

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

Mozafar Khazaei,<sup>a</sup> Seyed Nouredin Nematollahi-Mahani,<sup>b</sup> Tahmineh Mokhtari,<sup>c</sup> Fatemeh Sheikhbahaei<sup>b</sup>

<sup>a</sup>Fertility and Infertility Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran.

<sup>b</sup>Department of Anatomy, Afzalipour School of Medicine, Kerman University of Medical Sciences, Kerman, Iran.

<sup>c</sup>Research Center of Nervous System Stem Cells, Department of Anatomy, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran.

Correspondence to Fatemeh Sheikhbahaei (email: am23384@gmail.com).

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**Objective** Herbal medicines and the use of these drugs in treating and preventing of certain diseases in the world and Iran have increased dramatically. *Teucrium polium*, one of the plants that has been used in traditional medicine nearly 2,000 years ago belongs to Labiatae family and is used as a diuretic, tonic, antipyretic, anti-fungal, anti-spasmodic, anti-rheumatic, carminative and an antibacterial agent.

**Methods** Information of this article has collected from the database of PubMed, ScienceDirect and Scopus.

**Results** The effects of *T. polium* on the liver, kidney, stomach, brain has investigated and antidiabetic, antioxidant, antimicrobial, and anticancer effects of this agent, has introduced. Several studies revealed that *T. polium* has a hypoglycemic effect and can help to control blood sugar. In addition, due to the undeniable effects of this plant against cancer cells, it can be considered as a natural resource, for the treatment of cancer.

**Conclusion** This review investigates multiple properties of *T. polium*.

**Keywords** cytotoxicity, medicinal properties, *Teucrium polium*

## Introduction

Treatment of various diseases using medicinal plants traced back to ancient times. *Teucrium polium*, the herb that has 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.<sup>1,2</sup> This herbaceous plant, belonging to the Lamiaceae family and flowering time is between June and August.<sup>3</sup> (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.<sup>4</sup> This plant has diuretic, tonic, antipyretic, anti-fungal, anti-spasmodic, anti-rheumatic, carminative and antibacterial properties.<sup>5,6</sup>

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.<sup>7</sup> In addition, *T. polium* has anti-inflammatory activity,<sup>8</sup> as well as reduce high body weight and high blood pressure<sup>9</sup> 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.<sup>10</sup> *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).<sup>2</sup> Some compounds of *T. polium* have been introduced in different investigations including tannin, terpenoid, saponin, flavonoid, sterol,  $\beta$ -caryophyllene, diterpenoids, caryophyllene oxide, asparagine, ditryne and resinous substances.<sup>11,12</sup> Vokou and Bessiere<sup>13</sup> 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,  $\alpha$ -pinene, menthofuran, monoterpenes (myrcene, ocimene, pulegone have presented as the main of *T. polium* components).

$\beta$ -Eudesmol has detected in *T. polium* in Tunisia.<sup>14</sup> In the region of Saudi Arabia (subspecies not listed), monoterpenes ( $\beta$ -pinene, limonene,  $\alpha$ -phellandrene, linalool, and terpinen-4) and terpenes ( $\gamma$ -cadinenes, cedrenol, guaiol) have detected.<sup>6</sup> In Greece (subspecies not reported), *T. polium* contains terpenes:  $\alpha$ - and  $\tau$ -cadinols and  $\beta$ -caryophyllene.<sup>13</sup> It has been reported that this agent in Spain is rich of monoterpenes that often consisting of  $\alpha$ - and  $\beta$ -pinenes, limonene, terpinen-4 and pinocarveol-18 (Table 1).<sup>15</sup>

## Antioxidant Capacity of *T. polium*

Therapeutic benefits of medicinal plants are often attributed to their antioxidant properties.<sup>16,17</sup> 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, teucrium, pennyroyal and thyme have strong antioxidant activity.<sup>18</sup> Number of phenolic compounds with strong antioxidant activity in extracts of these plants have been identified.<sup>19</sup> HPLC analysis

Fig 1. *Teucrium polium*.Table 1. Isolated chemical compounds of *T. polium* in different studies

Chemical compound	Country	Year	Author (Reference)
$\beta$ -pinene, limonene, $\alpha$ -phellandrene, linalool, terpinen-4-ol, $\gamma$ - and $\delta$ -cadinenes, cedrol, cedrenol, guaiol	Saudi Arabia	1979	Hassan et al. <sup>(6)</sup>
Tannin, terpenoid, saponin, sterol, and flavonoid	Greece	1985	Vokou et al. <sup>(13)</sup>
Myrcene, $\alpha$ -pinene, menthofuran, ocimene, pulegone	Egypt	1974	Wassel et al. <sup>(14)</sup>
$\alpha$ - and $\beta$ -pinenes, sabinene, terpinen-4-ol and pinocarveol	Spain	1993	Pérez-Alonso <sup>(14)</sup>

showed that the highest levels of flavonoid in *T. polium* species are in chamaedrys and *T. polium*. *In vitro* research showed that *T. polium* has the antioxidant activity and free radical scavenging activity.<sup>19,20</sup> In several research, the effect of *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 *T. polium* protects red blood cells against lipid peroxidation induced by hydrogen peroxide.<sup>21</sup> Kadifkova Panovska et al.<sup>20</sup> reported that different factions of *T. polium* (diethyl ether, ethyl acetate and *n*-butanol) have inhibitory effect against oxidation. Aqueous extracts prepared from leaves of *T. polium*, suppresses iron-induced lipid peroxide oxidation in rat liver as well as Trolox, i.e., analog of vitamin E.

### Anti-diabetes Effects of *T. polium*

Some plants are used as hypoglycemic agents and their extracts have studied in the treatment of diabetic patients.<sup>22,23</sup> Several animal studies were carried out to evaluate the effect of *T. polium* on blood glucose concentrations. In a study by Jemal et al. (2012), it was shown that intravenous injection of boiled *T. polium* caused a significant reduction in blood glucose in

diabetic group, compared with a control group that received normal saline.<sup>7</sup> Hydro-alcoholic extract of *T. polium* can reduce blood cholesterol and glucose and also improves insulin secretion in diabetic rats.<sup>24</sup> Esmaili et al. (2009) reported that flavonoid compounds of *T. polium*, increase insulin secretion from pancreatic beta cells (56%). This finding was related to flavonoid antioxidant effects of *T. polium*.<sup>25</sup> Zal et al.<sup>26</sup> demonstrated that *T. polium* decreased blood glucose in diabetic mice and it has been normal within 8 days. Other studies have shown that aqueous extract of *T. polium* reduces blood sugar in diabetes rat with single dose; it increases insulin secretion and thereby decreases blood glucose in diabetic rats.<sup>27</sup> But, the extracts of this plant did not have a significant effect on blood sugar of rabbits.<sup>28</sup> According to studies that evaluated the effect of *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 *T. polium* as hypoglycemic agent is difficult and clinical research seems is necessary.

### Anti-cancer Effects of *T. polium*

Cancer has remained a major cause of disability and mortality in worldwide.<sup>29</sup> 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.<sup>30</sup> In recent years, anti-cancer properties of *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 *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 *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.<sup>31</sup> Flavonoids have been considered as the most potent inducer of apoptosis.<sup>32</sup> Anti-cancer and cytotoxic effects of *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-I23), prostate cancer (DU145, PC3).<sup>33–36</sup> Additionally, the cytotoxic effects of ethanolic extract of *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 *T. polium* with taxol, an anti-cancer agent. The results demonstrated that ethanolic extract of *T. polium*, inhibits growth of all cell lines effectively.

Table 2. *T. polium* biological activities and medical characteristics according to the different studies

Authors	Groups	<i>T. polium</i>
Twajj (1987)	Rat	Recovery of stomach ulcer
Munir (1988)	Rat	A significant reduction in blood glucose concentration
Lalibert and Villeneuve (1996)	Human	Lethargy, jaundice, elevated liver enzymes (using <i>T. polium</i> 6 months)
Zal et al. (2001)	Rat	Glucose reduction within 8 days
Zal et al. (2001)	Rat	Degenerative changes in liver lobules
Rasekh (2001)	Hyperlipidemic rat	Lower cholesterol and triglycerides
Affi et al. (2005)	Rabbit	No significant effect on blood sugar
Baluchnejadmojarad T et al. (2005)	Rat	Analgesic effect
Shahraki et al. (2006)	Rat	Lower blood sugar levels of diabetic mice
Shahraki et al. (2006)	Rat	Analgesic effect of visceral and somatic
Panovska et al. (2007)	Rat	Repair and regeneration of liver
Mehrabani et al. (2009)	Rat	Reducing gastric ulcer index by 90%
Mousavi (2011)	Rat	Lower obesity parameters
Ayoubi et al. (2013)	Rat	Lower glucose in diabetic mice
Belmekki et al. (2013)	<i>In vitro</i>	The inhibitory effects on bacteria
Tabatabaei et al. (2014)	<i>In vitro</i>	Antimicrobial effect against gram positive bacteria
Mousavi et al. (2015)	Rat	Improving the devastating effects of diabetes on memory
Nematollahi (2007)	<i>In vitro</i>	Inhibit the growth of cell lines: IC <sub>50</sub> : BT20:106 µg/ml IC <sub>50</sub> : MCF-7:140 µg/ml IC <sub>50</sub> : PC12:120 µg/ml IC <sub>50</sub> : A549:90 µg/ml
Eskandary (2007)	<i>In vitro</i>	Reduce the formation of clonal cell lines REYF-1 Methanolic extract: IC <sub>50</sub> : 95 µg/ml
Mahdinia (2012)	<i>In vitro</i>	Cytotoxicity on (U87) IC <sub>50</sub> : 64.47 µg/ml
Rajabalian et al. (2008)	<i>In vitro</i>	Cytotoxicity on cell lines: IC <sub>50</sub> : Saos-2:109 µg/ml IC <sub>50</sub> : Skmel:3-83 µg/ml IC <sub>50</sub> : MCF-7:174 µg/ml IC <sub>50</sub> : SW480:139 µg/ml IC <sub>50</sub> : KB:174 µg/ml IC <sub>50</sub> : EJ:108 µg/ml IC <sub>50</sub> : A431:93 µg/ml
Kundaković (2011)	<i>In vitro</i>	Cytotoxicity on cell lines: IC <sub>50</sub> : MDA-MB-361:130 µg/ml IC <sub>50</sub> : MDA-MB-453:367 µg/ml
Menichin (2009)	<i>In vitro</i>	Cytotoxicity on cell lines: IC <sub>50</sub> : RAW264/7:29/4 µg/ml IC <sub>50</sub> : CACO-2:52/7 µg/ml IC <sub>50</sub> : 2C32:91 µg/ml IC <sub>50</sub> : 23COR-L:104 µg/ml

Among the cell lines, A549 was more sensitive to PC12.<sup>37</sup> Cytotoxic 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 methanolic extract was more effective than aqueous extract, due to the better solubility of the active chemical components in methanol.<sup>34</sup> It has been reported (2012) that terpenoids and antioxidants compounds derived from petroleum ether fraction of *T. polium* accelerate cytotoxic effects against U87.<sup>38</sup>

## Antimicrobial Effects of *T. polium*

*Teucrium polium* aqueous extract has anti-bacterial properties, but anti-fungal effect has not been confirmed.<sup>39</sup> The results demonstrated that *T. polium* extract significantly has antimicrobial activity *in vitro*, especially on the strains of gram-positive bacteria.<sup>40</sup> 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*.<sup>41</sup> Raei et al.<sup>42</sup> confirmed the antibacterial activity of *T. polium* essential oil against urinary-isolated *Klebsiella pneumoniae*. Motamedi et al.<sup>43</sup> evaluated the antibacterial 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*. Sevindik et al.<sup>44</sup> determined the antimicrobial activity and chemical composition 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.<sup>44</sup> So, this natural antibacterial source can be carried out to produce new drugs against different bacteria.

## Antinociceptive and Analgesic Effects of *T. polium*

Oral administration of this plant 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 concluded that this plant extract may have 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.<sup>69</sup> Verdi et al.<sup>45</sup> proved that aqueous extract of *T. polium* leaves induced antinociceptive effects through the central mechanisms in rat model of pain. Zendehdel et al.<sup>46</sup> 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 peroxidation in the hippocampus and cerebral cortex. Different doses of this agent were able to prevent learning difficulties.<sup>47</sup> 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 have any positive effect on memory disorders.<sup>48</sup> As well, Mousavi et al. (2015) investigated the beneficial effects of *T. polium* on diabetes-induced brain tissue oxidative damage and memory deficits in rats. Their findings proved that *T. polium* protected the rat against the memory impairments induced by diabetes by reducing the brain tissue oxidative damage in rats.<sup>47</sup> Simonyan et al.<sup>49</sup> demonstrated that hydroponic *T. polium* had protective effects on hippocampal neurodegeneration by modulating neurotransmitters activities and network plasticity in ovariectomized 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 hyperplasia, migration of inflammatory cells were observed.<sup>50</sup> 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%.<sup>51</sup>

## 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, mediated by endothelium. It seems that factors secreted by the endothelium that affect vessels, are important due to relaxant properties of this plant that effect through the endothelium, in addition to the smooth muscle. This effect mainly applies via the inhibition of calcium influx.<sup>52</sup>

## 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* compared to the control group. However, 28 days after stopping the drug, kidney damage, emerged including degeneration, degradation and vacuolization compared to the control group.<sup>53</sup>

## 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.<sup>26</sup> observed degenerative changes in hepatic lobules in diabetic rats and it was concluded that although *T. polium* has hypoglycemic effect, but should be cautious about taking it. In another study, Mehdiinia et al.<sup>54</sup>

evaluated *T. 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.<sup>55</sup> 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.<sup>56</sup> 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.<sup>57</sup> 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.<sup>58</sup> 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.<sup>12</sup> 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.<sup>59,60</sup> Hepatocyte necrosis, following *T. polium*, has reported in several studies, as well as elevated liver enzymes such as ALP, ALT, AST.<sup>52,61</sup> Panovska 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.<sup>62</sup> 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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