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A Systematic Review of the Efficacy and Safety of *Teucrium* Species; from Anti-oxidant to Anti-diabetic Effects

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Abstract: This review focuses on the efficacy and safety of *Teucrium* species that are effective in the management of different conditions in human and animal. Embase, Scopus, Pubmed, Google Scholar and IranMedex databases were searched up to 11th May 2009. The search terms were *Teucrium* or germander or Calpoureh. All of the human and animal studies considered the effects of *Teucrium* with the key outcome of change in blood glucose, serum lipids, anti-oxidant parameters, hepatic enzymes, anti-inflammation, analgesic effects, anti-ulcer effects anti-microbial effect and toxic effects were included. Studies performed on cell lines, *in vitro* studies, reviews and letters to editors were excluded. Of initial search, 7325 record were reviewed for inclusion or exclusion in study. Finally, 68 studies were included. Some animal and one human study showed hypoglycemic effects of *Teucrium*. In one animal study, *Teucrium* decreased serum cholesterol and triglyceride in hyper-lipidemic rats. Some studies indicated anti-oxidant, anti-spasmodic, anti-nociceptive and anti-inflammatory properties of *Teucrium*. According to histopathological and biochemical evidences, high doses or long-term administration of *Teucrium* may induce progressive impairment of neuromuscular coordination and reversible or irreversible hepatic damage. *Teucrium* has antidiabetic effect by enhancing secretion of insulin from the pancreas. The flavonoids and sterols are responsible for the anti-inflammatory activity of this plant. Isolation and characterization of *Teucrium* constituents is suggested to reach suitable drugs.

Key words: *Teucrium*, diabetes, oxidative stress, systematic review

INTRODUCTION

For a very long time, plants were used in the treatment of many diseases especially in the East region countries. In the recent years, the popularity of alternative medicine has increased again. Surveys conducted in Australia and US indicates that almost 48.5 and 34% of respondents had used at least one form of unconventional therapy, including herbal medicine, respectively. The World Health Organization (WHO) has also recommended evaluation of effective plants for conditions like diabetes due to lack of safe modern drugs (Kim *et al*., 2007). In some countries, herbal medication is the most popular complementary and alternative medicine (CAM) modality (Sadighi *et al*., 2004; Rahimi *et al*., 2010).

Most pharmacists are not adequately prepared educationally to meet patients' requests for information on herbal products. Many herbs have been identified as unsafe, including borage, calamus, coltsfoot, comfrey, life root, sassafras, chaparral, *Teucrium* (Germander), Licorice and Ma-huang. Potentially safe herbs include Feverfew, Garlic, Ginkgo, Asian Ginseng, Saw-palmetto, St. John's wort and Valerian. The clinical trial results are suggestive of efficacy of some herbal therapies for some conditions (Klepser and Klepser, 1999).

Commonly called Germanders, the *Teucrium* species are perennials, subshrubs, or shrubs with attractive aromatic simple or lobed leaves that can be evergreen or deciduous (Ellis, 1999). *Teucrium* species are rich of neo-clerodane diterpenoids. Although, several furanoid diterpenes with neo-clerodane skeleton have been isolated from many plants, the genus *Teucrium* is the most abundant natural source of these components. Therefore, *Teucrium* species are accepted as chemotaxonomic markers for neo-clerodanes. Flavonoids and aromatic compounds, although not as abundant as in the genus salvia from the same family, have been found in the genus *Teucrium* (Atta-ur-Rahman, 2003).

Teucrium species have been used for over 2000 years in traditional medicine for their diuretic, diaphoretic, tonic,

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anti-pyretic, anti-spasmodic and cholagogic properties (Ljubuncic *et al*., 2006). *Teucrium polium* and *Teucrium persicum* are wild-growing flowering plant belonging to the family Labiatae found abundantly in Iran and used in traditional Iran and Arab medicine (Azaizeh *et al*., 2005). This plant has been used for the treatment of diabetes, gastric inflammation and convulsion (Shahraki *et al*., 2007). *Teucrium buxifolium* the Spanish endemic, has been used for the treatment of rheumatic and other inflammatory disorders (Puntero *et al*., 1997).

The present study aimed to evaluate the current science on the efficacy and safety of *Teucrium* species by reviewing all human and animal studies.

MATERIALS AND METHODS

Data sources: Embase, Scopus, Pubmed, Google Scholar and IranMedex databases were searched up to 11th May 2010 for studies investigating *Teucrium* as a medicinal plant. The initial search terms were *Teucrium* or germander or calpoureh and diabetes, anti-oxidant, anti-inflammatory, analgesic, anti-nociseptive, anti-ulcer, anti-microbial, toxicity or side effect. Then searches were done by *Teucrium* alone as a key word without narrowing or limiting search elements and continued manually for relevant data. The reference lists of articles were also reviewed for additional studies.

Study selection: Inclusion criteria: All of the human and animal studies considered the effects of *Teucrium* with the key outcome of glucose, lipids, anti-oxidant parameters, hepatic enzymes, anti-inflammation, analgesic, anti-ulcer, anti-microbial and toxic effects were included. Exclusion criteria: *In vitro* studies, studies performed on cell lines, review articles and letters to editor were excluded. Unpublished data such as thesis were not included.

One reviewer independently examined the title and abstract and references of each article to eliminate duplications and *in vitro* studies. The reviewers independently extracted data according to *Teucrium* species, dose, trial duration, outcome, results and side effects.

RESULTS AND DISCUSSION

Of publications identified in the initial database, 7325 search results were reviewed for inclusion or exclusion and finally, 68 studies were included.

Beneficial effects of *Teucrium* species: Information of human and animal studies considering beneficial effects of *Teucrium* is summarized in the Table 1.

Studies on blood glucose, lipid and pressure: Some animal (Esmaeili and Yazdanparast, 2004; Gharaibeh *et al*., 1988; Karimi *et al*., 2002; Rasekh *et al*., 2001; Roman-Ramos *et al*., 1991; Shahraki *et al*., 2007; Vessal *et al*., 2003; Yazdanparast *et al*., 2005; Zal *et al*., 2001) and one human study showed significant decrease in blood glucose after treatment with *Teucrium*. Three animal studies showed ineffectiveness of *Teucrium* in treated animals (Afifi *et al*., 2005; Iriadam, 2004; Konuklugil *et al*., 1997). Glicazide an oral anti-diabetic agent was more potent than *Teucrium* (Konuklugil *et al*., 1997). One animal study showed reduction of serum cholesterol and triglyceride in hyper-lipidemic rats treated with *Teucrium* (Rasekh *et al*., 2001) but in another study cholesterol, triglyceride and LDL increased after treatment with *Teucrium* (Shahraki *et al*., 2007). Different species of *Teucrium* reduced mean arterial blood pressure and heart rate (Bello *et al*., 1997; Catalayud *et al*., 1998a, b). One of these studies showed that both methanol and dichloromethanol extracts of *Teucrium* have antihypertensive effect (Catalayud *et al*., 1998b).

Anti-oxidant effect: *Teucrium* species possess free radical and hydroxyl radical scavenging activity as well as anti-oxidant activity *in vitro* (Azaizeh *et al*., 2005). Seven animal studies showed anti-oxidant properties of *Teucrium* that are summarized in the Table 1. In Panovsca study, the inhibitory effect of the extract in NADPH-induced lipid peroxidation was greater than that of reference substance, luteonin and similar with that of thymol.

Anti-nociceptive and anti-inflammatory effects: Anti-spasmodic, anti-nociceptive, anti-inflammatory and CNS-depressant properties of different *Teucrium* species (Abdollahi *et al*., 2003a; Abdolghaffari *et al*., 2010: Barrachina *et al*., 1995; Baluchnejadmojarad *et al*., 2005; Beitran *et al*., 1998; Bello *et al*.,1995, 1998; Capasso *et al*., 1983; Heidari *et al*., 1999; Parsaei and Shafiei Nik, 2006; Radhakrishnan *et al*., 2001; Shahraki *et al*., 2006b; Shakhanbeh and Atrouse, 2001; Tariq *et al*., 1989), are summarized in Table 1. Some studies showed anti-ulcer, anti-pyretic or hepatoprotective effects (Ansari *et al*., 2009; Autore *et al*., 1984; Galati *et al*., 1997, 2000; Islam *et al*., 2002; Mehrabani *et al*., 2009; Niazmand *et al*., 2007; Orhan and Aslan, 2009; Panovska *et al*., 2007; Rasheed *et al*., 1995; Wasfi *et al*., 1995).

Adverse effect and toxicity of *Teucrium* species: In the recent years, terpenoid-containing dietary supplements have been implicated in causing severe and sometimes fatal hepatotoxicity. Germander was the first of these herbal products to be clearly linked to cases of acute liver

Table 1: Human and animal studies considering beneficial effects of *Teucrium*

Author	Target	*Teucrium* species	Dose/Duration	Effect
Studies on blood glucose, lipid, pressure				
Shahraki *et al.* (2007)	Diabetic male rat		*T. polium* 50 mg/kg/4 week	Serum glucose values decreased significantly ($p<0.05$), but Ch, TG, LDL, SGOT, SGPT increased significantly after use of T. polium ($p<0.05$)
Afifi *et al* (2005)	Alloxan-induced hyperglycemic rabbit	*T. polium*	Intranasal extract 10%	No significant difference was observed between the extract treated and non-treated animals.
Esmaelli and Yazdanparast (2004)	STZ- induced diabetic rat	*T. polium*	0.5 g/kg/6 week	A decrease (64%) in BG was observed in the treated animals compared to the untreated diabetic rats without any measurable effects on the major biochemical factors. The extract significantly enhanced the blood insulin level by almost 160%
Iriadam (2004)	Diabetic rabbit	*T. polium*	-	No anti-diabetic effect
Vessal *et al.* (2003)	Diabetic rat	*T. polium*	-	A reduction in the level of serum glucose during oral glucose tolerance tests was seen. The number of pancreatic islets per unit area increased and glucokinase activity was elevated
Rasekh *et al.* (2001)	Hyperlipidemic rat		*T. polium* 50-150 mg/kg/10 day	The serum levels of Ch and TG reduced in hyperlipidemic rats
Roman-Ramos *et al.* (1991)	Rabbit	*T. cubense*	-	The area under glucose tolerance curve reduced
Gharaibeh *et al.* (1988)	STZ-induced diabetic rat	*T. polium*	4 h after iv and 24 h after ip injections	Significant reduction in BG 4 h after iv administration and 24 h after ip administration
Yazdanparast *et al.* (2005)	STZ-induced diabetic rat	*T. polium*	6 w	BG decreased by 64%, total bilirubin by 35%, SGOT by 48% and SGPT by 30% Blood insulin level was enhanced by 160%
Zai *et al* (2001)	Diabetic rat	*T. polium*	-	Reduction of serum glucose after 24 h that reached those of the normoglycemic animals in 8 days. Liver sections showed marked cytoplasmic hydropic changes in 1/3 to 2/3 of the liver lobules. Apoptopic bodies were noted. Regenerative changes were observed
Karimi *et al.* (2002)	Human (DM-2)	*T. polium*	125 mg/kg/42 day	Mean of glycosylated hemoglobin decreased. Mean TG and total Ch and BMI decreased HDL-Ch, LDL-Ch and liver function tests showed no change
Konuklugil *et al.* (1997)	Healthy rat submitted to glucose tolerance test	*T. polium*	-	Decoction of *T. polium* slightly, but not significantly attenuated the glycemia when compared with oral anti-diabetic agent glicazide
Catalayud *et al.* (1998a)	Rat	*T. Flavum* L	-	Mean arterial blood pressure was reduced. The methanol extract decreased heart rate.
Catalayud *et al.* (1998b)	Normotensive rat	*T. cartaginenses* L.	-	Both extracts reduced mean arterial blood pressure and heart rate, while only the dichloromethanol extract prevented noradrenaline-induced hypertension
Bello *et al* (1997)	Normotensive rat	*T. pumillum* L. *T. buxifolium*	iv	Both extracts reduced mean arterial blood pressure in a dose dependent manner
Studies on anti-oxidant effects				
Aghazadeh and Yazdanparast (2009)	Rat (MCD-fed)	*T. polium*	0.5 g/kg/8 week	Pronounced improvements in liver steatosis, ballooning degeneration and inflammation. Significant decrease of elevated MDA and caspase-3 levels. Significant reduction in the phosphorylated form of JNK along with an increase in the phosphorylated level of ERK1/2
Amini *et al.* (2009)	Rat (MCD-fed)	*T. polium*	-	Inflammation and ballooning degeneration abated to grade 0 in 80% of the rats. Lipoprotein profiles significantly improved. Dramatic reduction in the sera alkaline phosphatase, aspartate aminotransferase and alanine aminoteransferase activities. The activities of the liver superoxide dismutase, glutathione peroxidase and glutathione reductase enzymes were enhanced
Ardestani *et al.* (2008)	STZ-induced diabetic rats	*T. polium*	0.5 g /kg/30 day	Significant increase of GSH levels and enhanced CAT and SOD activities in pancreatic tissue. BG levels, serum NO, pancreatic MDA, PCO, and AOPP levels were all lower than in the diabetic group.
Amini and Yazdanparast (2009)	Rat (MCD-fed)	*T. polium*	0.5 g /kg/8 week	Hepatic TNF-α, TGF-β, MDA, and liver histopathology, lobular inflammation and ballooning degeneration decreased significantly. Significant increase of GSH

Table 1: Continued

Author	Target	*Teucrium* species	Dose / Duration	Effect
Hasani *et al.* (2007)	Rat	*T. polium*	50, 100, 200 mg/kg/d/2 week	Anti-oxidant potential
Dilsiz *et al.* (2006)	Ischemia reperfusion in the rat retina	*T. multicaule* (Germander)	6 h before the ischemia	Anti-oxidant. In the order of Lutein>Trigonella>Vitamin E>*Teucrium*, all four compounds were effective in preventing retinal damage. They decreased the formation of MDA and inhibited activation of caspase-3 and decelerated the loss of GSH
Kadifkova-Panovska *et al.* (2005)	Rat liver	*T. polium* species	-	Anti-oxidant. The NADPH-induced lipid peroxidation was inhibited by the extract. The inhibitory effect of the extract in experimental system was greater than that of reference substance, luteonin, and similar with that of thymol and BHT
Studies on anti-nociceptive and anti-inflammatory effects				
Abdolghaffari *et al.* (2010)	Rat with immunologic colitis	*T. persicum*	100, 200, 400 mg/kg/10 day	Improvement of both macroscopic and histological damages. Reduction of colonic MPO activity and concentrations of cellular lipid peroxides, TNF-alpha, and IL-1beta, with a concomitant increase in FRAP value at all doses
Parsaei and Shafiei Nik (2006)	Guina pig ileum	*T. polium*	30-240 mg kg^{-1}	Maximum inhibition response on acetylcholine (220 nM)-induced contraction was 93.5%. The extract increased reaction time dose-dependently. The anti-nociceptive effect of extract was less than that of morphine 10 mg kg^{-1}
Abdollahi *et al.* (2003a)	Writing test in mouse	*T. polium*	9.37-300 mg kg^{-1}	The essential oil in doses of 9.37, 18.75, 37.5, 75, and 150 mg kg^{-1} induced reduction in writhing response with the ED50 of 29.41 mg kg^{-1}
Radhakrishnan *et al.* (2001)	Rat	*T. stocksianum*	-	T. stocksianum showed analgesic and anti-inflammatory activities in all the models studied (hot plate method, tail-flick method and acetic acid writhing method, carrageenan-induced paw edema, and cotton-pellet method)
Shakhanbeh and Atrous (2001)	Rat	*T. polium*	2% Extract	Direct application to the nerve trunk caused immediate complete inhibition of compound action potentials (CAPs) of all types of primary afferent nerve fibers. Carrageenan-induced acute skin inflammation was reduced by 56.86%.
Bello *et al.* (1998)	Rat	*T. Flavum* (methanol extract)	200 mg kg^{-1}	Some fractions showed CNS depressant activity and some others induced slight CNS stimulant action. Some fractions were found responsible for the analgesic activity of the extract
Puntero *et al.* (1997)	Experimentally-induced arthritis and edema	*T. buxifolium*	-	A potent anti-inflammatory effect against experimentally-induced arthritis and carrageenan paw edema
Barrachina *et al.* (1995)	Carrageenan-induced paw edema in rats	*T. cartaginenses* *T. flavum* *T. pumillum* *T. buxifolium*	*T. flavum* (200 mg kg^{-1}, i.p.) *T. pumillum* (50 mg kg^{-1}, i.p.) *T. buxifolium* (26 mg kg^{-1}, i.p.) *T. cartaginenses* (200 mg kg^{-1}, i.p.)	*T. flavum* showed anti-inflammatory effect through the 24 h period. *T. pumillum* and *T. buxifolium* exhibited anti-inflammatory effects only in the acute phase of the edema (2 h) without affecting the chronic phase (24 h)
Bello *et al.* (1995)	Mouse	*T. cartaginenses* *T. flavum* *T. pumillum* *T. buxifolium*	-	Different extracts showed a CNS depressant activity, but they lacked anti-convulsive effects. None of the extracts increased the threshold of pain thermal stimulus. The methanol and dichloromethanol extracts of *T. cartaginenses* and *T. buxifolium* showed analgesic effects
Beitran *et al.* (1998)	Mouse	*T. buxifolium* L.	-	Analgesic activity
Heidari *et al.* (1999)	Mouse	*T. polium*	50-300 mg/kg	The maximum analgesic effect was induced with the dose of 200 mg kg^{-1}. The dose of 100 mg kg^{-1} was able to inhibit the second phase of pain. The doses of 200 and 300 mg kg^{-1} induced the highest analgesic effect and inhibited both phases of pain. The analgesic effect of extract was less than that of (2.5 mg kg^{-1}) morphine
Shahraki *et al.* (2006a)	Rat	*T. polium*	4 week	No significant change in tail reaction time in extract-treated animals
Tariq *et al.* (1989)	Carrageenan-induced acute inflammation	*T. polium*	500 mg/kg	The ethanolic extract inhibited carrageenan-induced inflammation and cotton-pellet granuloma. Biochemical studies showed a decrease in glucose level
Capasso *et al.* (1983)	Rat	*T. polium*	-	All tested extract inhibited carrageenan-induced edema comparable to that of indomethacin
Baluhnegadmojarad *et al.* (2005)	STZ-induced diabetic rat	*T. polium*	100-200 mg/kg/d/2 week	A lower nociceptive score was observed in diabetics

Table 1: Continued

Author	Target	*Teucrium* species	Dose/Duration	Effect
Studies on anti-ulcer effect				
Mehrabani *et al.* (2009)	Rat (indomethacin-induced stomach ulcer)	*T. polium*	1,2,4 week	After 4 weeks more re-epithelialization, proliferation, mucosal hyperplasia, migration of the gastric epithelial cells, and decrease in inflammatory cells were observed. Reduction of the ulcer indices by >50% after 1 week, >80% after 2 week, and >90% after 4 week.
Ansari *et al.* (2009)	Rat	*T. polium*	1 g/18 day	Significant difference of burn wound healing percentage on days12 and 18 in the treated group (39 and 78%) compared to the controls (30.2 and 61.4%), respectively. Significant increase of strain (tissue length under maximum strain) in the treated group compared to the control group was shown. In histopathology examinations, healing process was better achieved in the treated group with more oriented matrix arrangement and less inflammatory reaction than control group
Islam *et al.* (2002)	Rat	*T. stocksianum* Boiss	200-400 mg kg^{-1}	The extract inhibited gastric mucosal damage induced by NSAIDs, hypothermic-restraint stress, and pylorus ligated rats. No change was observed in the gastric acidity. Indomethacin attenuated the cytoprotection effects of *T. stocksianum*. Alcoholic extract possesses both anti-ulcerogenic and cytoprotective effects on various experimentally-induced gastric lesions
Galati *et al.* (1997)	Rat with ethanol-induced ulcer in stomach	*T. divariactum* Heldr SSP.	500 mg/kg/d/7 day	The ulcer index significantly decreased after treatment with a lyophilized decoction of *T. divaricatum* compared to the control. The ultrastructure modifications of gastric mucosa were observed by transmission electronic microscopy confirming the anti-secretory effect
Galati *et al.* (2000)	Rat with ASA-induced ulcer	*T. divaricatum* Heldr SSP	500 mg/kg/d/7 day	The ulcer index decreased after treatment with a lyophilized decoction of *T. divaricatum* The ultrastructure modifications of gastric mucosa were observed by transmission electronic microscopy confirming the anti-secretory effect.
Wasfi *et al.* (1995)	Rat	*T. stocksianum*	500 mg kg^{-1} twice per day	Given orally but not ip exhibited a gastric cytoprotective effect without significant effect on the healing process of ethanol-induced gastric ulcers 24, 48, and 72 h after induction of ulcer
Miscellaneous				
Orhan and Aslan (2009)	Mouse	*T. polium*		Dose-dependently effective in antiamnesia experiment by passive avoidance test.
Autore *et al.* (1984)	Rat	*T. polium*	-	The extract was effective against both yeast and carrageenan-induced pyrexia in rats. It exhibited a marked anti-bacterial action against both gram positive and gram negative organisms and was found to be non-toxic in acute studies.
Niazmand *et al.* (2007)	Rat	*T. polium*	20-40-80 mg/kg/ip	*T. polium* aqueous extract decreased frequency of contraction. Its effects on intragastric pressure in basal condition in presence of 20 mg kg^{-1} and in vagal stimulation in presence of 40 mg kg^{-1} dose of the extract were time-dependent
Panovska *et al.* (2007)	Rat with CCL4-induced liver damage	*T. polium*	25 mg kg^{-1}	The liver biopsy of all rat groups treated with plant showed significant restoration of the normal histomorphological pattern of liver cells
Rasheed *et al.* (1995)	Mouse with hepatic damage	*T. stocksianum*	0.5 and 1 g/kg/5 day	Paracetamol at an oral dose of 0.6 g kg^{-1} produced about 94% mortality in mice while pretreatment with the plant extract reduced the death rate to 0%. Pretreatment of mice with *T. stocksianum* ameliorated all the paracetamol-induced signs of liver damage

T: *Teucrium*; ip: intraperitoneal; iv: intravenous; DM: Diabetes mellitus, m: month, w: week, d: day, h: hour, HDL: high density lipoprotein, LDL: low density lipoprotein, Ch: Cholesterol, TG: triglyceride, BMI:body mass index; MPO: myeloperoxidase; TNF-alpha: tumor necrosis factor-alpha; IL-1beta: interlukin-1beta; FRAP : ferric reducing antioxidant power; w: week; MDA: malondialdehyde; JNK: c-Jun N-terminal kinase; ERK1/2: extracellular signal-regulated kinase; CAT: catalase; SOD: superoxide dismutase; GSH: reduced glutathione; NO: nitric oxide; PCO: protein carbonyl content; AOPP: advanced oxidation protein products; BG: blood glucose; TGF-β: transforming growth factor-β

failure. Similar hepatotoxicity was observed with other members of the *Teucrium* genus (Chitturi and Farrell, 2008). Human and animal studies considering adverse effects of *Teucrium* are summarized in Table 2.

Animal studies for acute and chronic toxic effects: Histopathological and biochemical studies revealed that high doses of *Teucrium* species or its long-term administration may induce progressive impairment of neuromuscular coordination and reversible or irreversible hepatic damage (Al-Ashban *et al.,* 2005; De Vincenzi *et al*., 2003; Kouzi *et al*., 1994; Rasekh *et al*., 2005; Shahraki *et al*., 2006a, b; Tanira *et al*., 1996, 1997). There was no significant difference in hematological parameters according to sex (De Vincenzi *et al*., 2003).

Hepatotoxicity with *Teucrium* in human: Drug-induced hepatotoxicity due to administration of medicinal plants has been infrequently reported. In Table 2, multiple case reports of hepatotoxicity by *Teucrium* species are described. Most of patients were presented with very high liver aminotransferases or developed jaundice. Hepatitis and intrahepatic cholestatic liver disease were the etiology of liver damage in these cases (Ben Yahia *et al*., 1993; Castot and Larrey, 1992; Dourakis *et al*., 2002; Larrey *et al*., 1992; Mazokopakis *et al*., 2007; Mimidis *et al*., 2009; De Miera Olivera *et al*., 2009; Pauwels *et al*., 1992; Perez Alvarez *et al*., 2001; Poon *et al*., 2008; Savvidou *et al*., 2007; Soylu *et al*., 1998; Starakis *et al*., 2006).

In this study, the activities of *Teucrium*, as a traditionally-used medicinal plant has been evaluated using a systematic search and review. Most of studies showed anti-diabetic effect of *Teucrium*. Insulinotropic potential of *Teucrium* has been tested by an *in vitro* investigation using isolated pancreatic rat islets (Esmaeili and Yazdanparast, 2004). Data indicated that *Teucrium* crude extract is able to enhance secretion of insulin by almost 135% after a single dose of the plant extract (equivalent to 0.1 mg plant leaf powder mL^{-1} of the culture medium) at high glucose concentration (16 mmol L^{-1}). Meanwhile, the time pattern of insulin secretion was not affected by the plant extract in comparison to the untreated islets. These data clearly show that the plant extract, probably without metabolic transformation, is able to reduce blood glucose levels through enhancing pancreatic secretion of insulin (Esmaeili and Yazdanparast, 2004; Yazdanparast *et al*., 2005). Another study showed that the number of pancreatic islets $unit^{-1}$ area was increased and activity of glucokinase was elevated by *Teucrium* (Vessal *et al*., 2003).

In two other studies, negative results on blood glucose level by *Teucrium* was obtained in normoglycemic and alloxan-induced hyperglycemic rabbits. *Teucrium* was administered intranasal as crude extract (10%) dissolved in 5% (w/w) Pluronic F127. No significant difference between the extract-treated and non-treated control animals receiving only water was observed (Afifi *et al*., 2005). The rout and the dose of administration might be responsible for these negative results.

The aqueous extract of *Teucrium* aerial parts, given intraperitoneally at doses of 50 to 150 mg kg^{-1} for 10 days, reduced serum cholesterol and triglycerides in hyperlipidemic rats (Rasekh *et al*., 2001). Considering other studies with negative result (Esmaeili and Yazdanparast, 2004; Karimi *et al*., 2002), further studies are needed for confirmation.

In another study, the essential oil of *Teucrium* was introduced as responsible component for analgesic effects. The anti-spasmodic properties of *Teucrium* was found comparable to hyoscin and indomethacin. The presence of flavonoids and sterols was suggested responsible for anti-inflammatory effects of *Teucrium* (Abdollahi *et al*., 2003a, b).

Several studies showed cytoprotective and anti-ulcer effects of *Teucrium* (Galati *et al*., 1997, 2000; Islam *et al*., 2002; Wasfi *et al*., 1995). Treatment with *Teucrium* blocked secretion of acid from parietal cells while stimulated forming of zymogen granules in chief cells (Wasfi *et al*., 1995). Another study indicated that ethanolic extract of *Teucrium* contains hepatoprotective constituents (Rasheed *et al*., 1995). Further works should be conducted to isolate and characterize the hepatoprotective constituents of *Teucrium*.

As a matter of fact, the therapeutic benefit of many medicinal plants is often attributed to their anti-oxidant properties. The aqueous extract of the leaves and stems of *Teucrium* was found to inhibit iron-induced lipid peroxidation in rat liver homogenate. In addition, organic extract of the aerial parts of *Teucrium* inhibited oxidative processes (Ljubuncic *et al*., 2006). Oxidative stress is known responsible in pathogenesis of various diseases like inflammatory bowel disease, diabetes, hyperlipidema, hepatothoxicity, osteoporosis and exposure to xenobiotics. In most of these conditions, use of antioxidants have been beneficial in ameliorating or even reversing the disease (Abdollahi *et al.,* 2003a, b, 2005; Ben Yahia *et al*., 1993; Castot and Larrey, 1992; Chitturi and Farrell, 2008; Larrey *et al*., 1992; Pauwels *et al*., 1992; Rahimi *et al*., 2005; Rezaie *et al*., 2007; Sarkhail *et al*., 2007; Soylu *et al*., 1998). Medicinal plants with antioxidative properties may be useful for the prevention of atherosclerosis and cardiovascular diseases

Table 2: Human and animal studies considering adverse effects of Teucrium

Author	Target	*Teucrium* species	Dose/Duration	Effect
Animal studies for acute and chronic toxic effects				
Al-Ashban *et al.* (2006)	Mouse	*T. polium*	2 h duration for acute and 3 months for chronic toxicity	Histopathological and biochemical studies revealed congestion and necrotic changes in the liver, an increase SGOT and SGPT of liver, and a reduction in blood glucose.
Tanira *et al.* (1997)	Mouse	*T. stocksianum*	%2-4/d/8 week	Progressive impairment of neuromuscular coordination was seen. After photochemical challenge, the time for first observable platelet aggregation in arterioles was shorter than for the control group by 22 and 45% in the 2 and 4% T. stocksianum-treated groups.
Tanira *et al.* (1996)	Rat	*T. stocksianum*	2-4 g/kg single dose for acute and 4%/2 day for chronic phase	Histological examination revealed occasional hepatic apoptosis and cerebral neuronal loss in the cortex and hippocampus and focal loss of Purkinje cells in the cerebellum. The results did not indicate a major hepatotoxic effect of acute or chronic administration.
Kouzi *et al.* (1994)	Mouse	*T. chamaedrys*	-	Teucrin A was found causing the same midzonal hepatic necrosis as observed with extracts of the powdered plant material
Rasekh *et al.* (2005)	Rat	*T. polium*	100, 300, 600 mg/kg/d/44 day	In biochemical parameters, an increase was seen in both SGOT and SGPT in female rats receiving 300 mg/kg of extract. There was also a significant increase in liver weight of male rats receiving 600 mg/kg
Shahraki *et al.* (2006)	Rat	*T. polium*	4 week	Liver SGOT and SGPT were increased
De Vincenzi *et al.* (2003)	Rat	*T. chamaedrys*	0.056 g/kg/day (0.4 mg/kg/d of Teucrium)	At this dose the compound induced minor effects on body weight of both males and females and slight reversible liver changes, confined to females, which mainly consisted of hepatocellular hypertrophy
Hepatotoxicity with Teucrium in human				
Mimidis *et al.* (2009)	Human	*T. polium*		Severe acute cholestasis
De Miera Olivera *et al.* (2009)	Human	*T. chamaedrys*		Acute hepatitis
Poon *et al.* (2008)	Human	*T. viscidum*	3 day	Hepatitis
Savvidou *et al.* (2007)	Report of two female	*T. polium*	2-3 months	Histologic examination of liver biopsies showed hepatitis with moderate or severe necroinflammatory activity. Discontinuation of the herbal remedy resulted in normalization of the liver enzymes in both patients
Mazakopakis *et al.* (2007)	Case report	*T. polium*	-	Intrahepatic cholestatic liver disease
Starakis *et al.* (2006)	Case report; 70 years old	*T. polium*	Daily consumption for 1 month	The patient presented with jaundice after consumption of large quantities of this herb in a tea form.
Dourakis *et al.* (2002)	Case report	*T. capitatum*	Daily consumption for 4 months	Liver histology demonstrated changes consistent with acute hepatitis with bridging necrosis. The medicinal plant was withdrawn. The patient recovered clinically and serum bilirubin and aminotransferases returned to normal levels within a 9-week time period
Perez Alvarez *et al.* (2001)	Case report	*T. chamaedryl*	Several months	Acute hepatitis
Soylu *et al.* (1998)	Case report	*T. polium*	2 months	Jaundiced with elevated liver enzymes reversible when the offending agent was withdrawn.
Ben Yahia *et al.* (1993)	3 cases	*T. multicaule* (Germander)	6-7 months	Hepatotoxicity
Castot *et al.* (1992)	26 cases	*T. multicaule* (Germander)	9 week	Hepatotoxicity
Pauwels *et al.* (1992)	2 cases	*T. multicaule* (Germander)	1-2 months	Severe acute hepatocellular liver injury. Clinical course was favorable after the treatment was discontinued. Involuntary rechallenge in one case resulted in reappearance of symptoms of liver injury
Larry *et al.* (1992)	7 cases	*T. multicaule* (Germander)	3-18 week	Liver biopsy specimens in three patients showed hepatocyte necrosis. After discontinuing treatment with germander, jaundice disappeared within 8 weeks and recovery was complete in 1.5 to 6 months

by reducing formation of oxidized lipids and altering their metabolism (Hasani-Ranjbar *et al*., 2008, 2009).

Herbal remedies have become increasingly popular throughout the globe as a result of disappointment with conventional medicines and also of the alleged belief that herbal preparations are basically harmless. On the other hand, their effects can be exceedingly potent or even lethal if used improperly. Drugs and other chemicals account for less than 5% of cases of jaundice or acute hepatitis and smaller number of cases of chronic liver disease. Drug reactions can mimic any hepatobiliary disease, posing a diagnostic challenge for physicians and pathologists (Starakis *et al*., 2006). *Teucrium* species are rich in neo-clerodane diterpenoids that is possibly the cause of hepatotoxicity (Sundaresan *et al*., 2006). Therefore, using *Teucrium* in those with hepatic abnormalities should be cautiously (Perez Alvarez *et al*., 2001).

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