascular hemolysis and improved with supportive therapy.

Baradaran et al. (2013) evaluated the nephrotoxic effects of TP whole plant hydroalcoholic extract in male Wistar rats. No renal injury was observed during the treatment period; however, renal damage characterized by vacuolation, degeneration, and tissue destruction became evident after cessation of treatment, and acute kidney injury developed approximately two months following TP administration (Baradaran et al. 2013) (Figure 3).

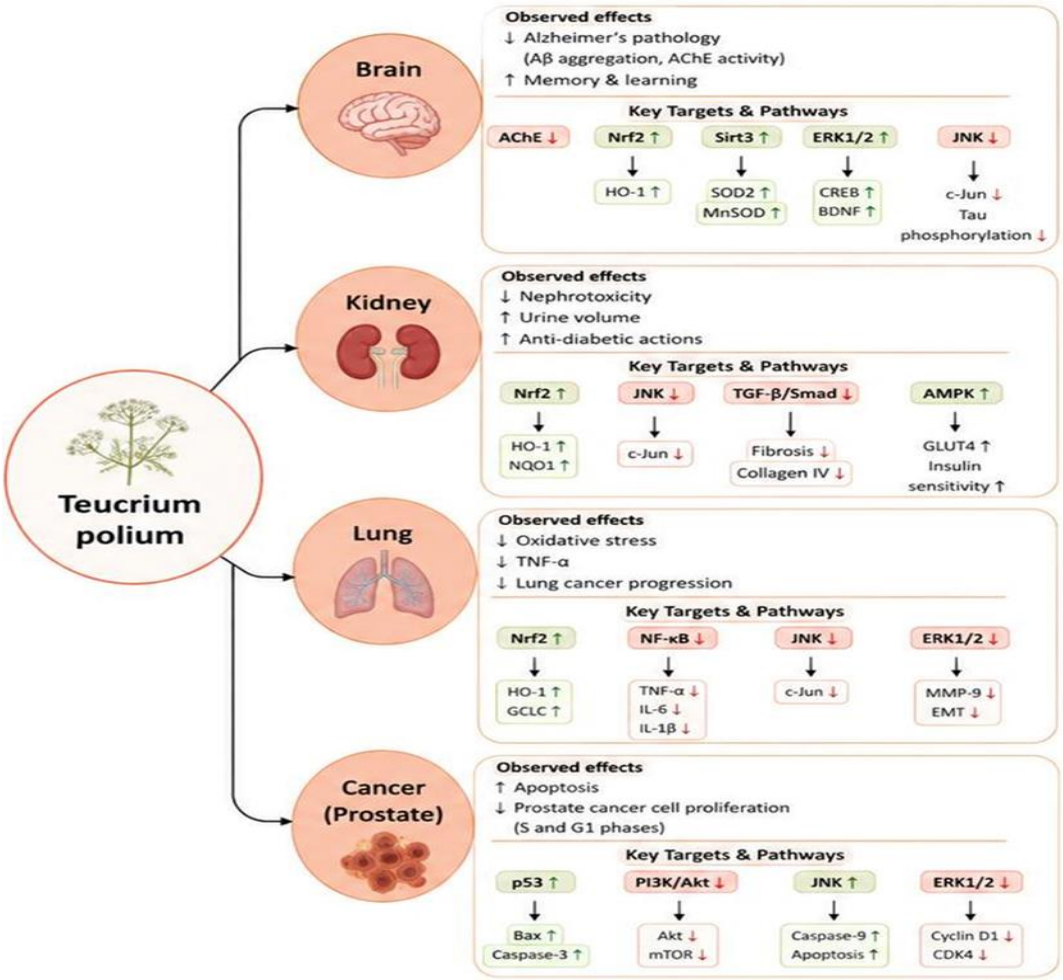


Figure 3.Therapeutics effects of TP on the brain, kidney, lung and prostate cancer with associated molecular targets and signaling pathways.

Calcium oxalate (CaOx) nephrolithiasis is the most common type of kidney stone (Huang et al. 2020). Oxalate induces nephrolithiasis in experimental animals through its conversion to endogenous oxalic acid in the liver (Brzica et al. 2013)

Diuretics are commonly used to increase urinary flow and facilitate the elimination of urinary sediments. TP whole plant hydroalcoholic extract exhibits significant diuretic activity by increasing urine volume compared with controls. This effect is likely related to the presence of flavonoids, glycosides, saponins, carbohydrates, tannins, and terpenoids (Al-Mamoori et al. 2022).

Although TP exhibits diuretic activity that may be beneficial in urolithiasis, evidence from experimental and clinical studies indicates that prolonged or high-dose administration may induce renal tubular injury. These findings underscore the importance of dose optimization and careful monitoring in any potential clinical use of TP (Al-Mamoori 2020; Khazaei et al. 2018).

TP and blood parameters

Hematological assessment provides important information on the effects of pharmacological agents on erythrocyte, leukocyte, and platelet populations. Several studies have evaluated the impact of TP on blood parameters in experimental models of hepatotoxicity and metabolic disease (Etim et al. 2014).

Carbon tetrachloride administration induces hepatotoxicity and decreases hematological parameters such as white blood cell (WBC) count, red blood cell (RBC) count, mean corpuscular hemoglobin concentration (MCHC), and platelet (PLT) count. Rahmouni et al. (2017) reported that treatment with TP or vitamin C attenuated carbon tetrachloride-induced hemotoxicity and hepatic injury and improved these hematological parameters(Rahmouni et al. 2017).

Significant increases in blood urea, sodium, and potassium levels were observed, and elevated urea concentrations were associated with enhanced protein catabolism and impaired renal function.

Furthermore, co-administration of the extract with carbon tetrachloride increased ALT and AST levels in rats with hepatotoxicity. Platelet and white blood cell counts also increased compared with controls. In contrast, treatment of hyperlipidemic mice with TP hydroalcoholic extract reduced serum cholesterol and triglyceride levels in a dose-dependent manner (Rahmouni et al. 2017).

TP and pulmonary system

The lungs are highly susceptible to oxidative stress, inflammation, and fibrosis. The antioxidant and anti-inflammatory properties of TP have been investigated in several experimental models of pulmonary injury and lung cancer.

Pulmonary fibrosis represents a terminal stage of chronic lung injury. TP may attenuate the progression of pulmonary damage through its antioxidant properties. Hasani et al. (2007) evaluated the antioxidant activity of whole plant hydroalcoholic extract of TP at doses of 50, 100, and 200 mg/kg for two weeks and reported a significant reduction in oxidative stress in mice (Hasani et al. 2007).

TP exhibits antibacterial, antioxidant, and anti-inflammatory activities. The authors attributed this effect to the high phenolic and flavonoid contents of the extract and its potent antioxidant activity.

Molavinia et al. (2023) reported that hydroalcoholic extract of TP whole plant significantly improved paraquat-induced lung injury in a dose-dependent manner(Molavinia et al. 2023a).

One study demonstrated that TP extract inhibited lung cancer cell proliferation and disrupted cell-cycle progression, ultimately inducing significant cell death. Treatment with TP whole plant extract at concentrations of 100, 150, and 200 µL/mL resulted in a dose-dependent increase in cell death in H322 and A549 lung cancer cell lines (Alachkar and Al Moustafa 2011).

Rajabalian (2008) reported that combinations of TP whole plant methanolic extract with anticancer agents such as vincristine and doxorubicin induced greater apoptosis in several human cancer cell lines compared with either treatment alone (Rajabalian 2008).

Kandouz et al. (2010) demonstrated that TP extract inhibited β-catenin phosphorylation through Src dephosphorylation, thereby affecting signaling pathways involved in cell adhesion and tumor progression. The anticancer effects of TP may also be attributed to its flavonoid constituents, which induce apoptosis through p53-dependent and other apoptosis-regulating pathways (Kandouz et al. 2010a).

The protective potential effects of hydroalcoholic extract of TP whole extract against paraquat-induced lung fibrosis was shown (Molavinia et al. 2023b) (Figure 2).

TP and antidiabetic properties

Diabetes mellitus is a chronic metabolic disorder associated with cardiovascular disease, cancer, and chronic respiratory diseases. Loss of pancreatic β-cells is a characteristic feature of diabetes, and oxidative stress contributes to β-cell dysfunction and destruction (Cnop et al. 2005). Therefore, compounds with antioxidant activity may promote β-cell regeneration and restore insulin secretion.

Experimental evidence suggests that aqueous and methanolic extracts of TP aerial part exerts antidiabetic effects through stimulation of insulin secretion and enhancement of β-cell regeneration (Mirghazanfari et al. 2010). Some studies reported that dried TP whole extract contained flavonoids with insulinotropic activity at a concentration of 500 µg/mL. However, no significant changes in serum cholesterol or triglyceride levels were observed in diabetic animals following treatment (Petreska et al. 2011; Stefkov et al. 2011).

It has been reported that rutin and apigenin, two major flavonoids of TP, stimulated insulin secretion, an effect attributed to their antioxidant properties (Hosseinzadeh and Nassiri-Asl 2014).

TP is widely recognized for its antidiabetic potential. Its extracts reduce blood glucose levels in experimental diabetic models and stimulate insulin secretion from pancreatic β-cells *in vitro*. These effects are largely attributed to bioactive flavonoids such as apigenin, quercetin, and rutin (Albadr et al. 2022).

TP and hepatocellular carcinoma

Movahedi et al. (2014) reported that the control group exhibited the highest mortality rate in an experimental HCC model. Although comparable mortality data for TP whole extract-treated groups remain limited, weight loss is commonly associated with advanced liver cancer (Movahedi et al. 2014).

TP and colorectal cancer

Colorectal cancer (CRC) is the third most common malignancy and the fourth leading cause of cancer-related mortality worldwide. The intestinal microbiota plays a crucial role in colorectal carcinogenesis, and dysbiosis can promote tumor development through chronic inflammatory pathways(Sánchez-Alcoholado et al. 2020).

Al-Otaibi and AlMotwaa (2022) reported that a nanoparticle formulation combining Oxa and TP essential oil exerted a synergistic anticancer effect. Cells treated with Oxa+TPO-NANO exhibited a significantly higher rate of apoptosis than cells receiving monotherapy. The proposed mechanism involved ROS-mediated mitochondrial apoptosis in both wild-type and mutant p53 colon cancer cells (Al-Otaibi and AlMotwaa 2022).

It has been shown that TP whole plant methanolic extract treatment significantly increased mitochondrial ROS production and Sirt3 activity in HT-29 colorectal cancer cells. Elevated ROS levels may trigger mitochondrial-mediated cell death pathways and alter Sirt3 signaling. In contrast, under non-cancerous conditions,

ROS-induced upregulation of Sirt3 contributes to the reduction of oxidative stress (Khodaei et al. 2018).

Although Sirt3 protects normal cells against cytotoxic stress by maintaining mitochondrial function, its dysregulation may also influence tumorigenic signaling pathways. Khodaei et al. (2018) further demonstrated that TP whole plant methanolic extract increased Sirt3 activity approximately seven-fold compared with the enzyme derived from HT-29 cells. These findings suggest that TP exerts anticancer activity through mitochondrial modulation, increased ROS generation, activation of Sirt3, and induction of cell death in colorectal cancer cells(Khodaei et al. 2018).

TP and human prostate cancer

Prostate cancer is the second most common cancer in men and the fifth leading cause of cancer-related mortality worldwide. The disease is often asymptomatic during its early stages and typically progresses slowly. Both the incidence and mortality of prostate cancer are strongly associated with age, with the highest rates occurring in men older than 65 years (Rawla 2019).

Kandouz et al. (2010) reported that TP extract inhibited cell proliferation and induced cell-cycle arrest in the S phase, accompanied by a reduction in the G0/G1 phase in PC3 and DU145 prostate cancer cell lines. TP extract also promoted differentiation toward an epithelial phenotype through mesenchymal-to-epithelial transition (MET), a process closely associated with reduced invasion and metastatic potential, resulting in significantly decreased invasiveness and motility of these cells (Kandouz et al. 2010b).

Tafrihi et al. (2014) investigated the effects of *Teucrium persicum*, an Iranian species belonging to the same genus as *T. polium*. Using the highly aggressive PC-3 prostate cancer cell line, the authors demonstrated that the methanolic extract markedly inhibited cell viability. Given the taxonomic relationship between *T. persicum* and *T. polium*, similar antitumor properties may exist in TP, although further studies are required to confirm this assumption (Tafrihi et al. 2014).

Abdollahi-Karizno et al. (2022) reported that TP whole plant treatment exerted beneficial effects on prostate weight, epithelial height, and secretory activity in diabetic animals. However, treatment of healthy mice resulted in a reduction in epithelial height, suggesting that the effects of TP may vary according to physiological conditions (Abdollahi-Karizno et al. 2022).

Kandouz et al. (2010) further demonstrated that treatment of PC3 and DU145 cells with TP extract (100 µL/mL) for 1–4 days inhibited cell proliferation and induced a modest degree of apoptosis. Cell-cycle analysis revealed a reduction in the proportion of cells in the G0/G1 phase, accompanied by accumulation in the S and G2/M phases following 48 h of treatment. Untreated PC3 and DU145 cells exhibited a mesenchymal morphology, whereas exposure to TP extract for 24 h induced a phenotypic transition toward an epithelial morphology. Treated cells became flatter and displayed enhanced cell-to-cell adhesion compared with untreated controls. These findings suggest that TP suppresses prostate cancer progression through inhibition of proliferation, modulation of cell-cycle progression, induction of apoptosis, and promotion of mesenchymal-to-epithelial transition(Kandouz et al. 2010a) (Figure 3).

TP and heart

The heart is highly susceptible to oxidative stress and ischemic injury. The cardioprotective potential of plant-derived compounds has gained increasing attention, and several studies have investigated the effects of TP on cardiac function and vascular tone (Kroeker 2018).

Niazmand et al. (2011) reported that administration of *TP aerial part hydroalcoholic* extract at a dose of 80

mg/kg reduced mean arterial blood pressure under normotensive conditions, suggesting a relaxant effect on vascular smooth muscle. The authors also demonstrated relaxant effects of TP on both ileal and vascular smooth muscle tissues (Niazmand et al. 2011).

Amraei et al. (2018) reported that a high-cholesterol diet significantly increased serum triglyceride (TG), total cholesterol, and LDL-C levels while reducing HDL-C concentrations. Treatment with hydroalcoholic extract of *T. polium* significantly decreased serum TG, cholesterol, and LDL-C levels and increased HDL-C concentrations, indicating a pronounced hypolipidemic effect. These findings are consistent with previous reports showing that hydroalcoholic TP extract reduced total cholesterol levels by 29–46% in animal models (Amraei et al. 2018b).

Mahmoudabady et al. (2018a) and Niazmand et al. (2017) demonstrated that administration of hydroalcoholic TP extract significantly increased myocardial antioxidant defenses, including SOD, CAT, and thiol levels, while reducing lipid peroxidation, as reflected by lower TBARS concentrations following ischemia-reperfusion injury. Pretreatment with TP reduced ischemia-reperfusion-induced oxidative damage and reactive oxygen species (ROS) production, resulting in improved cardiac function. These protective effects were associated with reduced necrotic injury, evidenced by lower lactate dehydrogenase (LDH) and creatine kinase (CK) release. Improvements in heart rate (HR), coronary flow (CF), and other hemodynamic parameters further supported enhanced left ventricular function in isolated rat hearts(Mahmoudabady et al. 2018; Niazmand et al. 2017).

The cardioprotective effects of TP are primarily attributed to suppression of oxidative stress and preservation of ventricular function (Niazmand et al. 2017). TP also exhibits positive inotropic and chronotropic activities(Niazmand et al. 2008; Niazmand et al. 2011). In addition, its hypotensive and vasodilatory properties have been reported, with vasodilation at lower concentrations being mediated by nitric oxide and prostacyclin pathways (Mahmoudabady et al. 2014). The beneficial effects of TP on left ventricular developed pressure (LVDP) and coronary flow further support its potential role in protecting the heart against ischemic injury (Mahmoudabady et al. 2018).

The cardioprotective and vasorelaxant effects of TP may be partly mediated by its flavonoid and polyphenolic constituents, which enhance endogenous antioxidant defenses and modulate inflammatory signaling pathways.

Toxicological concerns and dose-dependency

Although TP demonstrates a broad spectrum of beneficial pharmacological effects, evidence from experimental and clinical studies indicates that its administration may also be associated with significant toxic effects, particularly at high doses or following prolonged use. The hepatotoxic potential of TP has been documented in several studies. Administration of the petroleum ether fraction induced apoptosis and vacuole formation in liver tissue (Mazokopakis et al. 2004; Polymeros et al. 2002) , while very high doses (4 g/kg) caused liver necrosis (Nematollahi et al. 2022). These findings suggest that the hepatic effects of TP are both dose- and fraction-dependent, with a narrow margin separating hepatoprotective from hepatotoxic doses.

Nephrotoxic effects have also been reported. Experimental studies demonstrated that while renal damage was absent during the active treatment period, tubular degeneration, vacuolization, and acute kidney injury emerged following cessation of TP administration, suggesting a delayed nephrotoxic mechanism (Baradaran et al. 2013).

The molecular basis of TP-induced toxicity remains incompletely understood.

Tacrine A and several neoclerodane diterpenoids present in TP have been proposed as potential mediators of hepatotoxicity (Bahramikia et al. 2022b; Nematollahi et al. 2022). The variability in toxic potential across different extract types and fractions further highlights the importance of identifying the specific constituents responsible for adverse effects.

Taken together, these findings underscore the necessity of dose standardization, careful selection of extract type, and rigorous toxicological evaluation before TP can be considered for safe clinical application. The therapeutic index of TP should be systematically defined in future studies, with particular attention to vulnerable populations such as pregnant women and patients with pre-existing hepatic or renal impairment.

Proposed mechanisms underlying the toxicity of neoclerodane diterpenoids include metabolic activation by cytochrome P450 enzymes, particularly CYP3A4, which may generate reactive metabolites capable of depleting glutathione and promoting oxidative cellular injury. Subsequent oxidative stress and mitochondrial dysfunction may contribute to loss of mitochondrial membrane potential and activation of apoptotic pathways, whereas severe cellular injury and energy depletion may ultimately result in necrotic cell death(Fiorentino et al. 2011; Khodaei et al. 2018) .However, these mechanisms remain incompletely characterized for individual T. polium constituents and should therefore be considered proposed rather than definitive pathways.

Phytochemical constituents and mechanistic basis of biological activities

The biological activities of TP are closely associated with its rich phytochemical composition, particularly flavonoids, phenylpropanoid glycosides, terpenoids, and iridoids. Among these compounds, apigenin, luteolin, rutin, verbascoside, and poliumoside have been identified as major bioactive constituents responsible for many of the reported pharmacological effects of TP (Bahramikia et al. 2022a; Rahmouni et al. 2021).

A principal mechanism underlying the therapeutic potential of TP is the modulation of oxidative stress. Several studies have demonstrated that flavonoids isolated from TP, including apigenin and rutin derivatives, exhibit potent free-radical scavenging activity, inhibit lipid peroxidation, and enhance endogenous antioxidant defenses. These effects contribute to the hepatoprotective, cardioprotective, and neuroprotective activities reported for TP (Allemailem et al. 2024; Sadeghi et al. 2022).

In addition to their antioxidant properties, flavonoids such as apigenin and luteolin modulate inflammatory signaling pathways. These compounds suppress the activation of NF-κB and downstream inflammatory mediators, thereby reducing oxidative damage and inflammatory responses. Such mechanisms may explain the anti-inflammatory and tissue-protective effects observed in various experimental models(Sadeghi et al. 2022).

Overall, the pharmacological properties of TP appear to result from the synergistic action of multiple phytochemicals acting through interconnected pathways involving oxidative stress modulation, inflammatory signaling regulation, cholinesterase inhibition, and apoptosis induction.

Integrated mechanisms underlying the organ-specific effects of Teucrium polium

Although the biological effects of *Teucrium polium* have been described separately in the liver, kidney, and brain, several common mechanisms appear to contribute to its organ-specific effects. The available evidence particularly points to the modulation of oxidative stress, inflammatory signaling, mitochondrial function, and apoptosis. These mechanisms may partly explain both the beneficial and adverse effects reported for *T. polium*,

depending on the dose, extract or fraction used, and duration of exposure.

Oxidative stress appears to be an important common pathway underlying the biological effects of T. polium. In experimental models of liver injury, T. polium extracts enhanced endogenous antioxidant defenses, including superoxide dismutase, glutathione peroxidase, glutathione reductase, and reduced glutathione, while decreasing lipid peroxidation. Similarly, the ethyl acetate extract improved the antioxidant status and reduced oxidative damage in carbon tetrachloride-induced hepatic injury. These findings support a role for restoration of cellular redox balance in the hepatoprotective effects of T. polium (Amini et al. 2009b; Panovska et al. 2007).

Inflammatory signaling represents another potentially shared mechanism. In experimental models of liver injury, T. polium treatment reduced TNF-α expression and decreased other inflammatory and injury-related mediators, including TGF-β and phosphorylated JNK, while improving the hepatic biochemical profile (Baali et al. 2016b). These findings suggest that attenuation of inflammatory responses may contribute to the protective effects observed in different pathological conditions. However, the available evidence does not yet establish a uniform anti-inflammatory mechanism across all organs.

Mitochondrial function may provide an additional link between the observed antioxidant, anti-inflammatory, and cytoprotective effects. In an experimental model of acetaminophen-induced hepatotoxicity, T. polium polyphenols improved mitochondrial bioenergetics while suppressing CYP2E1, GSTπ, and TNF-α expression. Restoration of mitochondrial function may therefore reduce oxidative injury and improve cellular survival under conditions of toxic stress (Baali et al. 2016b).

Apoptosis and cellular degeneration may also contribute to the adverse effects of T. polium. In contrast to the protective effects observed with moderate doses of some extracts, high-dose or specific fractions have been associated with apoptosis, tissue degeneration, and vacuolation in hepatic and brain tissues. Renal toxicity has likewise been reported after prolonged exposure, with renal tubular degeneration, destruction, and vacuolization becoming evident after treatment cessation in experimental animals (Baradaran et al. 2013; Khazaei et al. 2018).

Taken together, the available evidence suggests that oxidative stress, inflammatory responses, mitochondrial dysfunction, and apoptosis constitute interconnected mechanisms that may underlie both the therapeutic and toxicological effects of T. polium. However, these mechanisms should not be considered independent or universally applicable to all organs. Differences in extract composition, dose, exposure duration, and tissue susceptibility are likely to determine whether these pathways result in cytoprotection or tissue injury. Further mechanistic studies are required to clarify the contribution of specific signaling pathways, including Nrf2- and NF-κB-related pathways, to the organ-specific effects of T. polium.

Discussion

Teucrium polium exhibits a broad spectrum of biological activities, exerting protective and therapeutic effects on multiple organ systems, including the heart, liver, kidneys, brain, lungs, and gastrointestinal tract. Experimental and clinical evidence highlights its potential in the prevention and management of diverse pathological conditions such as colitis, cancer, and Alzheimer's disease, largely through its antioxidant, anti-inflammatory, and cytoprotective properties. Despite promising findings, variations in phytochemical composition, dosage, and preparation methods underline the necessity for well-designed clinical trials to validate its efficacy, establish safety

profiles, and clarify underlying mechanisms. Overall, T. polium emerges as a valuable medicinal plant with significant pharmacological promise, meriting further exploration as a complementary or adjunctive therapeutic agent.

The studies reviewed in this article provide valuable insights into the biological effects of TP; however, several limitations should be acknowledged. The majority of available evidence is derived from in vitro and animal studies, and well-designed clinical trials evaluating the efficacy and safety of TP in human subjects remain scarce. Furthermore, the phytochemical composition of TP varies considerably depending on geographic origin, growth stage, harvesting conditions, and extraction method, making direct comparisons across studies difficult. The lack of standardized dosing protocols and extract preparations further limits the reproducibility and clinical applicability of existing findings. In addition, the dose-dependent duality observed for hepatic and renal effects highlights the narrow therapeutic window of TP and underscores the need for rigorous toxicological profiling before any clinical application. The pharmacokinetic properties of TP bioactive constituents, including absorption, distribution, metabolism, and excretion, have not been systematically characterized, representing a critical gap in the current literature.

Future research should prioritize the development of standardized TP extracts with defined phytochemical profiles to ensure consistency across studies. Well-controlled clinical trials are needed to validate the efficacy of TP in conditions such as Alzheimer's disease, diabetes, inflammatory bowel disease, and cancer, and to establish safe dosage ranges in human populations. Mechanistic studies investigating the specific molecular targets of key flavonoids such as apigenin, luteolin, and rutin across different organ systems would further strengthen the scientific basis for therapeutic application. Given the evidence of both hepatoprotective and hepatotoxic effects, studies specifically aimed at defining the therapeutic index of TP and identifying the fraction or constituent responsible for its toxic effects are particularly warranted. Finally, the development of novel drug delivery systems, such as nanoparticle formulations, may help optimize the bioavailability and safety profile of TP-derived compounds for future clinical use.

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Conflicts of interest

No conflicts of interest are declared by the authors.

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Authors' Contributions

Mohammad Amin Rajizadeh and Zakieh Keshavarzi : conceived and designed the study and Writing the manuscript. Fatemeh Maghool and Vahid Hajali : Writing the manuscript , performed the literature search. Mohammad Mahdi Akbari : Writing the manuscript.

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