

Phytochemical Constituents, Safety and Efficacy Study of *Thymus schimperi* and *Thymus serrulatus*

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ABSTRACT

Background: The genus *Thymus* is one of the most taxonomically complex genera in the *Lamiaceae* family and it includes 250-350 taxa (species and varieties). *T. serrulatus* Hochst. ex Benth and *T. schimperi* Ronniger are the two species of thymus which are endemic to Ethiopia; locally known as Tosign. According to WHO 2018 report, NCDs (non-communicable disease) are estimated to account for 39% of all deaths in Ethiopia and Infectious diseases also represent a continuous and increasing threat to human health in developing countries like Ethiopia. In Ethiopia, 80% of the population use plant remedies or medicinal plants over centuries.

Objective: The present study aimed to review Phytochemical-constituents, Safety and Efficacy Study of *Thymus schimperi* and *Thymus Serrulatus*.

Method: A web-based literature search was done by using scientific databases including Pub Med, Science Direct, Google Scholar and Scopus. Searching was made using key words: *Thymus*, *Thymus schimperi*, *Thymus serrulatus*, *phytochemistry*, *pharmacology*, *ethnomedicine*, efficacy and safety.

Results: *T. serrulatus* grows in Tigray, Gondar, Bale, in the highlands of Semien Shoa and Wollo whereas *T. schimperi* is widely distributed in Oromia, Amhara and Southern Nations Nationalities & Peoples Regions. *T. serrulatus* and *T. schimperi* belong to the chemotypes Carvacrol-Thymol. Carvacrol (63%), thymol (36%-38%), Thymol (49%) are the major constituent of the essential oil of *T. schimperi* collected from Bale, *T. schimperi* from Gonder, Shewa & Wello, *T. serrulatus* from the Tigray region respectively. Treatment of mice with 2000 mg/kg dose of the essential oil of *T. schimperi* caused 50% mortality indicating that it's the LD50 is about 2000 mg/kg. However, n-butanol fraction of the aqueous and crude methanol leaf extract *T. serrulatus* with the oral limit dose of 5,000 mg/kg showed no sign of overt behavioral changes and toxicity where the LD50 were above 10,000 mg/kg. n-butanol fraction and the crude aqueous extract of *T. serrulatus* has exhibited an increase in urine volume with the highest urine output at the highest dose (1,000 mg/kg) and an appreciable diuretic activity of 94% and 92% respectively.

Conclusion and Recommendation: The essential oil of *T. schimperi* did not cause a rise in serum enzyme level and major organ damage (kidney and liver), but the dose range of 2000 mg/kg causes 50% mortality. The n-butanol fraction of crude aqueous leaf extract of *T. serrulatus* showed an increase in urine volume with the highest urine output at the highest dose (1,000 mg/kg) and appreciable diuretic activity (94%). Additional chemical isolation, development of dosage form, clinical trial and toxicological study is recommended.

Keywords: *Thymus serrulatus*; *Thymus schimperi*; Efficacy; Safety; Ethnomedicine

INTRODUCTION

The genus *Thymus* is one of the most taxonomically complex genera in the *Lamiaceae* family. It includes 250-350 species and varieties of wild growing evergreen species of herbaceous perennials, subshrubs and aromatic [1,2]. The *Thymus* species in Eritrea and Ethiopia are restricted to Afromontane and afro alpine regions the species are well known medicinal plants because of their biological and pharmacological properties [3]. Thyme is largely distributed in temperate zones where Ethiopia has considerably abundant

Lamiaceae family herb growing at different regions possessing a variety of the wild growing species of this family.

The two species, *T. serrulatus* Hochst. ex Benth and *T. schimperi* Ronniger, both locally known as Tosign, which are endemic species represented in Ethiopia [4-7]. They grow in an open grassland, edges of roads, on bare rocks and on slopes, in the altitude range of 2200-4000 m [8,9].

According to WHO 2018 report, NCDs (non-communicable diseases) are estimated to account for 39% of all deaths in Ethiopia

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Received: July 06, 2019; Accepted: September 04, 2019; Published: September 10, 2019

Citation: Abera T, Debebe E, Ashebir R, Abebe A, Basha H, Kasahun T, et al. (2019) Phytochemical Constituents, Safety and Efficacy Study of *Thymusschimperi* and *Thymus serrulatus*. J Clin Exp Pharmacol 10: 263. doi: 10.35248/2161-1459.19.10.263

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which was 16% due to cardiovascular diseases and hypertension, is the prominent risk factor for chronic kidney disease, coronary heart disease and ischemic, as well as stroke and hemorrhagic [10]. Infectious diseases also represent a continuous and increasing threat to human health and developing countries like Ethiopia are carrying the major part of the burden. The number of infections caused by new, reemerging or drug resistant pathogens is growing from time to time. So, to fill such gaps in which new antimicrobial agents are urgently needed [11].

80% of the population of Ethiopia use plant remedies or medicinal plants over centuries. Moreover, medicinal plants remain the most crucial or sometimes the only source of therapeutics by playing a key role in the increase and progress of modern studies by being a base for the development of novelties in drugs [12-16]. In indigenous communities like Africa, Plants have played a central part in combating many ailments both in human and livestock. In Ethiopia, the plant based health care endures as the main alternative treatment for different ailments, mainly due to the scarcity of modern medicine, absence of nearby health service stations, expensive prices of conventional drugs for small holder farmers and pastoralists, appearance of drug resistant microbes and/or helminthes and emergence & recurrence of certain diseases [17-19].

Many of the modern pharmaceuticals are derived from medicinal herbs. Some of these include digitalis, a heart medication, derived from the Foxglove plant; salicylic acid, the source of aspirin, from Willow bark; and taxol for treating ovarian cancer, from the Pacific Yew tree, quinine and artemisinin are also well known antimalarial drugs derived from the bark of Cinchona tree and *Artemisia annua*, respectively [20,21]. In Ethiopia, the dried leaves of *T. serrulatus* and *T. shimperi* are used as traditional medicine for the treatment of headache, cough, stomachache, earache, liver disease and gonorrhoea. They are also used as flavor tea, coffee and different kinds of stew [5].

In Ethiopia *T. shimperi* possesses antibacterial, anthelmintic and antifungal activity [8,11,22]. It is also one of the most widely used medicinal plants for the treatment of renal diseases, hypertension, inflammation, infections, pain, to wash skin, mouth wash. The essential oil from leaves of *T. serrulatus* is used as for the treatment of hypertension, renal diseases and used as diuretic, anthelmintic, disinfectant, antispasmodic, carminative, deodorant, diaphoretic, expectorant, sedative, tonic, anti-inflammatory, antimicrobial, antibacterial, antifungal, antiviral, germicidal and libido enhancer [7,8,22]. Historically, In Ethiopia, there are documentations of *T. shimperi* and *T. serrulatus* used traditionally for the treatment of different human diseases in different parts of the country. However, the preclinical study such as phytochemical constituents, safety, efficacy and pharmacologic property of *T. shimperi* and *T. serrulatus* are not well reviewed in detail from different literature. Therefore, the aim of this study is to review the phytochemistry, efficacy and safety of *T. serrulatus* and *T. shimperi*.

Description of the plant species *T. shimperi* and *T. serrulatus*

T. shimperi Ronniger and *T. serrulatus* Hochst. ex Benth are perennial herbs, woody at the base and 5-40 cm high. The inflorescence is commonly crowded into globose and oblong heads with pink corollas [9]. *T. shimperi* is widely grown in different part of Ethiopia such as in Oromia, Amhara and Southern Nations Nationalities

& Peoples Regions. It is found in Ankober, Denkoro forest, Chanco, Menz Gera Midir (Guassa) Tarma Ber wereda of North Shewa and Gondar areas. *T. shimperi* is found in Dinsho, Sanetti Mountains, Adaba Dodola, Goma, Asendabo Jimma zone, Debre Zeyit, National Park of Awash and Menagesha Suba State Forest [5,23]. According to Shewaye, et al. [3] *T. shimperi* occurs in the wild at high altitudes such as in Debre Sina and Bale mountains. *T. serrulatus* is distributed around Bale, in the highlands of Semien Shoa, in Tigray, Wollo and Gonder [5,9,23-25].

Phytochemistry of *Thymus shimperi* and *Thymus serrulatus*

Thyme oils contain phytochemicals such as carvacrol, thymol, γ -terpinene, and p-cymene. These phytoconstituents are present in various proportions and characterized by a large amount of monoterpenes which accounts for 90% of the oil. Thymol and carvacrol occur more commonly and accompanied by the couple c-terpinene/p-cymene, the four monoterpenes being biogenetically closely correlated [1,26]. The presence of intraspecific chemotype variation being common in the genus *Thymus*. Each of the six chemotypes; thymol, carvacrol, geraniol, α -terpineol, thuyanol-4 and linalool are named after its major constituent monoterpene [27,28]. *T. serrulatus* and *T. shimperi* belong to the thymol-carvacrol chemotypes [26]. Both the chemical composition and the isolation yield of thyme oils depend on a number of factors, such as the environment or region in which they are grown, the practice in cultivation, the development stage of the plant, harvesting time and habitat [1,6,28,29].

T. shimperi from Bale is composed of carvacrol (63%) as the major constituent whereas *T. shimperi* from Gonder, Shewa and Wello is composed of thymol (36%-38%) as a dominant phytoconstituent. The essential oil of *T. serrulatus* collected from the Tigray region had thymol (49%) as the major constituent, similar to *T. shimperi* which is found around Dinsho [5,6]. However, the essential oil of *T. shimperi* collected from medicinal market of Merkto was analyzed to contain thymol (56.5%), linalool (18.5%), and carvacrol (8.9%) as major constituents [3]. According to Ermias, et al. [6] the essential oil of *T. shimperi* which is grown in Addis Ababa is rich in carvacrol (66.2%) and γ -terpinene (13.2%). Destaw, et al. [30] also reported the chemical composition of six essential oils of *T. serrulatus* and *T. shimperi* from six localities in Ethiopia, namely Ofla, Alamata, Yilmana Densa, Tarmaber, Butajira and Bale. According to the report of Destaw the major components of essential oil from Ofla are Alamata's thymol (65.6%), thymol (49.6 %), Yilmana Densa's carvacrol (80.4%), Tarmaber's thymol (48.8 %), Carvacrol (71.8%) were the prominent components of the essential oil from Butajira and in the case of Bale were thymol (53.6%). He also studied that *T. serrulatus* from Alamata and Ofla, *T. shimperi* from Bale and Tarmaber are of thymol chemotypes. The other two *T. serrulatus* from Yilmana Densa and *T. shimperi* of Butajira were found to contain carvacrol chemotypes. *T. shimperi* and *T. serrulatus* essential oil contains similar components with other species of thyme, The major components of thymus vulgaris from Romania were thymol (47.59%) and γ -terpinene (30.90%), which indicates that the essential oil analyzed belongs to the thymol chemotype. Carvacrol and thymol were the major compounds found in essential oils of *T. capitata* and *T. zygis* from Spain, respectively [27,28,31]. The crude extract and powdered plant leaves of *T. shimperi* is composed of secondary metabolites; tannins, phenols and saponins as major constituents [32].

The crude extracts and solvent fractions of *T. serrulatus* leaves have been reported by Amelework, et al. [25] to contain different secondary metabolites. Alkaloids, Saponins, Polyphenols, Tannins and Phytosterols were found in aqueous crude leaf extract of *T. serrulatus*. Saponins, flavonoids tannins and phytosterols were found in dichloromethane fraction of aqueous crude leaf extracts of *T. serrulatus*. n-butanol fraction of crude aqueous leaf extract of *T. Serrulatus* is composed of alkaloids, saponins, polyphenols, tannins and phytosterols which was comparable with the secondary metabolites of hexane, ethyl acetate, chloroform, butanol and methanol leaves extracts of *T. vulgaris* [33]. Aqueous and 80% methanol crude extract of *T. schimperi* leaves was qualitatively analyzed and the presence of steroids, alkaloids, flavonoids, saponins and tannins has been detected [34]. The other report showed that the wild Abyssinian thyme aerial parts the flower had highest total phenolic content (0.5 µg/ml) and the leaf the lowest and the whole thyme plant had the highest condensed tannin content (0.9 µg/ml). Distribution of macro and micro nutrients in *T. schimperi* Ca (2,776 ± 130 µg/g) was observed to be of the highest concentration followed by Mg (1,786 ± 13 µg/g). From the studied microelements, Fe (728 ± 58 µg/g) was found in a significant amount compared to Mn, Co, Cu, Zn, Ni, and Cd [35,36].

Safety of *T. schimperi* and *T. serrulatus*

Kassahun, et al. [37] acute toxicity study on mice revealed that the essential oil of *T. schimperi* causes depression, shivering, loss of balance and abnormal body movements. Mice treated with 2000 mg/kg dose of *T. schimperi* oil showed 50% mortality indicating that its LD50 is about 2,000 mg/kg. However, Sub-acute toxicity study of *T. schimperi* on mice did not cause major organ damage (liver and kidney) and rise in serum enzyme level as compared with the control group plus the ointment prepared from essential oil of *T. schimperi* which did not show any abnormal skin irritation up on follow up for 14 days. Destaw, et al. [38] also investigated that essential oils of Burning sensations and the most irritation in mice oil was observed during acute oral toxicity study on Alamata (thymol chemo type) oil. The carvacrol chemo-types (Yilmana and Butajira) resulted in reduced growth of mice than did the thymol chemo-types (Ofila, Alamata, Tarmaber, and Bale). The LD50 of the essential oils are in 2,000 µL/Kg to 5,000 µL/Kg dose ranges of body weight of the test mice which was comparable to with the study of other types of thymus species of essential oils of *T. algeriensis* [39]. Acute toxicity study on 5000 mg/kg oral limit dose of aqueous extract of *T. schimperi* leaves showed no clinical signs of toxicity, mortality and behavioral changes [32] whereas, n-butanol fraction of the aqueous crude extract and crude methanol leaf extract of *T. serrulatus* with the oral limit dose of 5,000 mg/kg showed no sign of toxicity and overt behavioral changes [22,25]. Nigatu, et al. [7] report on intra gastric uptake of extracts at doses 300, 2,000, 5,000, and 10,000 mg/kg did not produce any sign of morbidity and mortality in female mice during the acute toxicity study time period and showed that the LD50 of the aqueous leaf extracts of *T. serrulatus* were above 10,000 mg/kg. He also studied the chronic effect of aqueous leaf extract of *T. serrulatus* on the general body weight of the mice which showed the overall increment in body weight with time and the concentration of Urea/BUN its level decreased considerably at doses of 200 mg/kg (46.66 ± 2.08) and 600 mg/kg (34.6 ± 3.05) compared with the control groups (53.33 ± 3.05). The study of the gross appearance of internal organs (kidney and liver) of treated mice and rat showed no abnormal changes in shape, texture, size or color compared to the control.

In another report the methanol and aqueous crude extracts of *T. schimperi* showed no morbidity 14 days (acute toxicity) at dose of 2 g/kg body weight which signifies that the LD50 could be greater than 2 g/kg per body weight in mice [34].

Efficacy of *T. schimperi* and *T. serrulatus*

T. serrulatus with 80% methanol crude extract have shown an increase urine volume. Doses of 125 mg/kg and 500 mg/kg were the lowest and the highest urinary excretions with a diuretic index of 1.13 and 1.60 respectively. 88% at 500 mg/kg diuretic activity has been recorded from the extract. *T. Serrulatus* crude extract from n-butanol fraction of the 80% methanol also increased urine volume and the highest diuretic index (P<0.01) was evident at 1000 mg/kg which was even greater than that of the HCT. The 80% methanol crude extract of *T. Serrulatus* showed the prominent natriuresis at 500 mg/kg (P<0.001), and 125 mg/kg was the lowest amount recorded. The chloroform fraction of the crude extract did not show significant urinary excretion of both Sodium and Potassium ions. However, showed significant kaliuresis only at 1000 mg/kg (P<0.05). A dose-dependent increase in the urinary excretion of Sodium and Potassium ions were observed from n-butanol fraction of the 80% methanol extract of *T. serrulatus*. At the dose of 1000 mg/kg (P<0.001 and P<0.01, respectively) the highest natriuresis and kaliuresis were observed [25].

Amelework, et al. [22] study revealed that the crude aqueous extract of *T. serrulatus* increased the urine volume at the dose of 250 mg/kg, (1,000 mg/kg) which is the lowest and the highest urine output was recorded respectively, with a considerable diuretic activity of 92 percent in comparison with the standard drug, HCT (hydrochlorothiazide). The dichloromethane fraction of the aqueous extract of *T. serrulatus* failed to increase in urinary output at 2,50,500, and 1,000 mg/kg doses but, the n-butanol fraction increased the urine output at all test doses (2,50,500, and 1,000 mg/kg). Even the lowest test dose of n-butanol fraction exhibited a significant (P<0.05) diuretic activity of 70% and the highest diuretic activity of the fraction was demonstrated at 1,000 mg/kg, which was about 94%.

According to Bekesho, et al. [8] *in vitro* vasodilatory effect of aqueous leaf extract of *T. serrulatus* on thoracic aorta of Guinea pigs. Sequential administrations of relatively low to high concentrations of *T. serrulatus* aqueous leaf extract (0.5-5 mg/mL) to the organ bath fluid significantly (P<0.001, in all cases) attenuated the force of contractions on thoracic aorta of guinea pigs, which were provoked by KCl in concentration dependent manner both in intact (n=5) and denuded (n=5) endothelium. The percent of aorta relaxation of the *T. serrulatus* aqueous leaf extract showed a significant (P<0.05) difference between intact and denuded endothelium of the guinea pigs thoracic aorta with a statistical mean of (43.10 ± 0.52)% and (35.60 ± 0.52) % respectively.

Aqueous and methanol 80% extract of *T. schimperi* showed a reduction in blood glucose levels in a dose- and time-dependent manner. *T. schimperi* aqueous extracts of 250 and 500 mg/kg showed reduction of 22.65% and 33.15% in plasma glucose levels, respectively after 4 h of extract administration and In case of 80% methanol extraction at 250 and 500 mg/kg showed reduction of 30.06% and 38.35% in plasma glucose levels, respectively [34]. The oral administration of aqueous extract of *T. schimperi* leaves and its essential oil distillate at doses of (250, 500, 750 and 1000 mg/kg) and (1 and 1.5 ml/kg) was respectively evaluated for

their diuretic and anti-hypertensive activity against salt-sucrose induced hypertensive rats. The aqueous extract of *T. schimperi* leaves for all mentioned doses showed positive diuretic activity at 5 hr and the two higher doses significantly increased Na^+ , K^+ and Cl^- content of urine (Figure 1) [32].

A 50 mg/ml concentration Ethanol, Methanol and Chloroform extract of *T. schimperi* showed antibacterial activity against standard and clinical isolates of human pathogenic bacteria [40] which was similar pharmacologic activity with other species of thymus [28,41]. Ethanol and Methanol extract inhibited gram positive bacteria MRSA, *S. aureus*, *S. pneumoniae* (standard) and *S. pneumoniae* (clinical isolate). Methanol extract showed higher ($P < 0.05$) inhibition zone against the tested bacteria (*E. coli*, MRSA, *S. flexneri*, *S. aureus*, *K. pneumoniae* (clinical isolate), *S. pneumoniae*, and *S. pneumoniae* (clinical isolate) as compared to ethanol extract. However, Chloroform extract showed 100% inhibition against all the tested bacteria with higher inhibition zone for most of test bacteria except for standard *S. aureus* (17 mm). The maximum inhibition zone of Ethanol extract (19 mm) was recorded for MRSA and standard *S. pneumoniae* while the minimum was obtained for standard *S. aureus* (17 mm). Similarly, the maximum inhibition zone for methanol extract was obtained for MRSA (19.3 mm) whilst the minimum was obtained for standard *S. aureus* (18.3 mm). MRSA showed highest inhibition zone with chloroform extract as compared to other test bacteria and the MIC value for chloroform extract ranged from 6.25 mg/ml to 12.5 mg/ml. Five of test bacteria (MRSA, *S. flexneri*, *K. pneumoniae*, *S. pneumoniae* standard and clinical isolate) got high MIC value (12.5) whilst only two of test organisms (*E. coli* and *S. aureus*) showed lowest MIC value (6.25 mg/ml). However, the minimum MBC value was 6.25 mg/ml while, the maximum value was 25 mg/ml. The highest MBC value (25 mg/ml) was obtained for three test bacteria (*K. pneumoniae*, clinical *S. pneumoniae* and standard *S. pneumoniae*). The lowest MBC value (6.25 mg/ml) was recorded only for *E. coli*.

T. schimperi oil had moderate antibacterial effect on tested Enterobacteriaceae; 17 mm and 24 mm inhibition zone in diameter against *E. coli* and *K. pneumoniae* respectively. It had also considerable inhibition zone in diameter; MSSA and MRSA (24 mm) [42]. Mohammed, et al. [43] on the other study, reported that *T. schimperi* had the greatest inhibition zone diameter of 88.66 mm against *R. rubra* and 73.33 mm against clinical isolates of *Trichophyton species* and *Microsporum species*. The least inhibition

zone exhibited by *T. schimperi* was 35.66 mm against *C. albicans*. *T. schimperi* essential oil possessed potential antibacterial activity against *Bacillus*, *E. coli*, *Shigella* and *Streptococcus* species when Bacteria susceptibility to the essential oils was studied by the agar diffusion method. *T. schimperi* oils highest antibacterial activity was 90 mm in *E. coli*, *Shigella species* and *Streptococci* and relatively least activity was recorded in *Bacillus* species to be 63 mm.

The highest MIC values of *T. schimperi* oil was 0.08 $\mu\text{l/ml}$ against *Trichophyton species* (scalp isolate), *Microsporum* and *R. rubra species*. *T. schimperi* oil showed activities in the range of concentration from 0.31 $\mu\text{l/ml}$ to 0.63 $\mu\text{l/ml}$ which is comparable with other species of thymus [44]. *T. serpyllum* essential oil showed the strongest activity in both cases (MIC 2.5-5 $\mu\text{g/ml}$, MBC 5-10 $\mu\text{g/ml}$; MIC 1-2 $\mu\text{g/ml}$, MFC 2-4 $\mu\text{g/ml}$). *T. algeriensis* inhibited the growth of selected microorganisms in medium range of MIC 20-80 $\mu\text{g/ml}$, MBC 40-160 $\mu\text{g/ml}$ (for bacteria) and MIC 5-10 $\mu\text{g/ml}$, MFC 10-20 $\mu\text{g/ml}$ (for fungi). The essential oils of *T. serpyllum*, *T. algeriensis* and *T. vulgaris* showed significant antibacterial activity, especially against *S. mutans*, a recognized cariogenic species and their oils also efficiently inhibited the growth of *Candida* species

Shewaye, et al. [3] studied the antifungal activity of the oil of *T. schimperi* against *Aspergillus niger*. The essential oil of *T. schimperi* indicated strong effect on the fungal pathogen (*Aspergillus niger*) after applying 10 $\mu\text{l/disc}$ of the oil, which completely inhibited up to a diameter of 36 mm and its minimum inhibitory concentration (MIC) was estimated to be lower than 5 $\mu\text{l/disc}$, which was related with other finding [45]. This is due to the presence of thymol and carvacrol as observed from GC and GC/MS analysis. Awol et al. [11] study, the oil of *T. schimperi* has shown the greatest inhibition zone diameter of 33 mm against *S. epidermidis* bacteria and inhibited the growth of two *Trichophyton* and two *Aspergillus* species at a concentration lower than 15.75 mg/mL. Higher concentration (23.25 mg/mL) of *T. schimperi* essential oil inhibits the growth of *P. aeruginosa* which was comparable with the essential oil of *T. kotschyanus* species [46].

The oils of *T. schimperi* and *T. serrulatus* from different Ethiopian localities had promising protective activity against paracetamol induced hepatic damage in rats. Treatment with 200 $\mu\text{l/kg}$ of the essential oils of *T. schimperi* (Tarmaber) and *T. serrulatus* (Yilmana, Alamata) was found to reverse increased levels of AST, ALT and ALP in PAR (paracetamol) treated rats [30].

Pharmacological properties of *T. schimperi* and *T. serrulatus*

The oils of *T. schimperi* possess antifungal and antibacterial activity against different species of fungus and bacteria [3,11,40,43] which was similar with pharmacologic activity of oils of *T. hirtus*, *T. kotschyanus boiss*, *T. vulgaris*, *T. mastichina*, *T. serpyllum* and *T. algeriensis* species [28,41,46,47]. *T. schimperi* oil had antioxidant and preservative effects [4] and consistent with other species of thymus [2,41,44,46,48,49] and seem to be applicable in both medicine and food industry. The oils of *T. serrulatus* and *T. schimperi* from different Ethiopian localities had promising protective activity against paracetamol induced hepatic damage in rats [30]. *T. schimperi* was one of Ethiopian anticancer plants since it has antioxidant properties [50]. Diuretic activity was observed from the aqueous, 80% methanol crude extract and its different solvent

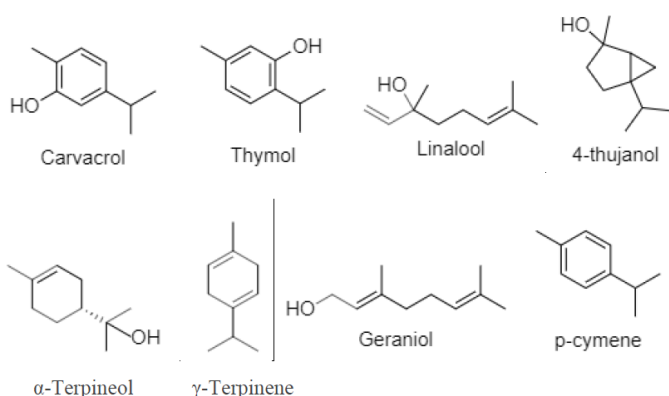


Figure 1: Some of the chemical structures for potentially active compounds of thymus species in Ethiopia.

Table 1: Ethno botanical studies of *T. schimperi* and *T. serrulatus*.

Parts used	Plant Species used	Disease treated	Method of preparation	Mechanism of action	Reference
Leaf	<i>T. schimperi</i> <i>Ronniger</i>	Abdominal disease	Concocted, crushed and mixed with milk	Inhibit the growth of pathogenic microorganism	[53]
Leaf	<i>T. schimperi</i> <i>Ronniger</i>	Cough	Powdered, mix with water and drunk	Reduce the surface tension and viscosity of the mucus	[56]
Leaf Flower	<i>T. schimperi</i> , <i>T. serrulatus</i>	Blood pressure	Dried crushed and drunk as tea	Blocks the alpha receptor and relax the muscles	[23]
Leaf Flower	<i>T. schimperi</i> , <i>T. serrulatus</i>	General pain syndrome	Dried, crushed and drunk as tea	By binding to protein targets on cell membranes and affecting the biochemical processes of the body	[23]
Leaf Flower	<i>T. schimperi</i> , <i>T. serrulatus</i>	Influenza	Dried, crushed and drunk as tea	Inhibits polymerase acidic endonuclease	[23]
Aerial parts	<i>T. schimperi</i> , <i>T. serrulatus</i>	Abdominal pain	Dried, crushed and drunk as tea	Inhibit the growth of pathogenic microorganism	[15,23]
Leaf	<i>T. schimperi</i> , <i>T. serrulatus</i>	Ascariasis	Dried, crushed and drunk as tea	Inhibits tubulin polymerization	[23]
Whole plant	<i>T. schimperi</i>	Snake bite	Drunk orally, body wash	Reducing systemic toxicity by limiting lymphatic flow	[55]
Stem	<i>T. schimperi</i>	Devil Disease	Drunk orally, body wash	Inhibit abnormal cell growth	[55]
Root	<i>T. schimperi</i>	Intestinal parasite	Drunk orally	Inhibit the growth of parasite	[55]
Whole plant	<i>T. schimperi</i>	Toothaches	Chew it with the affected tooth	Resist acid and block the cavity forming action of bacteria	[15]
Leaf	<i>T. schimperi</i>	Hypertension	Boiled leaves and drunk as tea	prevent aldosterone release	[56]
Leaf	<i>T. schimperi</i>	Whooping cough	Boiled leaves and drunk as tea	reduce the surface tension and viscosity of the mucus	[56]
Root	<i>T. schimperi</i>	hypertension	Root dried, powdered, and drink with tea	prevent aldosterone release	[54]
Leaf	<i>T. schimperi</i> <i>Ronniger</i>	Cancer	Dry leaves are decocted and drunk	Inhibit the abnormal growth of cells	[50]
Leaf and Flower	<i>T. serrulatus</i>	Renal disease	Fresh leaves are soaked with hot water and the filtrate taken orally	reduced renal inflammation, cellular infiltration and fibrosis	[32]
Stem, Leaf, Whole plant	<i>T. schimperi</i> , <i>T. serrulatus</i>	Diabetes	Dried stem and leaf powder boiled with tea is given orally	Reduce intestinal glucose absorption	[56]

fractions of the leaves of *T. serrulatus* [22,25] and also vasodilatory effect on KCl induced pre contracted guinea pigs' isolated thoracic aorta rings which might result to antihypertensive effect [8]. *T. vulgaris* oil showed proliferation inhibition of human cancer cell lines in dose dependent manner [51], *T. algeriensis* possesses gastro protective effect resulted in maintaining the mucosal integrity and a mild mucosal ulceration at a dose of 117 and 180 mg/kg respectively [39].

T. serpyllum had potent effect on inhibition of human tumor cells lines growth [44]. *T. longicaulis*, *T. pulegioides*, *T. vulgaris*, *T. serpyllum*, *T. striatus* and *T. praecox* also showed anti-acetylcholinesterase activities [2]. All this entire species of thymus had comparable pharmacologic property with *T. schimperi* and *T. serrulatus*.

Ethno-medicinal uses of *T. schimperi* and *T. serrulatus*

Ethnobotanical study and knowledge of medicinal plants would contribute to improved human health on a local and/or a global level [52]. In west highlands of Ethiopia *T. schimperi* is one of herbal spices grown in home garden and used as ingredients of mixed spice used in cooking and medicinally important [53] which was

consistent with the previous report [54]. *T. serrulatus* grown in Tigray used as ascaricidal, intestinal paraciticidal and both of *T. schimperi* and *T. serrulatus* used for treatment of general pain syndrome, blood pressure, influenza and abdominal pain [53], which was similar to ethnobotanical use of *T. serpyllum* species in in Pakistan [55]. *T. serpyllum* used as laxative, a good tonic for the kidney and eye diseases, useful in bronchitis and purify the blood in Sudan [56]. *T. schimperi* was used not only for human disease, but also for cattle and its flower for honey around Odo Bulu, Bale and Demaro region of Ethiopia [52]. *T. schimperi* is also used for treatment of circulatory disorder in Ada'a District, East Shewa Zone of Oromia Regional State, Ethiopia [56].

In the overall our ethnobotanical review data in Table 1 reveals that, most Ethiopian community utilized *T. schimperi* and *T. serrulatus* for the managements of different types of diseases especially in rural communities of the country.

CONCLUSION AND RECOMMENDATION

This review highlighted phytochemical-constituents, safety and efficacy study of *Thymus schimperi* and *Thymus serrulatus* which were endemic species represented in Ethiopia. *T. schimperi* and *T. serrulatus* belong to the thymol-carvacrol chemo-types. The

isolation yield and the chemical composition of the thyme oil are dependent on the environment, growth region, cultivation practices, and the development stage of the plant, habitat and harvesting time. The essential oils of *T. schimperi* possess antibacterial, antifungal, antioxidant and preservative effects. This review also showed the diuretic and vasodilatory effect of *T. serrulatus* which was safe and effective. The leaves of *T. schimperi* was widely used for different ailments at different parts of Ethiopia and more frequently cited by ethno-botanical study than *T. serrulatus*. Even though, the acute toxicity study of the essential oils of *T. schimperi* did not cause increase in serum enzyme level and major organ damage (liver and kidney), it causes 50 percent mortality at the dose of 2,000 mg/kg. The n-butanol fraction of crude aqueous extract of *T. serrulatus* increase urine volume and the highest urine output was observed at the highest dose (1,000 mg/kg) with an appreciable diuretic activity 94%. Further chemical isolation, dosage form development, clinical trial and toxicological study is recommended for both species.

CONFLICT OF INTEREST

The author has declared that there is no conflict of interest with regarding to the authorship and publication of this review article.

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