REVIEW OF THE TAXONOMY, ETHNOBOTANY, PHYTOCHEMISTRY, PHYTOTHERAPY AND PHYTOTOXICITY OF GERMANDER PLANT (TEUCRIUM POLIUM L.)

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Review Article

REVIEW OF THE TAXONOMY, ETHNOBOTANY, PHYTOCHEMISTRY, PHYTOTHERAPY AND PHYTOTOXICITY OF GERMANDER PLANT (*TEUCRIUM POLIUM L.*)

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ABSTRACT

Medicinal plants and phytogenic products have used for treatment of various diseases from ancient times in the folklore medicine all over the world. Crude plants extracts are now considered a valuable source for natural products used in the development of medicines against various diseases, for the development of pharmaceutical preparations, and for novel biomedical researches.

Germander (*Teucrium polium* L.) is a shrubby plant widely distributed in the mountains, hills and deserts of the Mediterranean regions and considered one of the most useful traditional medicinal plants in Palestine and other Middle Eastern countries. It has been used for centuries in the ethnopharmacology for the treatments of many pathophysiological conditions, such as diabetes, gastrointestinal disorders, rheumatism, inflammations, also used as diuretic, antipyretic, tonic, diaphoretic, analgesic, antihyperlipidemic and other disorders. During the last five decades, apart from the phytochemical characterization of the components of the *T. polium* plant, there has been significant interest in the medicinal applications and biological activity of this plant. This review summarizes more than 50 years of scientific knowledge of Germander. It provides an overview on its taxonomy, biological activities, the most well-known isolated compounds from all the plants parts, clinical studies, and pharmacological activities. Evidence-based medicinal applications of the plant extracts have been discussed along with their safety evaluation, especially the recent evidence for hepatotoxicity secondary to the long term use of this plant.

Keywords: *Teucrium polium* L, Biological activity, Ethnobotany, Phytochemical constituents, Phytotherapy, Phytotoxocity.

INTRODUCTION

The uses of the plants date back to the ancient times for treatment of different diseases, for drug discovery, cosmeceuticals and other ailments [1,2].

However, the astounding advantages of conventional medicine and synthetic medications overshadowed herbal and traditional alternative medicine [3,4].

The herbal utilizations as traditional health remedies are the most popular for 80% of the world population in Latin America, Africa, and Asia and have reported to have minimum side effects [5].

The use of herbal alternative medicinal therapeutics has increased the interest of herbalists and pharmacologists over the past decade. Historically, plants have provided excellent sources of inspiration for new effective medications, as herbal medicines have made contributions to the human health and well-being [6].

Thus, natural plants medications for over 50 years became less common, but still used in the developing countries and poor sections populations [7-9].

However, nowadays the majority of the world's populations in the developed and in the developing countries return back to the natural herbal products because the synthetic drugs could not cure recently discovered illnesses including AIDS and other serious types of viral infections, most common types of cancer and other diseases, otherwise the synthetic drugs could not treat chronic diseases but reduced their symptomatic complications, add to that the serious side-effects and adverse reactions of these synthetic chemical medications [10,11].

Flowering branches and leaves (aerial parts) of *Teucrium polium* plant have been used for over 2000 years in traditional folkloric medicine and its medical uses and applications have been reported in traditional herbal medicine by Jalinous and Socrates due to its diaphoretic, tonic, diuretic, antipyretic, stomachic, and antispasmodic properties [12,13].

TAXONOMICAL CLASSIFICATION

The *Teucrium* genus belongs to the Lamiaceae family, Ajugoideae subfamily [14] and in the international flora the genus *Teucrium* has been divided into six sections with forty nine species [15].

The species *Teucrium arduini* L. represent the *Stachyobotrys* section, the section *Chamaedrys* by *Teucrium chamaedrys* L., the section *Scorodonia* by *Teucrium scordium* L., and the section polium by *T. polium* L. and *Teucrium montanum* L. These are mostly perennial herbs, sub shrubs or shrubs except *Teucrium botrys* is an annual herbaceous plant. The species of this genus are commonly available in all continents of the world, but very large number of these species are presented, and wild grew in the Mediterranean regions from the ancient times [16].

VERNACULAR NAMES

T. polium L. common names are d'aja, j'ada, جعدة (Arabic); polium, pouliot de montagne, germandée tomenteuse (French); germander, mountain germander, felty germander, cat thyme, hulwort (English); camendrio di montagna, polio, polio primo, timo bianco (Italian); poleigamander, berggamander (German) [17,18].

DISTRIBUTION

Teucrium genus is a large and polymorphic plant widely distributed mainly in the sandy and rocky areas of Mediterranean regions, Europe, North Africa and in the temperate parts of Asia specially the South Western regions of Asia [19,20].

ECOLOGY

T. polium grows wildly in well-drained soil and usually developed in sunny regions belonged to the semiarid and arid bio-climates. It grows on hillsides, sands and in the stony mountains [21].

BOTANICAL DESCRIPTION

T. polium is a perennial shrubby and very polymorphous plant about 10-35 cm height. The flowers have a white or yellow corolla, in a globular small inflorescence. The calyx has bell shaped with 5 sub equal flat, triangular or acuminate triangular teeth. The leaves are white, tomentose on both sides, with downwards rolled rounded-toothed margins (Fig. 1). The fruits are light-brown to dark brown nutlets with a latticed surface; the flowering time takes place from April until June. All the plant aerial parts have aromatic, pleasant odor and bitter taste [22].

PHYTOCHEMISTRY

The phytochemical compounds isolated from different parts of the *T. polium* plant classifications and names are:

A. The volatile oils composition from Yugoslavian and Iranian Germander were mainly represented with germacrene D (11.9% and 23.6-13.2% respectively), while the major components of the Turkish polium species were ß - caryophyllene (18%), ß - pinene (18%) and α-pinene (12%). α -Pinene and ß-pinene were the major components of the volatile oils of *T. polium* ssp. valentinum from Turkey (7.58% and 10.18%, respectively) and Spain (15.8% and 1.7%, respectively) [23-27].

While Jordanian Germander contain 8-cedren-13-ol (24.8%), β-caryophllene (8.7%), sabinene (5.2%) and germacrene D (6.8%) [28].

Furthermore, the volatile oils components, which obtained from the aerial parts of *T. polium* ssp. aurasiacum by using water distillation from Algeria were α-cadinol (46.8%), 3ß-hydroxy- α- muurolene 22.5%, (It is the first time that this compound has been isolated from *T. polium* volatile oil) α -pinene (9.5%) and ß-pinene (8.3%) as the main constituents [29].

Phytochemical screening the Saudi Arabia *T. polium* volatile oils identified the presence of ten isoprenoidal phytochemical compounds including alcohols as linalool, cedrenol, cedrol, guaiol and terpine-4-ol and the hydrocarbons as β-pinene, γ-, δ-cadinene, limonene and α-phellandrene [30].

B. From the *T. polium* aerial parts isolated three new isoprenoids teuvincentins A, B and C and neo-clerodane diterpenoids have been isolated besides 4 already known diterpenes (isoeriocephalin, 19-acetylgnaphalin, eriocephalin and 3-deacetyl-20-*epi*-teulanigin) and the flavones cirsiliol and apigenin [31].

C. From the aerial parts were identified by gaschromatographic and spectroscopic techniques (1H-NMR and MS) stigmasterol, beta-sitosterol, brassicasterol, clerosterol and campesterol [32].

Fig. 1: *Teucrium polium* leaves and flowers

D. In the aqueous phase, the alcoholic extract were identified glucose, raffinose, fructose and rhamnose [32].

E. The major flavonoids compounds with antioxidant activity from *T. polium* L were rutin, apigenin (Fig. 2), apigenin-4, 7-dimethylether, cirsimaritin, cirsiliol, luteolin, 6-hydroxyluteolin, luteolin-7-O-glucoside, salvigenin, apigenin 7-glucoside, eupatorin, apigenin-5 galloylglucoside, 3′,6- dimethoxy apigenin, 4′,7- dimethoxy apigenin and salvigenin [33,34].

F. As well as from the aerial parts isolated iridoid glycoside teucardoside (Fig. 3) [35].

G. Four sesquiterpenoid compounds have been identified by using NMR technique, which names are:

- 4 β,5 α -epoxy-7 α H-germacr-10(14)-en-6 β -ol-1-one,
- 4 β,5 α -epoxy-7 α H-germacr-10 (14)-en,1 β -hydroperoxyl,6 β -ol,
- 4 β,5 β -epoxy-7 α H-germacr-10(14)-en,1 β hydroperoxyl,6 β -ol
- 4 α,5 β -epoxy-7 α H-germacr-10(14)-en,1 β -hydroperoxyl,6 α -ol [36].

ETHNOBOTANICAL USES

In the traditional herbal alternative medicine, *T. polium* has been prepared as decoctions and used for treatment of different pathophysiological disorders such as inflammations, gastrointestinal tract disorders, rheumatism, and diabetes. The tea of *T. polium* is usually used as traditional Iranian medicine for treating many diseases such as indigestion, abdominal pain, Type 2 diabetes and common cold [37], while used in the Palestinian folk medicine for treatment of gastrointestinal inflammations, as well as anti-spasmodic, anthelmintic and for treatment small box [38].

Other folk medicines in another countries are for treatments of liver diseases, ulcers, indigestion, common cold, headache, wound healing, abdominal colic, kidney stones, as well as hypoglycemic, antipyretic, anti-inflammatory, vermifuge, appetizer, expectorant and for treatment of smallpox [28,37-42].

PHYTOTHERAPEUTIC EFFECTS OF *T. POLIUM*

Hypoglycemic effect

The testing of an aqueous decoction extract from aerial parts of *T. polium* on rats with normoglycemic and streptozotocin-hyperglycemic, showed a significant reductions in rats blood glucose concentration after 24 hrs of intra-peritoneal administration and 4 hrs of intravenous administration, which could be due to the enhancement of glucose peripheral metabolism rather than an increase in insulin release.

Antidiabetic effect of an aqueous extract of the plant aerial parts was assessed in streptozotocin and normoglycemic hyperglycemic rats. The results of this experiment indicate that this extract have significant antihyperglycemic effect 4 hrs after intravenous administration and 24 hrs after intra-peritoneal administration. This result could be due to enhancement of peripheral metabolism of glucose rather than an increase in insulin release [43].

In addition, an oral administration of the crude extract for 6 weeks on rats with streptozotocin diabetes, showed a significant decrease in rat's blood glucose concentration for about 64% when compared with untreated diabetic rats. In addition to that, the crude extract showed a significant enhancement in the blood insulin level to almost 160%. Furthermore, a single dose administration of *T. polium* crude extract was able to enhance insulin secretion for about 135% at high glucose concentration, when it is *in-vitro* tested using isolated pancreatic rat islets. On the other hand, plant extract does not affect the pattern of insulin secretion when compared with untreated islets.

Another investigation demonstrated that the crude plant extract (500 mg of the plant powder per kg body weight) was orally administered to a group of streptozotocin diabetic rats for 6 consecutive weeks. A significant decrease (64%) was observed in the treated animals compared to the untreated diabetic rats, without any measurable

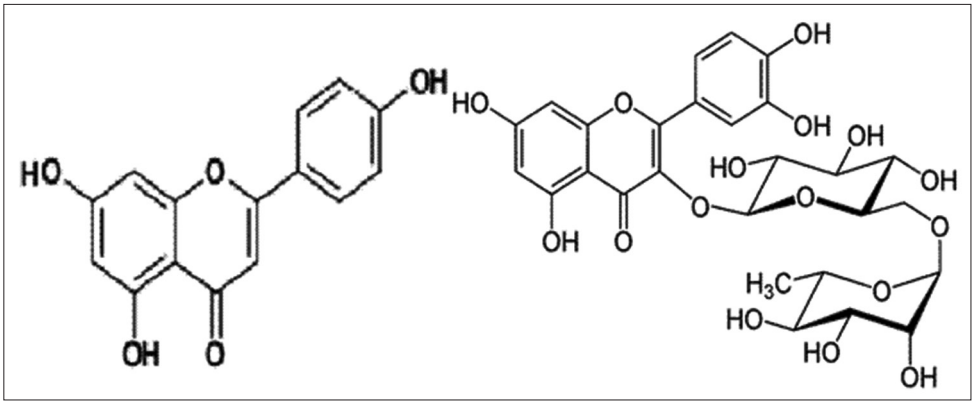

Fig. 2: Chemical structures for Apigenin and Rutin

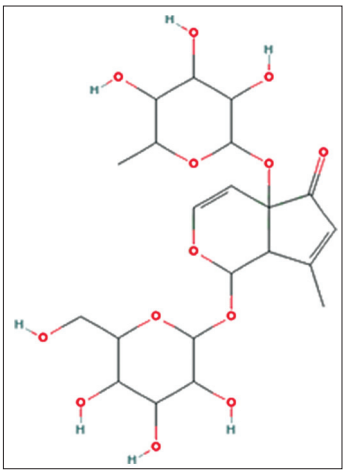

Fig. 3: Chemical structure for teucardoside

effects on the major biochemical factors. In addition, the crude extract significantly boosted the blood insulin level by almost 160% compared to the untreated diabetic rats. The insulin-tropic property of the Germander extract was further assessed by an *in vitro* investigation using isolated pancreatic rat islets. Our data indicated that the plant crude extract is able to enhance insulin secretion by almost 135% after a single dose of plant extract (equivalent to 0.1 mg sample plant aerial parts powder per mL of the culture medium) at high glucose concentration (16 mmol/L). Meanwhile, the time pattern of insulin secretion was not affected by the plant extract compared with the untreated islets [44].

A similar study was carried by Yazdanparas and his team (2005) on the function of streptozotocin diabetic rats after treated with crude extract of *T. polium*. The same result showed the decrease in blood glucose. Moreover, a significant decrease in the total bilirubin by 35%, glutamate pyruvate transferase by 30% and glutamate oxaloacetate transferase by 48%. Furthermore, they got same result when the studied the enhancement of insulin level and insulin secretions.

Another effort to evaluate the hypoglycemic activity of *T. polium* demonstrated that the crude plant aqueous extract, which was administered orally to a group of *Streptozotocin* induced diabetic rats for 6 consecutive weeks. Significant decrease in blood glucose by 64%, total bilirubin by 35% and glutamate oxaloacetate transferase by 48% and glutamate pyruvate transferase by 30% was observed compared with untreated diabetic rats. The blood insulin level was enhanced by almost 160%. The insulin-tropic property of the *T. polium* crude extract was further assessed by an *in vitro* investigation using isolated rat islets. These data indicated that *T. polium* crude extract is capable of enhancing insulin secretion by almost 135% after one dose of treatment at high glucose concentration. Meanwhile, without affecting the time pattern of insulin secretion by the islets, the plant extract seems to be capable of regenerating the islets of Langerhans in the treated compared to the untreated diabetic rats. These data clearly provide a mechanistic view concerning the hypoglycemic effect of *T. polium* extract through its significant effect on the pancreas [45].

T. POLIUM DECOCTION PHYSIOLOGICAL EFFECT IN DIABETIC RATS

Another study carried out by Hasanein and Shahidi showed a significant decrease in the triglyceride and glucose serum after an administration of 4% *T. polium.* Although, there are no significant effect of *T. polium* on the urea, aspartate aminotransferase (AST), uric acid, creatinine (CRT), cholesterol and alanine aminotransferase (ALT) level when compared tested and control groups. Also, there is no any significant effect shown after an administration of 2% *T. polium* except on the body weight of rats.

The results of this study showed that 4% dose of *T. polium* can decrease serum glucose level and triglyceride significantly, but cholesterol, urea, U acid, ALT, AST and CRT were not significant between the test and control groups after using *T. polium*. 2% concentration of the plant does not have any effect except on body weight [46].

Phytotherapeutic effects on the oxidative stress in pancreas of streptozotocin induced diabetic rats

A study was carried to prove that anti-oxidative activity of *T. polium* occurs by quenching the extent of protein oxidation and lipid. Therefore, the evaluation of potentially anti-oxidative effect of aqueous extract of *T. polium* on the progression and development of diabetes and its complications in order to protect rat pancreatic tissue against streptozotocin where done by an oral administration of 0.5 g/kg plant powder for 30 consecutive days to streptozotocin diabetic rats showed a change in the antioxidant status after it was evaluated by the determination of superoxide dismutase (SOD), catalase (CAT) activities and the glutathione (GSH) level in pancreatic tissue, which showed a significant enhancement in activities of SOD and CAT along with a higher level in GSH levels in pancreatic tissue. In addition, under diabetic condition a determination of pancreatic tissue malondialdehyde (MDA) level, serum nitric oxide (NO) concentration and reliable markers of protein oxidation such as advanced oxidation protein products (AOPP) and protein carbonyl content (PCO) were carried out and it was found a significant suppression in the levels of blood glucose, Pancereatic MDA, serum NO, AOPP and PCO levels.

Another study aimed to evaluate the anti-oxidative potential of *T. polium* aqueous extract for protecting rat pancreatic tissue against the streptozotocin (STZ)-induced oxidative stress. Diabetes was induced in rats by intra-peritoneal injections of at a single dose of STZ at 40 mg/kg. The crude extract (equivalent to 500 mg of plant powder/kg of body weight) was administered intra-gastrically)

to a group of STZ diabetic rats for 30 consecutive days. Changes in antioxidant status were evaluated by determining CAT and activities and the level of reduced GSH in pancreatic tissue. In addition, serum NO concentration, pancreatic tissue MDA (an index of lipid peroxidation) level, and reliable markers of protein oxidation such as PCO and AOPP were also determined. Under diabetic conditions, blood glucose level, serum NO concentration, and pancreatic MDA, PCO, and AOPP levels were all increased. The diabetic rats also exhibited pancreatic GSH depletion along with significant reductions in activities of CAT and SOD. Rats treated with *T. polium* extract had significantly higher GSH levels along with enhanced CAT and SOD activities in pancreatic tissue. In addition to suppress blood glucose levels, serum NO, pancreatic MDA, PCO, and AOPP levels were all lower than in the diabetic group. These results strongly approve that anti-oxidative activity of *T. polium* occurs by quenching the extent of lipid and protein oxidation. Based on these observations, it is concluded that *T. polium* may have a protective effect on pancreatic tissue in STZ-induced oxidative stress due to its high antioxidative potential [47,48].

ANTIOXIDANT ACTIVITY

An *in-vitro* and *in-vivo* tests were carried to measure the antioxidant activity of *T. polium* extract to explore the potential antioxidant activities of *T. polium*. Therefore, three tests including inhibition of total antioxidant power, 1,1-diphenyl-2-picrylhydrazyl radical and thiobarbituric acid reactive substances in serum. An *in-vivo* and *in-vitro* results showed a significant antioxidant activity of Germander plant.

Another scientific study was undertaken to explore antioxidant potential of *T. polium in vitro* and *in vivo.* Antioxidant activity was measured by three tests, including inhibition of 1,1-diphenyl-2-picrylhydrazyl radical (DPPH), total antioxidant power, and thiobarbituric acid reactive substances in serum. The results showed that this plant has significant antioxidant activity *in vitro* and *in vivo* [49-51].

T. polium enhanced the apoptotic and cytotoxic effects of anticancer medications as vinblastine, vincristine and doxorubicin against a panel of cancerous cell lines

The vincristine/methanolic extract of *T. polium*, vinblastine/methanolic extract of *T. polium* and doxorubicin/methanolic extract of *T. polium* mixtures showed a strong synergistic effect in the cell growth inhibition (0.13< confidence interval <0.36). Similar results were observed by colony formation assay.

The combinations of vincristine/methanolic extract of *T. polium* and vinblastine/methanolic extract of *T. polium* resulted in a massive apoptosis (>80%) compared with effect of individual drugs (0-3%). At the additional experiments, the methanolic extract of *T. polium* reduced marginally to significantly the cytotoxic effects of vincristine and vinblastine toward the human fibroblasts.

These results showed that the methanolic extract of *T. polium* has the potential to be an effective and safe chemo-sensitizer agent for cancer chemotherapy [52].

ANTIBACTERIAL, ANTIFUNGAL AND ANTIVIRAL ACTIVITIES

In the folk medicine, *T. polium* was used by several nations to treat bacterial, fungal and viral infections. The flowering tops of *T. polium* ethanol extract were effective against both carrageenin pyrexia and yeast in rats. The ethanolic extract also exhibited a marked antibacterial action against both Gram-positive and Gram-negative microorganisms. In another study showed that the *T. polium* aqueous extract inhibited the growth of Yarrowia lipolytica and Saccharomyces cerevisiae. *T. polium* aerial parts were also investigated against eight different species of bacteria by means of a disc diffusion method and the whole plate diffusion method. The results indicated that the aqueous and organic extracts of *T. polium* (1 g/mL) were active against both Gram-positive and Gram-negative bacteria. The organic extract showed higher activity than the aqueous extract.

Antiviral screening of *T. polium* ethanol and aqueous extracts against rinderpest virus using an agar-overlay plaque-reduction antiviral assay system, which indicated that this plant had moderate antiviral activity [39,53-58].

ANTI-INFLAMMATORY ACTIVITY

In a study focus on the evaluation of anti-inflammatory activity of *T. polium*, the anti-inflammatory activities of the *T. polium* ethanolic extract was measured using different methods carrageenan-induced acute inflammation some of the biochemical parameters and cotton-pellet granuloma. The plant showed an inflammatory inhibition, which is due to the presence of sterols and flavonoids. Also, significant reduction in the glucose levels was noticed after the measurements of the biochemical parameters.

The present study reported the effect of *T. polium* ethanolic extract on carrageenan that induced acute inflammation, cotton-pellet granuloma and some of the biochemical parameters. The *T. polium* ethanolic extract at a dose of 500 mg/kg body weight produced significant inhibition of cotton-pellet granuloma and carrageenan-induced inflammation. Biochemical studies showed a significant decrease in glucose level. Due the presence of flavonoids and sterols in the plant may be responsible for anti-inflammatory activity of this plant [42].

ANTINOCICEPTIVE EFFECTS OF *T. POLIUM* L. TOTAL EXTRACT ESSENTIAL OIL IN MOUSE WRITHING TEST

A study was conducted in order to confirm the antivisceral pain properties of *T. polium*. Therefore, *T. polium* essential oil and total extract were administered intra-peritoneally, and it was found that total extract showed reduction in the response of writhing also essential oil showed a significant reduction in the response of writhing.

Moreover, in order to ensure the essence importance in the production of visceral antinociception, a free essential oil extract was prepared and injected into mice (dose of 225 mg/kg), which is the most effective dose of the extract, and with a comparison to total extract, the antinociception, reduced from 65.44 to 49.85%. It is concluded that the analgesic properties was due to the essential oil is of *T. polium* [59].

ANTISPASMODIC EFFECT

The study of (Kamel, Sandra 1994) showed that *T. polium* oil has antispasmodic activity, which might be thus attributed to its sesquiterpene alcohols high content [60].

Inhibitory effects of *T. polium* ethyl acetate extract *in vitro* protein glycoxidation

Ardestani and his team demonstrated that the inhibitory effect of ethyl acetate extract from *T. polium* in preventing the damages of oxidative protein including effect on thiol oxidation and protein carbonyl formation which are believe to form under the glycoxidation process. These results clearly demonstrate that, the ethyl acetate fraction, besides having its antioxidant content, it is also capable of suppressing the formation of advanced glycation end products and protein oxidation *in vitro* [47].

T. polium chronic effects on some blood parameters and histopathology of liver and kidney in the rats

The effects of chronic treatment with small sublethal doses (20 mg/kg and 50 mg/kg) of *T. polium* ethanolic extract were investigated on the hematological and biochemical composition of the blood, histopathology of the liver and kidney, and fertility in the rat. Hematological and biochemical parameters of the blood, as well as sperm count, morphology and motility were normal after 6 weeks of herbal treatment. However, blood urea ($p<0.05$) and cholesterol ($p<0.005$) were significantly increased, with marked cytoplasmic vacuolation of the liver and kidney cells after chronic treatment with 50 mg/kg of the plant. These results demonstrate some histopathological effects of *T. polium* on the liver and kidney under long-term administration conditions [61].

Hepatoprotective effect of *T. polium* L. ethyl acetate extract against carbontetrachloride induced hepatic injury in rats

In a study conducted to substantiate the possible hepatoprotective activity of *T. polium* L ethyl acetate extract an investigation by Panovska and his research team (2007), using rats with CCl -induced liver damage was carried out. Specific biochemical parameters (superoxide dismutase, GSH peroxidase, total antioxidative status and reduced GSH) were estimated in blood and in liver homogenate. Lipid peroxidation in CCl -intoxicated rats was evidenced by a marked in crement in the levels of thiobarbituric acid reactive substances.

Some biochemical parameters showed a significant difference value between groups treated with the *T. polium* extract and that treated with the CCl. Besides that, the histopathological study for the liver biopsy of all experimental rat groups treated with the ethyl acetate extract from *T. polium* showed significant restoration of the normal histomorphological pattern of liver cells [62].

HYPOLIPIDEMIC EFFECTS

An investigation on hyperlipidemic rats treated with aqueous extract of ***T. polium*** aerial parts carried out by Rasekh and his team (2001) showed a significant reduction in the serum level of triglycerides and cholesterol [63].

ANTICANCER ACTIVITY

The study investigated by Movahedi and his team (2014) showed the capability of the decoction of *T. polium* to protect liver cells against hepatocellular carcinoma in carcinogenesis-induced animal model. After 28 weeks of treatment with decoction of *T. polium*, serum biochemical markers including ALT, AST, alpha fetoprotein, gamma glutamyl transferase, alkaline phosphatase, homocysteine, tumor necrosis factor alpha, alpha 2macroglobulin, and corticosteroid binding globulin have been regulated auspiciously. Total antioxidant status also has been increased intensely. Liver lesion score in the treated group was lessened, and glucocorticoid activity has been intensified significantly. In conclusion, *T. polium* decoction might inhibit or suppress liver cancer development [64].

Anticonvulsant activity against aeizure induced by pentylenetetrazole and maximal electroshock stimulation in Mice

An investigation for the protective effects of *T. polium* ethanolic and aqueous extracts and related fractions on seizures induced by pentylenetetrazole and maximal electroshock stimulation was carried out by corticosteroid binding globulin and his team (2010). It was found that aqueous extract (ED_{50} = 22.4 mg/kg body weight) and related *n*-butanol fraction (ED_{50} = 12.6 mg/kg body weight) have anti-seizure effects comparing to control groups [65].

PREVENTIVE EFFECT ON MEMORY DEFICITS AND LEARNING AND IN DIABETIC RATS

Diabetes caused impairment in the acquisition of PAL and retrieval of memory. *T. polium* may be a promising candidate for memory improvement in diabetes. Therefore, study was conducted using T. *polium* was used as a tea to improve the memory and learning in control rats and the reversed learning and memory deficits in diabetic rats. The treatment of diabetic rats using *T. polium* showed a partially improved in the body weight and hyperglycemia, although the deviations were not significant compared with non-treated diabetic rats. These results showed prevention on the deleterious effects of diabetes on PAL and memory after the treatment with *T. polium*. Antioxidant, hypoglycemic and anticholinesterase effects of *Teucrium* may be involved in the obtained effects [46].

***T. polium* L. extract as a fortified sunscreen by adsorption on zinc oxide nanoparticles**

Study results, which done by Ansari and his team (2013) showed that the *T. polium* extract has a wide band of ultraviolet radiation spectrum absorption ranging from 250 nm to 380 nm. SPF of the combination product in the ultraviolet B area was >80, revealing a synergistic action between ZnO and *T. polium*. The adsorption of flavonoids of *T. polium* on Zinc-oxide nanoparticles (ZnOn) slowed down their release thereby lengthening their persistence on the skin and contributing to further duration of action [66].

Protective effect on acetaminophen-induced hepatotoxicity in mice

The results of this study showed the protective effect in all doses, but the most significant protection for the liver was observed in doses of 250 and 500 mg/Kg ($p<0.05$). Also, these findings were supported and confirmed by histological examination [67].

OTHER BIOLOGICAL AND PHYSIOLOGICAL ACTIVITIES

Other studies indicated that the *T. polium* extract had anorexic [43], anticholinesterase, antiamnesic [68], antipyretic [55], hypotensive effects [69] as well as relieved stomach disorders [70] and the volatile oil was also found to inhibit Ca^{2+} influx in the intestine [71].

Hepatitis, fibrosis, necrosis and acute liver failure after administration of *T. polium*

An increasing in the global popular throughout toward herbal remedies was as a result of the alleged belief that herbal preparations are basically harmless and also the disappointment from conventional medicines. On the other hand, the improperly used of herbal remedies can make their effects exceedingly potent or even lethal. Drugs and other chemicals account for less than 5% of cases of acute hepatitis or jaundice and chronic liver disease, but with smaller number of cases. Drug reactions can simulate any hepatobiliary disease, which present a diagnostic challenge for pathologists and physicians. Hepatotoxicity generally occurs after almost 2 months of ingestion and its features include nausea, abdominal pain, anorexia and jaundice, which associated with a marked elevation in serum aminotransferases. A case study on 70-year-old farmer with acute hepatitis was using *T. polium* as hypoglycemic aid. After 1 month consumption of large quantities of *T. polium* in a tea form, the patient presented with jaundice [72,73].

CONCLUSION

Recent years, traditional uses and ethnopharmacology of natural compounds, especially of plant origin received much attention as they are well tested for their safety use for the human and their efficacy. It is best classical approach in the search of new molecules for management of various diseases. It is a fact thorough screening of the literature on the available of *T. polium* that it is a popular remedy among the various ethnic groups, Arabic, Europian and traditional practitioners for treatment of various diseases. Researchers are discovering the therapeutic potential of this plant as it has many unknown therapeutic and toxic properties.

All information collected above about the *T. polium* plant, give a better scientific based understanding on the existing evidence and guide on the use of this plant also collected all the information about its phytochemical constituents, names, ecology, description and toxicity of the plant.

It has been found that the phytochemical compounds extracted from *T. polium* possess a broad spectrum of pharmacological effects including anticancer, antioxidant, hepatoprotective, hypoglycemic, anti-inflammatory, hypolipidemic, antifungal, antiviral, antibacterial, antispasmodic and other evidence based uses. The results of data analyses on the chemical, toxicological and pharmacological characteristics of *T. polium* support the view that this plant has beneficial therapeutic properties. However, further studies should be carried on to identify the active components and to verify their relevant pharmacological activities.

REFERENCES

1. Davis SC, Perez R. Cosmeceuticals and natural products: Wound healing. Clin Dermatol 2009;27(5):502-6.
2. Uniyal SK, Singh KN, Jamwal P, Lal B. Traditional use of

medicinal plants among the tribal communities of Chhota Bhangal, Western Himalaya. J Ethnobiol Ethnomed 2006;2:14.
3. Losoya Z. Synthetic drugs-emergence, legislation, and the criminal and legal aftermath of broad regulation. SMUL Rev 2013;66:401.
4. McKenna J. Natural Alternatives to Antibiotics: Using Nature's Pharmacy to Help Fight Infections. USA: Penguin; 1998.
5. Doughari J. Antimicrobial activity of *Tamarindus indica* Linn. Trop J Pharm Res 2007;5:597-603.
6. El Astal Z, Ashour A, Kerrit A. Antimicrobial activity of some medicinal plant extracts in Palestine. Pak J Med Sci 2005;21:187-93.
7. Abu-Irmaileh BE, Afifi FU. Herbal medicine in Jordan with special emphasis on commonly used herbs. J Ethnopharmacol 2003;89(2-3):193-7.
8. Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod 2012;75(3):311-35.
9. Patwardhan B, Vaidya AD, Chorghade M. Ayurveda and natural products drug discovery. Curr Sci Bangalore 2004;86:789-99.
10. Gurib-Fakim A. Medicinal plants: Traditions of yesterday and drugs of tomorrow. Mol Aspects Med 2006;27(1):1-93.
11. Patwardhan B, Mashelkar RA. Traditional medicine-inspired approaches to drug discovery: Can Ayurveda show the way forward? Drug Discov Today 2009;14(15-16):804-11.
12. Palevitch D, Price R, Yaniv Z. Medicinal plants of the Holy Land. Tel Aviv: Modan Publishing House; 2000.
13. Zargari A, MacDonald K. A history and philosophy of technology education. Technology Teach 1994;53:7-11.
14. Pedersen JA. Distribution and taxonomic implications of some phenolics in the family Lamiaceae determined by ESR spectroscopy. Biochem Syst Ecol 2000;28:229-53.
15. Evans WC. Trease and Evans' Pharmacognosy. Philadelphia: Elsevier Health Sciences; 2009.
16. Yazdi FT, Behbahani BA. Antimicrobial effect of the aqueous and ethanolic *Teucrium polium* L. extracts on gram positive and gram negative bacteria "*in vitro*". J Paramed Sci 2013;4:56-62.
17. The plant list. The Plant List.org Version 1.1. Available from: http://www.theplantlist.org/tpl1.1/record/kew-203217. [Last accessed on 2014 Nov 08].
18. Bedevian AK. Illustrated Polyglottic Dictionary of Plant Names. Cairo: Argus & Papazian Presses; 1936.
19. McClintock E, Epling C. A revision of teucrium in the new world, with observations on its variation, geographical distribution and history. Brittonia 1946;5:491-510.
20. Seyyednejad S, Motamedi H. A review on native medicinal plants in Khuzestan, Iran with antibacterial properties. Int J Pharmacol 2010;6:551-60.
21. Akhani H, Mahdavi P, Noroozi J, Zarrinpour V. Vegetation patterns of the irano-turanian steppe along a 3,000 m altitudinal gradient in the alborz mountains of Northern Iran. Folia Geobotanica 2013;48:229-55.
22. Barceloux DG. Medical Toxicology of Natural Substances*:* Foods, Fungi, Medicinal Herbs, Plants, & Venomous Animals. New Jersey: John Wiley and Sons; 2008.
23. Cakir A, Duru ME, Harmandar M. Ciriminna R, Passannanti S. Volatile constituents of *Teucrium polium* L. from Turkey. J Essent Oil Res 1998;10:113-5.
24. Eikani MH, Goodarznia I, Mirza M. Comparison between the essential oil and supercritical carbon dioxide extract of *Teucrium polium* L. J Essent Oil Res 1999;11:470-2.
25. Kovacevic NN, Lakusic BS, Ristic MS. Composition of the essential oils of seven Teucrium species from Serbia and Montenegro. J Essent Oil Res 2001;13:163-5.
26. Perez-Alonso M, Velasco-Negueruela A, Lopez-Saez J. The essential oils of two Iberian Teucrium species. J Essent Oil Res 1993;5:397-402.
27. Sarer E, Konuklugil B, Eczacilik F. Investigation of the volatile oil of *Teucrium polium* L. Turk Tipve Eczacillk Derg 1987;11:317-25.
28. Aburjai T, Hudaib M, Cavrini V. Composition of the essential oil from Jordanian germander (*Teucrium polium* L.). J Essent Oil Res 2006;18:97-9.
29. Kabouche A, Kabouche Z, Ghannadi A, Sajjadi S. Analysis of the essential oil of *Teucrium polium* ssp. aurasiacum from Algeria. J Essent Oil Res 2007;19:44-6.
30. Hassan MM, Muhtadi FJ, Al-Badr AA. GLC-mass spectrometry of *Teucrium polium* oil. J Pharm Sci 1979;68(6):800-1.
31. Carreiras MC, Rodríguez B, Piozzi F, Savona G, Torres MR, Perales A, *et al*. A chlorine-containing and two 17β-neo-clerodane diterpenoids from *Teucrium polium* subsp. *Vincentinum*. Phytochemistry 1989;28:1453-61.
32. Capasso F, Cerri R, Morrica P, Senatore F. Chemical composition and anti-inflammatory activity of an alcoholic extract of *Teucrium polium* L. Boll Soc Ital Biol Sper 1983;59(11):1639-43.
33. Harborne JB, Tomás-Barberán FA, Williams CA, Gil MI. A chemotaxonomic study of flavonoids from european teucrium species. Phytochemistry 1986;25:2811-6.
34. Sharififar F, Dehghn-Nudeh G, Mirtajaldini M. Major flavonoids with antioxidant activity from *Teucrium polium* L. Food Chem 2009;112:885-8.
35. Bianco A, Ramunno A, Serrilli AM, Lo Castro M, Ballero M, Serafini M. Phytochemical characters of *Teucrium marum* from Sardinia: An endemic plant. Nat Prod Res 2004;18(6):557-64.
36. Elmasri WA, Hegazy ME, Aziz M, Koksal E, Amor W, Mechref Y, *et al.* Biofilm blocking sesquiterpenes from *Teucrium polium*. Phytochemistry 2014;103:107-13.
37. Bahramikia S, Yazdanparast R. Phytochemistry and medicinal properties of *Teucrium polium* L. (Lamiaceae). Phytother Res 2012;26(11):1581-93.
38. Jaradat N. Ethnopharmacological survey of natural products in palestine. An-Najah Univ J Res(N Sc) 2005;19:14-67.
39. Essawi T, Srour M. Screening of some Palestinian medicinal plants for antibacterial activity. J Ethnopharmacol 2000;70(3):343-9.
40. Kamel A. 7-epi-Eudesmanes from *Teucrium polium*. J Nat Prod 1995;58:428-31.
41. Said O, Khalil K, Fulder S, Azaizeh H. Ethnopharmacological survey of medicinal herbs in Israel, the Golan Heights and the West Bank region. J Ethnopharmacol 2002;83(3):251-65.
42. Tariq M, Ageel AM, al-Yahya MA, Mossa JS, al-Said MS. Anti-inflammatory activity of *Teucrium polium*. Int J Tissue React 1989;11(4):185-8.
43. Gharaibeh MN, Elayan HH, Salhab AS. Hypoglycemic effects of *Teucrium polium*. J Ethnopharmacol 1988;24(1):93-9.
44. Esmaeili MA, Yazdanparast R. Hypoglycaemic effect of *Teucrium polium*: Studies with rat pancreatic islets. J Ethnopharmacol 2004;95(1):27-30.
45. Yazdanparas R, Esmaeili MA, Ashrafi Helan J. *Teucrium polium* extract effects pancreatic function of streptozotocin diabetic rats: A histopathological examination. Iran Biomed J 2005;9:81-5.
46. Hasanein P, Shahidi S. Preventive effect of *Teucrium polium* on learning and memory deficits in diabetic rats. Med Sci Monit 2012;18(1):BR41-46.
47. Ardestani A, Yazdanparast R, Jamshidi Sh. Therapeutic effects of *Teucrium polium* extract on oxidative stress in pancreas of streptozotocin-induced diabetic rats. J Med Food 2008;11(3):525-32.
48. Tatar M, Qujeq D, Feizi F, Parsian H, Sohan Faraji A, Halalkhor S, *et al.* Effects of *Teucrium Polium* aerial parts extract on oral glucose tolerance tests and pancreas histopathology in Streptozocin-induced diabetic rats. Int J Mol Cell Med 2012;1(1):44-9.
49. Djeridane A, Yousfi M, Nadjemi B, Boutassouna D, Stocker P, Vidal N, *et al.* Antioxidant activity of some Algerian medicinal plants extracts containing phenolic compounds. Food Chem 2006;97:654-60.
50. Hasani P, Yasa N, Vosough-Ghanbari S, Mohammadirad A, Dehghan G, Abdollahi M. *In vivo* antioxidant potential of *Teucrium polium*, as compared to alpha-tocopherol. Acta Pharm 2007;57(1):123-9.
51. Qabaha KI. Antimicrobial and free radical scavenging activities of five Palestinian medicinal plants. Afr J Tradit Complement Altern Med 2013;10(4):101-8.
52. Rajabalian S. Methanolic extract of *Teucrium polium* L. potentiates the cytotoxic and apoptotic effects of anticancer drugs of vincristine, vinblastine and doxorubicin against a panel of cancerous cell lines. Exp Oncol 2008;30(2):133-8.
53. Aggelis G, Athanassopoulos N, Paliogianni A, Komaitis M. Effect of a *Teucrium polium* L. extract on the growth and fatty acid composition of Saccharomyces cerevisiae and Yarrowia lipolytica. Antonie Van Leeuwenhoek 1998;73(2):195-8.
54. Alwan A, Jawad AL, Albana A, Ali K. Antiviral activity of some Iraqi indigenous plants. Pharm Biol 1988;26:107-11.
55. Autore G, Capasso F, De Fusco R, Fasulo MP, Lembo M, Mascolo N, *et al.* Antipyretic and antibacterial actions of *Teucrium polium* (L.). Pharmacol Res Commun 1984;16(1):21-9.
56. Rojas A, Hernandez L, Pereda-Miranda R, Mata R. Screening for antimicrobial activity of crude drug extracts and pure natural products from Mexican medicinal plants. J Ethnopharmacol 1992;35(3):275-83.
57. Sarac N, Ugur A. Antimicrobial activities and usage in folkloric medicine of some Lamiaceae species growing in Mugla, Turkey. Eurasian J BioSci 2007;4:28-37.
58. Darabpour E, Motamedi H, Nejad SM. Antimicrobial

properties of *Teucrium polium* against some clinical pathogens. Asian Pac J Trop Med 2010;3:124-7.
59. Abdollahi M, Karimpour H, Monsef-Esfehani HR. Antinociceptive effects of *Teucrium polium* L total extract and essential oil in mouse writhing test. Pharmacol Res 2003;48(1):31-5.
60. Kamel A, Sandra P. Gas chromatography– mass spectrometry analysis of the volatile oils of two *Teucrium polium* varieties. Biochem Syst Ecol 1994;22:529-32.
61. Khleifat K, Shakhanbeh J, Tarawneh K. The chronic effects of *Teucrium polium* on some blood parameters and histopathology of liver and kidney in the rat. Turk J Biol 2002;26:65-71.
62. Panovska TK, Kulevanova S, Gjorgoski I, Bogdanova M, Petrushevska G. Hepatoprotective effect of the ethyl acetate extract of *Teucrium polium* L. against carbontetrachloride-induced hepatic injury in rats. Acta Pharm 2007;57(2):241-8.
63. Rasekh HR, Khoshnood-Mansourkhani MJ, Kamalinejad M. Hypolipidemic effects of *Teucrium polium* in rats. Fitoterapia 2001;72(8):937-9.
64. Movahedi A, Basir R, Rahmat A, Charaffedine M, Othman F. Remarkable anticancer activity of *Teucrium polium* on hepatocellular carcinogenic rats. Evid Based Complement Alternat Med 2014;2014:726724.
65. Khoshnood-Mansoorkhani MJ, Moein MR, Oveisi N. Anticonvulsant Activity of *Teucrium polium* Against Seizure Induced by PTZ and MES in Mice. Iran J Pharm Res 2010;9(4):395-401.
66. Ansari M, Sharififar F, Kazemipour M, Sarhadinejad Z, Mahdavi H. *Teucrium polium* L. extract adsorbed on zinc oxide nanoparticles as a fortified sunscreen. Int J Pharm Investig 2013;3(4):188-93.
67. Forouzandeh H, Azemi ME, Rashidi I, Goudarzi M, Kalantari H. Study of the protective effect of *Teucrium polium* L. extract on acetaminophen-induced hepatotoxicity in mice. Iran J Pharm Res 2013;12(1):123-9.
68. Orhan I, Aslan M. Appraisal of scopolamine-induced antiamnesic effect in mice and *in vitro* antiacetylcholinesterase and antioxidant activities of some traditionally used Lamiaceae plants. J Ethnopharmacol 2009;122(2):327-32.
69. Suleiman MS, Abdul-Ghani AS, Al-Khalil S, Amin R. Effect of *Teucrium polium* boiled leaf extract on intestinal motility and blood pressure. J Ethnopharmacol 1988;22(1):111-6.
70. Malakov PY, Papanov GY. Furanoid diterpenes from *Teucrium polium*. Phytochemistry 1983;22:2791-3.
71. Aqel M, Gharaibeh M, Salhab A. The calcium antagonistic effect of the volatile oil of *Teucrium polium*. Pharm Biol 1990;28:201-7.
72. Starakis I, Siagris D, Leonidou L, Mazokopakis E, Tsamandas A, Karatza C. Hepatitis caused by the herbal remedy *Teucrium polium* L. Eur J Gastroenterol Hepatol 2006;18(6):681-3.
73. Mattéi A, Rucay P, Samuel D, Feray C, Reynes M, Bismuth H. Liver transplantation for severe acute liver failure after herbal medicine (*Teucrium polium*) administration. J Hepatol 1995;22(5):597.