Review on *Teucrium polium* biological activities and medical characteristics against different pathologic situations

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Introduction

Treatment of various diseases using medicinal plants traced back to ancient times. *Teucrium polium*, the herb that has been used in traditional medicine, almost 2,000 years ago, is found mainly in the Mediterranean region and different areas of Iran especially in semi-arid parts of the mountains and plains.1,2 This herbaceous plant, belonging to the Lamiaceae family and flowering time is between June and August.3 (Fig. 1). This plant includes 300 species around the world, and has identified in 12 species in Iran. Among them, *T. polium*, has been used in traditional medicine.4 This plant has diuretic, tonic, antipyretic, anti-fungal, anti-spasmodic, anti-rheumatic, carminative and antibacterial properties.3,5

Moreover, it has hypoglycemic effects and has been used in diabetic patients as a hypoglycemic agent. Daily consumption of this plant helps to maintain normal levels of blood sugar and can be appropriate for conventional medications to control blood sugar.7 In addition, *T. polium* has anti-inflammatory activity,7 as well as reduce high body weight and high blood pressure6 and has antioxidant and lipid-lowering properties.

Numerous studies investigated the effects of *T. polium* against different pathological situations in different organs. So, in this review, we tried to demonstrate the different biological activates and medical properties of *T. polium* as a traditional plant. Particularly, we focused on the mechanisms underlying *T. polium*’s antioxidant, antibacterial and anti-cancer properties.

Source and Chemical Compounds of *T. polium* pheochromocytoma

*Teucrium polium* is perennial, herbaceous, with almost woody plants, to a height of 30 cm and has a white appearance and cotton. Flowers can be seen in white, yellow and white to yellow. This variability is seen not only in color, but also in flower stems that are branched or lying.8,9 *T. polium* distributes in rocky and sandy areas of Mediterranean, different parts of Europe, North of Africa and Southwest of Asia, including Iran (in various regions of North, West, South and Central arid mountains).2 Some compounds of *T. polium* have been introduced in different investigations including tannin, terpenoid, saponin, flavonoid, sterol, β-caryophyllene, diterpenoids, carophyrene oxide, asparagine, ditryne and resinous substances.10-13 Vokou and Bessiere14 reported that *T. polium* contain tannin, terpenoid, saponin, sterol, and flavonoid. It is used in the treatment of gastrointestinal diseases. Several compounds extracted from different parts of this plant have been structurally characterized: including Iridoid, flavonoid, eudesman and clerodane. The first returns to the years 1974–1979. In Egypt, α-pinene, menthofuran, monoterpenes (myrcene, ocimene, pulegone have presented as the main of *T. polium* components).

β-Eudesmol has detected in *T. polium* in Tunisia.14 In the region of Saudi Arabia (subspecies not listed), monoterpenes (β-pinene, limonene, α-phellandrene, linalool, and terpinen-4) and terpenes (γ-cadinene, cedrenol, guaiol) have detected.8 In Greece (subspecies not reported), *T. polium* contains terpenes: α- and γ-cadinols and β-caryophyllene.12 It has been reported that this agent in Spain is rich of monoterpenes that often consisting of α- and β-pinenes, limonene, terpinen-4 and pinocarveol-18 (Table 1).15

Antioxidant Capacity of *T. polium*

Therapeutic benefits of medicinal plants are often attributed to their antioxidant properties.16,17 Different researches in recent years demonstrated that *T. polium* has high antioxidant properties. Many species of medicinal plants, especially those belonging to the mint family, such as sage, tucecum, pennyroyal and thyme have strong antioxidant activity.17 Number of phenolic compounds with strong antioxidant activity in extracts of these plants have been identified.18 HPLC analysis...
showed that the highest levels of flavonoid in \textit{T. polium} species are in \textit{chamaedrys} and \textit{T. polium}. In vitro research showed that \textit{T. polium} has the antioxidant activity and free radical scavenging activity.\textsuperscript{19,20} In several research, the effect of \textit{T. polium} on oxidation of various tissues have studied and the inhibitory effects of the plant extract against peroxidation, have proved. In this regard, the methanolic extract of \textit{T. polium} protects red blood cells against lipid peroxidation induced by hydrogen peroxide.\textsuperscript{21} Kadifkova Panovska et al.\textsuperscript{22} reported that different factions of \textit{T. polium} (diethyl ether, ethyl acetate and \textit{n}-butanol) have inhibitory effect against oxidation. Aqueous extracts prepared from leaves of \textit{T. polium}, suppresses iron-induced lipid peroxide oxidation in rat liver as well as Trolox, i.e., analog of vitamin E.

\textbf{Anti-diabetes Effects of \textit{T. polium}}

Some plants are used as hypoglycemic agents and their extracts have studied in the treatment of diabetic patients.\textsuperscript{22,23} Several animal studies were carried out to evaluate the effect of \textit{T. polium} on blood glucose concentrations. In a study by Jemal et al. (2012), it was shown that intravenous injection of boiled \textit{T. polium} caused a significant reduction in blood glucose in diabetic group, compared with a control group that received normal saline.\textsuperscript{24} Hydro-alcoholic extract of \textit{T. polium} can reduce blood cholesterol and glucose and also improves insulin secretion in diabetic rats.\textsuperscript{24} Esmaeili et al. (2009) reported that flavonoid compounds of \textit{T. polium}, increase insulin secretion from pancreatic beta cells (56\%). This finding was related to flavonoid antioxidant effects of \textit{T. polium}.\textsuperscript{25} Zal et al.\textsuperscript{26} demonstrated that \textit{T. polium} decreased blood glucose in diabetic mice and it has been normal within 8 days. Other studies have shown that aqueous extract of \textit{T. polium} reduces blood sugar in diabetes rat with single dose; it increases insulin secretion and thereby decreases blood glucose in diabetic rats.\textsuperscript{27} But, the extracts of this plant did not have a significant effect on blood sugar of rabbits.\textsuperscript{28} According to studies that evaluated the effect of \textit{T. polium} on blood sugar levels, it seems that the plant extract may improve insulin function in an animal model. But according to the conflicting reports and deficit of human studies on the effects of this herb on blood sugar level, currently commenting on proven effects of \textit{T. polium} as hypoglycemic agent is difficult and clinical research seems is necessary.

\textbf{Anti-cancer Effects of \textit{T. polium}}

Cancer has remained a major cause of disability and mortality in worldwide.\textsuperscript{29} Despite recent advances in early detection and treatment of cancer, continues to be unstoppable, threatening health and quality of human life. Traditionally, herbal compounds have long been considered in the treatment of cancer and drugs such as doxorubicin and paclitaxel that are derived from plants are also used in the treatment of cancer. Despite the abundance of different plant species in the world, only 1–10\% of plant species composition around the world, have been studied.\textsuperscript{30} In recent years, anti-cancer properties of \textit{T. polium} have evaluated in several experiments and cytotoxic effects of total extracts and derivatives of this plant against cancer cells has been reported. Anti-cancer properties of this plant know more about to terpenoid and flavonoid compounds. For example, in a study, anti-cancer effect of methanolic extract of \textit{T. polium} and vincristine, vinblastine and doxorubicin against cell lines is shown: Skmel -3 (melanoma), Saos-2 (osteosarcoma), SW480 (colon cancer), MCF-7 (breast cancer), KB (oral epidermal cell line), EL (bladder carcinoma) and A431 (epidermoid carcinoma). Administration of \textit{T. polium} and anti-cancer drugs such as vincristine, vinblastine or doxorubicin can enhance the ability of chemotherapy drugs to cancer and also minimizes side effects.\textsuperscript{31} Flavonoids have been considered as the most potent inducer of apoptosis.\textsuperscript{32} Anti-cancer and cytotoxic effects of \textit{T. polium} in different types of human cell lines is tested such as cervical cancer (HeLa), chronic myeloid (K562), colon cancer (Caco-2, HCT-116, LoVo, SW480), glioblastoma multiforme (REYF-1), hepatoblastoma (HepG2), carcinoma of the larynx (HEP-2), lung cancer (COR-123), prostate cancer (DU145, PC3).\textsuperscript{33–36} Additionally, the cytotoxic effects of ethanolic extract of \textit{T. polium} in four cell lines were examined to evaluate the formation of colonies: A549 (adenocarcinoma of the lung), BT20 (cancer of the ducts of the breast), MCF7 (breast adenocarcinoma) and PC12 (pheochromocytomaFV mice). As well, they compared cytotoxicity of \textit{T. polium} with taxol, an anti-cancer agent. The results demonstrated that ethanolic extract of \textit{T. polium}, inhibits growth of all cell lines effectively.

\begin{table}[h]
\centering
\caption{Isolated chemical compounds of \textit{T. polium} in different studies}
\begin{tabular}{|l|l|l|l|}
\hline
Chemical compound & Country & Year & Author (Reference) \\
\hline
β-pinene, limonene, α-phellandrene, linalool, terpinen-4-ol, γ- and δ-cadinenes, cedrol, cedrenol, guaiol & Saudi Arabia & 1979 & Hassan et al.\textsuperscript{29} \\
\hline
Tannin, terpenoid, saponin, sterol, and flavonoid & Greece & 1985 & Vokou et al.\textsuperscript{10} \\
\hline
Myrcene, α-pinene, menthofuran, ocimene, pulegone & Egypt & 1974 & Wassel et al.\textsuperscript{14} \\
\hline
α- and β-pinenes, sabinene, terpinen-4-ol and pinocarveol & Spain & 1993 & Pérez-Alonso\textsuperscript{14} \\
\hline
\end{tabular}
\end{table}
Table 2. *T. polium* biological activities and medical characteristics according to the different studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Groups</th>
<th><em>T. polium</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Twaij (1987)</td>
<td>Rat</td>
<td>Recovery of stomach ulcer</td>
</tr>
<tr>
<td>Munir (1988)</td>
<td>Rat</td>
<td>A significant reduction in blood glucose concentration</td>
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<tr>
<td>Lalibert and Villeneuve (1996)</td>
<td>Human</td>
<td>Lethargy, jaundice, elevated liver enzymes using <em>T. polium</em> 6 months</td>
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<tr>
<td>Zal et al. (2001)</td>
<td>Rat</td>
<td>Glucose reduction within 8 days</td>
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<tr>
<td>Zal et al. (2001)</td>
<td>Rat</td>
<td>Degenerative changes in liver lobules</td>
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<tr>
<td>Rasekh (2001)</td>
<td>Hyperlipidemic rat</td>
<td>Lower cholesterol and triglycerides</td>
</tr>
<tr>
<td>Afifi et al. (2005)</td>
<td>Rabbit</td>
<td>No significant effect on blood sugar</td>
</tr>
<tr>
<td>Baluchnejadmojarad T et al. (2005)</td>
<td>Rat</td>
<td>Analgesic effect</td>
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<tr>
<td>Shahraki et al. (2006)</td>
<td>Rat</td>
<td>Lower blood sugar levels of diabetic mice</td>
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<tr>
<td>Shahraki et al. (2006)</td>
<td>Rat</td>
<td>Analgesic effect of visceral and somatic</td>
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<tr>
<td>Panovska et al. (2007)</td>
<td>Rat</td>
<td>Repair and regeneration of liver</td>
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<tr>
<td>Mehrabani et al. (2009)</td>
<td>Rat</td>
<td>Reducing gastric ulcer index by 90%</td>
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<td>Mousavi (2011)</td>
<td>Rat</td>
<td>Lower obesity parameters</td>
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<tr>
<td>Ayoubi et al. (2013)</td>
<td>Rat</td>
<td>Lower glucose in diabetic mice</td>
</tr>
<tr>
<td>Belmekki et al. (2013)</td>
<td>In vitro</td>
<td>The inhibitory effects on bacteria</td>
</tr>
<tr>
<td>Tabataeabi et al. (2014)</td>
<td>In vitro</td>
<td>Antimicrobial effect against gram positive bacteria</td>
</tr>
<tr>
<td>Mousavi et al. (2015)</td>
<td>Rat</td>
<td>Improving the devastating effects of diabetes on memory</td>
</tr>
<tr>
<td>Nematollahi (2007)</td>
<td>In vitro</td>
<td>Inhibit the growth of cell lines:</td>
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<tr>
<td></td>
<td></td>
<td>$\text{IC}_{50}:$ BT20:106 µg/ml</td>
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<td></td>
<td></td>
<td>$\text{IC}_{50}:$ MCF-7:140 µg/ml</td>
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<td></td>
<td></td>
<td>$\text{IC}_{50}:$ PC12:120 µg/ml</td>
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<td></td>
<td></td>
<td>$\text{IC}_{50}:$ A549:90 µg/ml</td>
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<tr>
<td>Eskandary (2007)</td>
<td>In vitro</td>
<td>Reduce the formation of clonal cell lines REYF-1</td>
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<tr>
<td></td>
<td></td>
<td>Methanolic extract: $\text{IC}_{50}:$ 95 µg/ml</td>
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<tr>
<td>Mahdinia (2012)</td>
<td>In vitro</td>
<td>Cytotoxicity on (U87) $\text{IC}_{50}:$ 64.47 µg/ml</td>
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<tr>
<td>Rajabalian et al. (2008)</td>
<td>In vitro</td>
<td>Cytotoxicity on cell lines:</td>
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<tr>
<td></td>
<td></td>
<td>$\text{IC}_{50}:$ Saos-2:109 µg/ml</td>
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<td></td>
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<td>$\text{IC}_{50}:$ Skmel:3–83 µg/ml</td>
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<td></td>
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<td>$\text{IC}_{50}:$ MCF-7:174 µg/ml</td>
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<td>$\text{IC}_{50}:$ SW480:139 µg/ml</td>
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<td>$\text{IC}_{50}:$ KB:174 µg/ml</td>
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<td>$\text{IC}_{50}:$ EJ:108 µg/ml</td>
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<td>$\text{IC}_{50}:$ A431:93 µg/ml</td>
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<tr>
<td>Kundaković (2011)</td>
<td>In vitro</td>
<td>Cytotoxicity on cell lines:</td>
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<tr>
<td></td>
<td></td>
<td>$\text{IC}_{50}:$ MDA-MB-361:130 µg/ml</td>
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<td></td>
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<td>$\text{IC}_{50}:$ MDA-MB-453:367 µg/ml</td>
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<tr>
<td>Menichin (2009)</td>
<td>In vitro</td>
<td>Cytotoxicity on cell lines:</td>
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<tr>
<td></td>
<td></td>
<td>$\text{IC}_{50}:$ RAW264/7:29/4 µg/ml</td>
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<td></td>
<td></td>
<td>$\text{IC}_{50}:$ CACO-2:52/7 µg/ml</td>
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<td>$\text{IC}_{50}:$ 2C32:91 µg/ml</td>
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<td>$\text{IC}_{50}:$ 23COR-L:104 µg/ml</td>
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Among the cell lines, A549 was more sensitive to PC12. 17 Cyto-
toxic and anti-tumor effects of the aqueous and methanolic 
extract of T. polium on human glioblastoma cell line (REYF-1) 
has been studied and proved that methanolic extract of T. polium 
decreases colony formation in a dose-dependent. The metha-
nolic extract was more effective than aqueous extract, due to 
the better solubility of the active chemical components in 
methanol. 14 It has been reported (2012) that terpenoids and 
antioxidants compounds derived from petroleum ether frac-
tion of T. polium accelerate cytotoxic effects against U87. 28

Antimicrobial Effects of T. polium

Teucrium polium aqueous extract has anti-bacterial proper-
ties, but anti-fungal effect has not been confirmed. 59 The 
results demonstrated that T. polium extract significantly has 
antimicrobial activity in vitro, especially on the strains of 
gram-positive bacteria. 40 Oil extracted from the T. polium with 
a minimum concentration of 3–5 μl/ml, has the inhibitory 
effect on Bacillus cereus bacteria, Enterococcus faecalis and 
Escherichia coli. 61 Raei et al. 12 confirmed the antibacterial 
activity of T. polium essential oil against urinary-isolated Kleb-
siella pneumoniae. Motamedi et al. 41 evaluated the antibac-
terial effects of T. polium on Staphylococcus aureus strains and 
they suggested that T. polium was an effective medicinal plant 
for treatment of infections caused by S. aureus. Servindik et al. 64 
determined the antimicrobial activity and chemical composi-
ton of T. polium essential oils provided from North Anatolian. 
They showed that this plant had an inhibition effect on 
resistant micro-organisms including methicillin-resistant 
Pseudomonas aeruginosa, S. aureus ATCC 6538, S. aureus 
(MRSA), E. coli Q157:H7 and B. cereus CCM 99. 65 So, this nat-
ural antibacterial source can be carried out to produce new 
drugs against different bacteria.

Antinociceptive and Analgesic Effects of T. polium

Oral administration of this plan is used as a visceral analgesic 
agent. In one study, use of T. polium extract, increased the time 
of tail reaction to painful stimulus in rats and it can be con-
cluded that this plant extract may has a visceral analgesic in 
addition to somatic analgesic. Although the exact mechanism, 
needs further investigation. T. polium extract at a dose of 200 
mg/kg for a period of 2 weeks, has been created a significant 
analgesic effect. 66 Verdi et al. 66 proved that aqueous extract of T. polium 
leaves induced antinociceptive effects through the 
central mechanisms in rat model of pain. Zendehelel et al. 66 
showed that the analgesic effect of T. polium mediated by 
opioidergic and histaminergic H1 and H2 receptors in mice 
model of visceral pain.

Effects of T. polium on Nervous System 
Related Disorders

Teucrium polium extract had positive effects on mice that were 
suffering from amnesia with scopolamine. It has been reported 
that T. polium extract can significantly reduce lipid peroxida-
tion in the hippocampus and cerebral cortex. Different doses 
of this agent were able to prevent learning difficulties. 72 In 
another study, results revealed T. polium (200 and 400 mg/kg), 
prevents the damaging effects of diabetes on memory, but a 
dose of 100 mg/kg T. polium does not has any positive effect on 
memory disorders. 40 As well, Mousavi et al. (2015) investig-
gated the beneficial effects of T. polium on diabetes-induced 
tissue oxidative damage and memory deficits in rats. Their 
findings of proved that T. polium protected the rat against 
the memory impairments induced diabetes by 
reducing the brain tissues oxidative damage in rats. 47 Simonyan 
et al. 49 demonstrated that hydroponic T. polium had protective 
effects on hippocampal neurodegeneration by modulating 
neurotransmitters activates and network plasticity in ovariect-
omized rats.

Effects of T. polium on Gastric Disorders

Teucrium polium extract inhibits the movement of the stomach 
and in traditional medicine; it is used as an antispasmodic. In 
a study, rats were treated with indomethacin to induce gastric 
ulcer. T. polium reduced the scarring at a rate of 50% after a 
week, 80% after 2 weeks and 90% after 4 weeks. The mucosal 
healing, and the reduction of proliferation, mucosal hyper-
plasia, migration of inflammatory cells were observed. 40 This 
agent at a dose of 150 mg/kg promoted wound healing at the 
rate of 50% in mice that their stomach ulcers were induced by 
starvation. Whereas, oral consumption of the extract improves 
gastric ulcers at the rate of 85%. 51

Vascular Effects of T. polium

Teucrium polium decreases aortic smooth muscle contraction 
induced by KCl and phenylephrine. Endothelium can inhibit 
contraction of smooth muscle of vessels through the synthesis 
and secretion of substances such as nitric oxide (NO) and can 
induce the contraction through the synthesis and secretion of 
endothelin. The difference in the effect of the contraction 
induced by KCl and phenylephrine in the presence or without 
endothelium indicates that part of the effect, mediates by 
endothelium. It seems that factors secreted by the endothel-
ium that effect vessels, are important due to relaxant proper-
ties of this plant that effect through the endothelium, In 
addition to the smooth muscle. This effect mainly applies via 
the inhibition of calcium influx. 52

Effects of T. polium on Renal Disorders

Some herbs may lead to kidney damage and should be used 
with caution. In a study (2013), the effect of ethanolic extract 
of T. polium on rat kidney was evaluated. Treatment of mice 
with doses of 50, 100, 150, 200 mg/kg for 28 days, did not 
increase the kidney damage in-group receiving T. polium com-
pared to the control group. However, 28 days after stopping the 
drug, kidney damage, emerged including degeneration, degra-
dation and vacuolization compared to the control group. 53

Effects of T. polium on Hepatic Disorders

In recent years, extensive studies have been done to evaluate the 
effect of T. polium extract on the liver. In most of these studies, T. polium 
had been caused degenerative changes, necrosis, hepatic 
toxicity and general side effects. Zal et al. 28 observed degenerative 
changes in hepatic lobuli in diabetic rats and it was concluded 
that although T. polium has hypoglycemic effect, but should be 
cautious about taking it. In another study, Mehdinia et al. 54

evaluated *Teucrium polium* fractions of petroleum ether on the mice liver toxicity and their results presented that administration of the extract significantly decreased body weight and changes some liver enzymes. In humans, several cases about liver damage have been reported and in one case after eating *T. polium*, hepatitis created that need liver transplantation. 15 In another report, following 5–6 months after taking *T. polium*, patients getting lethargy, jaundice with elevated liver enzymes and jaundice disappeared after 8 weeks of discontinuation. 16 In five patients who were given *T. polium*, at least 1 month, liver biopsy showed acute hepatitis in these patients. Liver function tests, 10–30 days after use improved and liver function was normal after 2–6 months. 17 In another report, 62 years old man, has used tea containing *T. polium* once daily, due to hypercholesterolemia and diabetes. Then after taking drug for 4 months, getting jaundice and liver biopsy revealed acute hepatitis and necrosis. 18 Injection of *T. polium* in doses of 50–150 mg/kg for 10 days, significantly reduced serum cholesterol and triglyceride levels in rats with hyperlipidemia. 19 A number of studies have also reported that *T. polium* consumption has cholestatic effects and causes hepatitis symptoms and reduction of the nerve cells conduct. 20 Hepatocyte necrosis, following *T. polium*, has reported in several studies, as well as elevated liver enzymes such as ALP, ALT, AST. 21–23 Panonska et al. assessed protective activity of ethyl acetate extract of *T. polium* against carbon tetrachloride induced liver damage. In this study, injection of *T. polium* extract induced liver regeneration for 7 days. 24 Although, *T. polium* as the herbal medicine, can be useful agent, but according to the studies on the liver, it seems to have toxic effects on this tissue and its use in humans should be done with caution.

**Conclusion**

Due to the effect of different species of *T. polium* on cancer cell lines, this plant can be considered as a natural source of powerful anti-cancer drugs in the future. In addition, due to the important role of angiogenesis in tumor growth, it seems that it is necessary to study anti-angiogenesis effect of *T. polium*, as a confirmation of cancer prevention. Although, *T. polium* can reduce blood sugar by increasing insulin secretion or increase hepatic metabolism or glucose, but since the aqueous and alcoholic extracts of this plant have hepatotoxic and necrotic properties in liver cells, has limited the therapeutic application of this plant and recommendation to consume in humans requires more studies and surveys.

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**References**


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