

A Review on *Lycopus europaeus*: A Potential Medicinal Plant

Ali Esmail Al-Snafi

Department of Pharmacology, College of Medicine, Thi qar University, Iraq.

Corresponding Author: Ali Esmail Al-Snafi

Abstract: *Lycopus europaeus* was used traditionally to cure coughs, respiratory disorders and as a natural remedy for sleeplessness. It was also used as a natural treatment for hyperthyroidism and for some symptoms of Grave's disease, such as palpitations. It was also used in vascular excitement; hemorrhage, in small amounts, resulting from determination of blood to the lungs, kidneys, or gastro-intestinal organs; albuminuria, with frequent pulse; cough, with copious expectoration of mucus or muco-pus, especially debilitating chronic cough; wakefulness and morbid vigilance, with inordinately active circulation. *Lycopus europaeus* contained alkaloids, coumarin, tannic acid, phenolic compounds, flavonoids, minerals, essential and volatile oils and many other chemical constituents. It possessed endocrine, antimicrobial, antiparasitic, antioxidant, anti-inflammatory, analgesic, hypnotic, antitussive, dermatological and anti-diarrhoeal effects. The current review discussed the chemical constituents, pharmacological, therapeutic and adverse effects of *Lycopus europaeus*.

Keywords: *Lycopus europaeus*, constituents, pharmacology, therapeutic effects, side effects

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I. INTRODUCTION

Herbal medicine is the oldest form of medicine known to mankind. It was the mainstay of many early civilizations and still the most widely practiced form of medicine in the world today. Plants generally produce many secondary metabolites which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives⁽¹⁻²⁰⁾. *Lycopus europaeus* was used traditionally to cure coughs, respiratory disorders and as a natural remedy for sleeplessness. It was also used as a natural treatment for hyperthyroidism and for some symptoms of Grave's disease, such as palpitations. It was also used in vascular excitement; hemorrhage, in small amounts, resulting from determination of blood to the lungs, kidneys, or gastro-intestinal organs; albuminuria, with frequent pulse; cough, with copious expectoration of mucus or muco-pus, especially debilitating chronic cough; wakefulness and morbid vigilance, with inordinately active circulation. *Lycopus europaeus* contained alkaloids, coumarin, tannic acid, phenolic compounds, flavonoids, minerals, essential and volatile oils and many other chemical constituents. It possessed endocrine, antimicrobial, antiparasitic, antioxidant, anti-inflammatory, analgesic, hypnotic, antitussive, dermatological and anti-diarrhoeal effects. The current review was designed to highlight the chemical constituents, pharmacological, therapeutic and adverse effects of *Lycopus europaeus*.

Plant profile:

Synonyms:

Lycopus albus, *Lycopus aquaticus*, *Lycopus decrescens*, *Lycopus europaeus* f. *glabrescens*, *Lycopus europaeus* var. *glabrescens*, *Lycopus europaeus* var. *hirsutus*, *Lycopus europaeus* var. *incanus*, *Lycopus europaeus* subsp. *menthifolius*, *Lycopus europaeus* subsp. *menthifolius*, *Lycopus europaeus* var. *menthifolius*, *Lycopus europaeus* subsp. *mollis*, *Lycopus europaeus* var. *mollis*, *Lycopus europaeus* var. *pubescens*, *Lycopus europaeus* f. *pusillus*, *Lycopus europaeus* var. *subpinnatifidus*, *Lycopus europaeus* var. *trichophora*, *Lycopus europaeus* f. *velutina*, *Lycopus intermedius*, *Lycopus laciniatus*, *Lycopus menthifolius*, *Lycopus mollis*, *Lycopus niger*, *Lycopus palustris*, *Lycopus solanifolius*, *Lycopus souliei*, *Lycopus vulgaris*⁽²¹⁾.

Taxonomic classification:

Kingdom: Plantae, **Subkingdom:** Viridiplantae, **Infrakingdom:** Streptophyta, **Superdivision:** Embryophyta, **Division:** Tracheophyta, **Subdivision:** Spermatophytina, **Class:** Magnoliopsida, **Superorder:** Asterales, **Order:** Lamiales, **Family:** Lamiaceae, **Genus:** *Lycopus*, **Species:** *Lycopus europaeus*⁽²²⁾.

Common names:

Arabic: Farasyon Maeiy, Eshbat el-booq; **Chinese:** ou di un; **English:** bugleweed, European bugleweed, gypsywort; **Swedish:** strandklo⁽²³⁾

Distribution:

It was distributed in **Asia** (Afghanistan, Iran, Iraq, Syria, Turkey, Armenia, Azerbaijan, Georgia, Russian Federation, Siberia, Kazakhstan, Kyrgyzstan, Tajikistan, Uzbekistan, China, Japan, Pakistan), **Europe** (Denmark, Norway, Sweden, United Kingdom, Austria, Belgium, Czechoslovakia, Germany, Hungary, Netherlands, Poland, Switzerland, Belarus, Estonia, Latvia, Lithuania, Moldova, Russian Federation- European part, Albania, Bulgaria, Former Yugoslavia, Greece, Italy, Romania, France, Portugal, Spain) and it was naturalized in wide areas in the world and acclimated in North America and Australia⁽²³⁾.

Description:

Perennial herb, spreading by branching stolons. Stems 40–120 cm high, erect, quadrangular, pubescent. Leaves opposite, short-petioled, 3–12 cm long, 1–5 cm broad, lanceolate to ovate or elliptical, pubescent particularly along veins and glandular-punctate; base cuneate; apex acute to acuminate; margins sinuate or coarsely serrate with deepest lobes near base, or base pinnatifid in lower leaves. Inflorescences axillary, verticillate, bracteate; bracts lanceolate, 3–5 mm long, with narrow pointed apex. Calyx campanulate, 3.5–4.5 mm long, 13-nerved, pubescent; teeth 5, equal, longer than tube, awned. Corolla white with small purple spots, about 4 mm long, nearly radially symmetrical, tubular below, gradually widening above, 4-lobed; upper lobe slightly wider and crenate on outer margin. Stamens 2, protruding from corolla; anthers 2-loculed; staminodes 2, minute. Style gynobasic. Fruit 4 nutlets, 1.6–1.9 mm long, 1.0–1.3 mm broad, with a corky crest⁽²⁴⁾.

Traditional uses:

Traditionally, this herb was used to cure coughs, respiratory disorders and as a natural remedy for sleeplessness. It was also used as a natural treatment for hyperthyroidism and for some symptoms of Grave's disease, such as palpitations⁽²⁵⁾. Furthermore, it was used as astringent and cosmetic in Turkey, for the treatment of fever in Iraq and Turkey, as refrigerant, for the treatment of wounds and hyperthyroidism in India⁽²⁶⁾. It was also used in vascular excitement; hemorrhage, in small amounts, resulting from determination of blood to the lungs, kidneys, or gastro-intestinal organs; albuminuria, with frequent pulse; cough, with copious expectoration of mucus or muco-pus, especially debilitating chronic cough; wakefulness and morbid vigilance, with inordinately active circulation; frequent pulse, with high temperature, and in tubercular deposits⁽²⁷⁾.

Parts used: The above ground parts (leaves and flowers)⁽²⁵⁾

Chemical constituents:

Lycopus europaeus contained alkaloids, coumarin, tannic acid, delta-cadinene, luteolin-7-glucoside (23 mg/g), ursolic acid, rosmarinic acid (76 mg/g), apigenin-7-monoglucoside, lithospermic acid, ferulic acid, caffeic acid, chlorogenic acid, sinapic acid, sagerinic acid, ellagic, trioxxygenated $\Delta^8(9)$, 15-pimaric acid methyl ester, pimaric acid, 15-diene, oxygenated abietane-type diterpenoid (euroabienol), isopimarane diterpenoids (methyl-1 α -acetoxy-7 α -14 α -dihydroxy-8,15-isopimaradien-18-oate, and methyl-1 α , 14 α -diacetoxy-7 α -hydroxy-8,15-isopimaradien-18-oate), germacrene-d, trans-beta-farnesene, caryophyllene, caryophyllene-oxide, isopimarane derivatives, 5,9-dihydroxy geranylinalool, organic and inorganic matters, bitter principle, and a peculiar principle⁽²⁷⁻³⁴⁾.

Copper and zinc concentrations in the *Lycopus europaeus* were 9.07-10.40 and 73.31-77.55 mg/kg in the biomass respectively⁽³⁵⁾.

Fatty acid composition of the fruits of *Lycopus europaeus* were: saturated fatty acid 7.2-10.4% and unsaturated fatty acid 85.8-91.7%. Fatty acid composition of the fruits of *Lycopus europaeus* (methyl esters) were: methyl dodecanoate (methyl laurate), methyl tetradecanoate (methyl myristate), methyl 12-methyltetradecanoate, methyl pentadecanoate, methyl 14-methylpentadecanoate, methyl (9Z)-9-hexadecanoate (methyl palmitoleate), methyl hexadecanoate (methyl palmitate), methyl 14-methylhexadecanoate, methyl (9E)-9-heptadecanoate, methyl heptadecanoate, methyl (9Z,12Z)-9,12-octadecadienoate (methyl linoleate), methyl (9Z,12Z,15Z)-9,12,15-octadecatrienoate (methyl linolenate), methyl (E)-9-octadecenoate (methyl elaidate), methyl octadecanoate (methyl stearate), methyl 16-methyloctadecanoate, methyl (Z)-9-nonadecanoate, methyl nonadecanoate, methyl 18-methylnonadecanoate, methyl (11Z,14Z)-11,14-eicosadienoate, methyl (Z)-9-eicosenoate, methyl eicosanoate (arachidic acid methyl ester), methyl 18-methyleicosanoate, methyl heneicosanoate, methyl 20-methyl heneicosanoate, methyl docosanoate (methyl behenate), methyl 20-methyldocosanoate, Methyl tricosanoate, Methyl 22-methyltricosanoate, Methyl tetracosanoate (methyl lignocerate), methyl hexacosanoate, methyl octacosanoate, tert-butyl tetradecanoate, tert-butyl (9Z)-9-

hexadecenoate, tert-butyl hexadecanoate (tert-butyl palmitate), tert-Butyl 14-methylhexadecanoate, tert-butyl heptadecanoate. While, fatty acid composition of the fruits of *Lycopus europaeus*: (tert-butyl esters) were: tert-butyl (9Z,12Z)-9,12-octadecadienoate (tert-butyl linoleate), tert-butyl (9Z)-9-octadecenoate (tert-butyl oleate), tert-butyl (9Z,12Z,15Z)-9,12,15-octadecatrienoate (tert-butyl linolenate), tert-butyl (9E)-9-hexadecenoate (tert-butyl elaidate), tert-butyl octadecanoate (tert-butyl stearate), tert-butyl 16-methyloctadecanoate, tert-Butyl nonadecanoate, tert-butyl 18-methylnonadecanoate, tert-butyl (9Z)-9-eicosanoate, tert-butyl eicosanoate, tert-butyl 18-methyleicosanoate, tert-butyl heneicosanoate, tert-butyl 20-methylheneicosanoate, tert-butyl docosanoate, tert-butyl 20-methyldocosanoate, tert-butyl tetradecanoate⁽³⁶⁾.

The analysis of the volatile essential oil and lipid profiles of the aerial parts from the blooming and fruit-forming stages of both ripe and unripe fruit of two samples of *Lycopus europaeus* showed that the plant contained: 3-methyl-1-butanol: trace and not detected; 2-methyl-1-butanol: trace; 1-pentanol: trace and not detected; (Z)-2-penten-1-ol: trace and not detected; octane: trace; 4-methyl-1-pentanol: trace and not detected; furfural: trace and not detected; (E)-3-hexen-1-ol: trace and $0.1 \pm 0.01\%$; (Z)-3-hexen-1-ol: 3.1% and $1.5 \pm 0.07\%$; (Z)-2-hexen-1-ol: trace and $0.6 \pm 0.04\%$; 1-hexanol: $0.2 \pm 0.01\%$ and $0.6 \pm 0.03\%$; 2-butylfuran: trace and not detected; 3-ethyl-1-octene: not detected and trace; benzaldehyde: trace and trace; 1-octen-3-one: trace and not detected; 1-octen-3-ol: $0.6 \pm 0.04\%$ and $0.7 \pm 0.03\%$; 6-methyl-5-hepten-2-one: trace and $0.1 \pm 0.01\%$; 2-octanone: trace and not detected; 2-pentylfuran: trace and trace; 6-methyl-5-hepten-2-ol: trace and trace; 3-octanol: $0.1 \pm 0.01\%$ and $0.1 \pm 0.01\%$; (Z)-3-hexenyl acetate: trace and not detected; 2-ethyl-1-hexanol: trace and not detected; (Z)-b-ocimene: $0.1 \pm 0.01\%$ and $0.2 \pm 0.01\%$; 2,6,6-trimethyl cyclohexanone: not detected and trace; (E)-b-ocimene: trace and $0.1 \pm 0.01\%$; phenylacetaldehyde: $0.1 \pm 0.01\%$ and $0.6 \pm 0.03\%$; 2,6-dimethyl-2,6-octadiene: not detected and $0.2 \pm 0.01\%$; (E)-2-octen-1-ol: trace and not detected; 1-octanol: trace and trace; acetophenone: trace and not detected; 4,8-dimethyl-1,3,7-nonatriene (isomer 1h): trace and not detected; undecane: trace and trace; (E)-hotrienol: 4.5 ± 0.28 and $13.7 \pm 0.75\%$; nonanal: trace and trace; (E)-4,8-dimethylnona-1,3,7-triene: $0.1 \pm 0.01\%$ and $0.2 \pm 0.01\%$; 3-octyl acetate: trace and $0.1 \pm 0.01\%$; 2,6-dimethyl-1,3,5,7-octatetraene: trace and not detected; (Z)-epoxy-ocimene: trace and not detected; (3E,5E)-2,6-Dimethyl-1,3,5,7-octatetraene: trace and not detected; (E)-epoxy-ocimene: trace and not detected; exo-isocitral: trace and trace; (2E,6Z)-2,6-nonadienal: trace and trace; (Z)-isocitral: 0.1 ± 0.01 and $0.3 \pm 0.01\%$; lavandulol: trace and not detected; 1-nonanol: trace and not detected; (3E,5Z)-1,3,5-undecatriene: trace and not detected; borneol: not detected and $0.2 \pm 0.01\%$; (E)-isocitral: $0.1 \pm 0.01\%$ and $0.2 \pm 0.01\%$; 1-decen-3-ol: trace and not detected; (Z)-3-hexenyl butanoate: trace and not detected; terpinen-4-ol: trace and trace; 1,3,5-undecatriene: trace and not detected; 1-phenylethyl acetate: trace and not detected; (E)-3-hexenyl butanoate: trace and not detected; α -terpineol: tr and $0.1 \pm 0.01\%$; dodecane: $0.1 \pm 0.01\%$ and $0.1 \pm 0.01\%$; methyl salicylate: not detected and trace; safranal: trace and trace; decanal: trace and $0.1 \pm 0.01\%$; β -cyclocitral 0.1 ± 0.01 and $0.2 \pm 0.01\%$; 2,3-epoxygeranial: trace and not detected; (Z)-3-hexenyl 2-methylbutanoate: trace and not detected; Neral: $1.5 \pm 0.09\%$ and $3.5 \pm 0.22\%$; geraniol: trace and not detected; (2,6,6-trimethyl-1-cyclohexen-1-yl)-acetaldehyde: trace and trace; (E)-2-decenal: trace and $0.1 \pm 0.01\%$; geranial: $2.4 \pm 0.20\%$ and $5.9 \pm 0.29\%$; lavandulyl acetate: trace and not detected; bornyl acetate: not detected and trace; dihydroedulan I: trace and not detected; tridecane: $0.1 \pm 0.01\%$ and $0.2 \pm 0.01\%$; undecanal: trace and trace; (2E,4E)-2,4-decadienal: trace and not detected; α -cubebene: trace and trace; (E)-solanone: trace and not detected; (E)-2-undecenal: trace and trace; α -ylangene: trace and trace; α -copaene: $0.1 \pm 0.01\%$ and $0.3 \pm 0.01\%$; (E)-b-damasconone: trace and trace; β -bourbonene: $0.3 \pm 0.02\%$ and $1.6 \pm 0.08\%$; β -cubebene: detected and $0.3 \pm 0.01\%$; β -elemene: 0.6 ± 0.03 and not detected; (Z)-isoeugenol: trace and not detected; 4-(2,2-dimethyl-6-methylenecyclohexyl)-2-butanone (hydro-c-ionone): not detected and $0.1 \pm 0.01\%$; tetradecane: trace and not detected; (Z)-caryophyllene: trace and $0.8 \pm 0.04\%$; (E)-b-damascone: trace and trace; α -gurjunene: $1.0 \pm 0.07\%$ and not detected; (E)-caryophyllene: $13.9 \pm 0.8\%$ and $5.25.7 \pm 1.34\%$; acora-3,5-diene: trace and not detected; Υ -elemene: trace and not detected; β -copaene: $0.1 \pm 0.01\%$ and $0.3 \pm 0.01\%$; α -guaiane: trace and trace; geranyl acetone: $0.9 \pm 0.06\%$ and $5.6 \pm 0.34\%$; cis-muurolo-3,5-diene: trace and not detected; 6,10-dimethyl-5,9-undecadien-2-olh: $0.2 \pm 0.01\%$ and $1.3 \pm 0.07\%$; trans-muurolo-3,5-diene: trace and trace; allo-aromadendrene: trace and not detected; α -humulene: $1.3 \pm 0.11\%$ and $1.7 \pm 0.10\%$; 9-epi-(E)-caryophyllene: $0.5 \pm 0.04\%$ and trace; cis-muurolo-4(14),5-diene: trace and not detected; trans-cadina-1(6),4-diene: trace and not detected; Υ -muurolene: $0.5 \pm 0.04\%$ and $0.2 \pm 0.01\%$; (E)-b-ionone: trace and $0.1 \pm 0.01\%$; ar-curcumene: not detected and trace; germacrene D: $1.2 \pm 0.09\%$ and $1.0 \pm 0.06\%$; cis-b-guaiane: $0.1 \pm 0.01\%$ and trace; β -selinene: 0.1 ± 0.01 and non detected; trans-b-muurolo-4(14),5-diene: $0.1 \pm 0.01\%$ and trace; epicubebol: trace and $0.3 \pm 0.01\%$; bicyclgermacrene: $0.9 \pm 0.06\%$ and non detected; α -muurolene: $0.5 \pm 0.03\%$ and trace; β -curcumene: non detected and trace; (Z)-c-bisabolene: non detected and trace; germacrene A: $0.3 \pm 0.01\%$ and non detected; Υ -cadinene: $0.6 \pm 0.04\%$ and $0.3 \pm 0.01\%$; cubebol: non detected and trace; endo-1-bourbonanol: non detected and trace; δ -cadinene: $2.9 \pm 0.20\%$ and $0.8 \pm 0.05\%$; trans-calamenene: trace and trace; zonarene: trace and non detected; 10-epi-cubebol: $0.2 \pm 0.01\%$ and trace; trans-cadina-1,4-diene: trace and non detected; α -cadinene: $0.1 \pm 0.01\%$ and trace; α -calacorene: trace and trace; hedyacryol: trace and trace;

elemol: $0.1 \pm 0.01\%$ and $0.1 \pm 0.01\%$; cis-muurool-5-en-4b-ol: trace and non detected; isocaryophyllene oxide: non detected and $0.2 \pm 0.01\%$; cis-Muurool-5-en-4a-ol: trace and non detected; germacrene B: $0.3 \pm 0.02\%$ and trace; β -calacorene: trace and non detected; (3E,7E)-4,8,12-trimethyltrideca-1,3,7,11-tetraene: trace and trace; palustrol: $0.8 \pm 0.05\%$ and non detected; germacrene D-4-ol: $3.9 \pm 0.30\%$ and $0.4 \pm 0.02\%$; caryophyllene oxide: $2.4 \pm 0.18\%$ and $12.5 \pm 0.75\%$; viridiflorol: trace and non detected; guaial: $1.4 \pm 0.09\%$ and $1.0 \pm 0.05\%$; humulene epoxide I: trace and trace; ledol: $2.6 \pm 0.22\%$ and non detected; humulene epoxide II: trace and $0.7 \pm 0.04\%$; 1,10-di-epi-cubenol: $0.8 \pm 0.05\%$ and non detected; (6E,8Z)-4,6,8-megastigmatrien-3-one: trace and trace; muurola-4,10(14)-dien-1-b-ol: $0.1 \pm 0.01\%$ and $0.3 \pm 0.01\%$; 1-epi-cubenol: $0.2 \pm 0.01\%$ and trace; caryophylla-4(12),8(13)-dien-5a-ol: $0.5 \pm 0.03\%$ and $0.8 \pm 0.05\%$; caryophylla-4(12),8(13)-dien-5b-ol: $0.7 \pm 0.06\%$ and $2.5 \pm 0.14\%$; epi-a-cadinol (syn. s-cadinol): $1.2 \pm 0.08\%$ and $0.4 \pm 0.02\%$; epi-a-muuroolol (s-muuroolol): $1.8 \pm 0.15\%$ and trace; α -muuroolol (torreyol): trace and trace; α -cadinol: $3.6 \pm 0.20\%$ and $0.6 \pm 0.02\%$; bulnesol: $0.6 \pm 0.03\%$ and $0.1 \pm 0.01\%$; 14-hydroxy-9-epi-(E)-caryophyllene: trace and $0.9 \pm 0.05\%$; germacra-4(15),5,10(14)-trien-1a-ol: $0.7 \pm 0.04\%$ and $0.4 \pm 0.02\%$; shyobunol: $9.7 \pm 0.66\%$ and non detected; (2E,6Z)-farnesal: $0.2 \pm 0.01\%$ and trace; pentadecanal: trace and $0.3 \pm 0.01\%$; (2E,6E)-farnesal: trace and undetected; mint sulfide: trace and undetected; benzyl benzoate: trace and undetected; phenanthrene: trace and undetected; hexadecanal: trace and trace; isopropyl tetradecanoate: trace and undetected; hexahydrofarnesyl acetone: $0.1 \pm 0.01\%$ and $0.1 \pm 0.01\%$; 1-hexadecanol: $0.1 \pm 0.01\%$ and trace; (5E,9E)-farnesyl acetone: $0.6 \pm 0.04\%$ and $0.6 \pm 0.03\%$; methyl hexadecanoate: trace and trace; (Z,Z)-geranyl linalool: $0.5 \pm 0.03\%$ and trace; hexadecanoic acid: trace and undetected; (E,Z)-geranyl linalool: $0.2 \pm 0.01\%$ and un detected; (E,E)-geranyl linalool: $7.6 \pm 0.50\%$ and $1.1 \pm 0.06\%$; 1-octadecanol: $0.2 \pm 0.02\%$ and undetected; methyl (9Z)-9-octadecenoate (methyl oleate): undetected and trace; heneicosane: trace and trace; (E)-phytol: $4.7 \pm 0.28\%$ and $0.5 \pm 0.02\%$; docosane: undetected and trace; eicosanal: trace and trace; 2-methyldocosane: trace and undetected; tricosane: $0.1 \pm 0.01\%$ and trace; tetracosane: trace and trace; docosanal: trace and undetected; 2-methyl tetracosane: trace and undetected; pentacosane: $0.2 \pm 0.01\%$ and trace; 3-methyl pentacosane: trace and undetected; hexacosane: trace and trace; tetracosanal: trace and undetected; 2-methyl hexacosane: trace and undetected; heptacosane: $0.2 \pm 0.01\%$ and $0.1 \pm 0.01\%$; 3-methylheptacosane: trace and undetected; octacosane: trace and trace; (all E)-squalene: trace and undetected; 2-methyl octacosane: trace and undetected; nonacosane: $0.2 \pm 0.01\%$ and $0.2 \pm 0.01\%$; 3-methyl nonacosane: trace and undetected; triacontane: trace and trace; hentriacontane: $0.2 \pm 0.01\%$ and trace; dotriacontane: trace and undetected and tritriacontane: trace and undetected⁽³⁶⁾.

Pharmacological effects:

Effect on thyroid function:

The extracts of *Lycopus europaeus* reduced the weight of the thyroid, decreased thyroid hormone activity, and increased absorption and storage of iodine in rats. The extract retarded goiter formation in propylthiouracil-treated rats. All animals treated with the extract showed reduced metabolism⁽³⁷⁾.

High doses of *Lycopus europaeus* reduced TSH or thyroid hormone levels in animal experiments, hyperthyroid patients treated with low doses of *Lycopus europaeus* showed improvement of cardiac symptoms without major changes in TSH or thyroid hormone concentrations⁽³⁸⁾.

Lycopus europaeus hydroethanolic extract was tested in thyroxine treated hyperthyroid rats (0.7 mg/kg bw, ip). Co-treatment with hydroethanolic extract started one week later than T4- application and lasted 5.5 weeks. Atenolol was used as reference substance. The raised body temperature was reduced very effectively even by the low dose of the plant extract, whereas the reduced gain of body weight and the increased food intake remained unaffected by any treatment. No significant changes of thyroid hormone concentrations or TSH levels were observed. *Lycopus* extract and atenolol reduced the increased heart rate and blood pressure. The cardiac hypertrophy was alleviated significantly by both treatment regimes. beta-Adrenoceptor density in heart tissue was significantly reduced by the *Lycopus* extract or the beta-blocking agent showing an almost equal efficacy⁽³⁸⁾.

The endocrine effects of ethanolic extract of *Lycopus europaeus* orally in comparison with ip administration was studied in rats. The endocrine parameters were measured between 3 and 24 h after oral administration. The extract caused a long lasting (for a period of more than 24 h) decrease of T3 levels, presumably as a consequence of a reduced peripheral T4 deiodination. A pronounced reduction of T4 and thyroid stimulating hormone (TSH) concentrations was observed 24 h after application of the test solution by gavage. The luteinizing hormone was also decrease which indicated a central action of the plant extract⁽³⁹⁾.

Lycopus decreased the excessive thyroid stimulation, via adenylate cyclase blockade. So, when thyroid-stimulating hormone binds to the outer membrane of thyroid cells, it triggers a cAMP response on the inside of the cell via adenylate cyclase enzyme activation. Rosmarinic acid, the major compound isolated from *Lycopus europaeus* extract, decreased the TSH- stimulation of thyroid cells, via inhibition of adenylate cyclase

inhibition. Rosmarinic acid also inhibited the enzymatic deiodination processing of thyroxine outside the thyroid gland and inhibited conversion of T4 to T3⁽⁴⁰⁻⁴¹⁾.

An open post-marketing surveillance study consisting of (a) a prospective assessment in patients receiving Thyreogutt® mono for 4 weeks, a retrospective documentation of data from patients who had received at least one course (4 weeks) of Thyreogutt® mono therapy during the previous 2 years, and a control cohort receiving no drug treatment) was carried out on four hundred and three patients with mild symptomatic hyperthyroidism, to assess the effects and safety of an extract of *Lycopus europaeus* (Thyreogutt® mono tablets or drops). The extract of *Lycopus europaeus* was well tolerated and associated with a statistically significant and clinically relevant improvement of the symptoms in mild hyperthyroidism⁽⁴²⁾.

A prospective two-armed open study was carried out (patients with a basal TSH <1.0 mU/l and hyperthyroidism-associated symptoms) to study the effect of *Lycopus europaeus* on thyroid function and on associated symptoms during a 3-month follow up phase. Symptoms specific to the thyroid gland were diminished (the increased heart rate in the morning). The *Lycopus europaeus* preparation showed a good tolerance. The urinary T4 excretion was significantly increased in *Lycopus europaeus* - treated patients⁽⁴³⁾.

Antimicrobial effects:

The acetylated highly oxygenated abietane-type diterpenoid (euroabienol) isolated from *Lycopus europaeus* was screened for *in vitro* antimicrobial activity against fifteen strains of bacteria and six fungal strains. It showed a broad spectrum antimicrobial activity⁽³¹⁾.

The antibacterial effect of *Lycopus europaeus* leaves water extract was studied against *Staphylococcus aureus* clinical strains from catheter-related and skin infections by broth microdilution test. The extract showed bactericidal activity at concentrations from 2500 to 5000 µg/ml against all isolates, including methicillin resistant and polyresistant nosocomial strains⁽²⁹⁾.

The antimicrobial activity of the hexane extract of the whole *Lycopus europaeus* was studied *in vitro* against *Staphylococcus aureus* Cowan 1, *Micrococcus luteus* LA 2971, *Mycobacterium smegmatis* CCM 2067, *Bacillus subtilis* IGM 22, *Bacillus subtilis* var. niger ATCC 10, *Aeromonas hydrophila* ATCC 7966, *Klebsiella pneumoniae* FMC 5, *Pseudomonas aeruginosa* ATCC 27853 and *Candida albicans* ATCC 10231. The inhibition zone diameters at a concentration of 12.5 mg/ml were 14, 14, 15 and 15mm against *M. luteus*, *M. smegmatis*, *A. hydrophila* and *K. pneumoniae*, respectively, while the extract possessed no activity against other microorganisms⁽⁴⁴⁾.

The antimicrobial activity of the *Lycopus europaeus* essential oil was studied against many Gram positive, Gram negative bacteria and fungi. Minimum inhibitory concentrations (MIC) of the essential oil against *E. coli* isolate: was 0.156 mg/ml; *E. coli* ATCC 25922: 5.00 mg/ml; *E. coli* ATCC 8739: 5.00 mg/ml; *E. coli* Torlak 95: 5.00 mg/ml; *K. pneumoniae* ATCC 10031: 0.156 mg/ml; *K. pneumoniae* isolate: 5.00 mg/ml; *P. vulgaris* ATCC 8427: 5.00 mg/ml; *S. enterica* ATCC 13076 :5.00 mg/ml; *S. aureus* ATCC 25923: 5.00 mg/ml; *S. aureus* isolate: 2.50 mg/ml; *C. perfringens* ATCC 19574: 1.25 mg/ml; *C. sporogenes* ATCC 19404: 2.50 mg/ml; *S. lutea* ATCC 9341: 5.00 mg/ml; *B. subtilis* ATCC 6633: 5.00 mg/ml; *P. chrysogenum* isolate: 10.0 mg/ml; *A. restrictus* isolate: 5.00 mg/ml; *A. chrysogenum* isolate: 10.0 mg/ml; *A. fumigates* isolate: 0.625 mg/ml; *C. albicans* ATCC 10231: 10.0 mg/ml and *S. cerevisiae* ATCC 9763: 2.50 mg/ml⁽³⁶⁾.

Isopimarane diterpenes (methyl-1alpha-acetoxy-7alpha 14 alpha-dihydroxy-8,15-isopimaradien-18-oate, and methyl-1alpha,14alpha-diacetoxy-7alpha-hydroxy-8,15-isopimaradien-18-oate) isolated from the extract of *Lycopus europaeus* were tested for *in vitro* antibacterial and resistance modifying activity against strains of *Staphylococcus aureus* possessing the Tet(K), Msr(A), and Nor(A) multidrug resistance efflux mechanisms. At 512 microg/ml none of the compounds displayed any antibacterial activity but individually in combination with tetracycline and erythromycin, a two-fold potentiation of the activities of these antibiotics was observed against two strains of *S. aureus* that were highly resistant to these agents due to the presence of the multidrug efflux mechanisms Tet(K) (tetracycline resistance) and Msr(A) (macrolide resistance)⁽³⁴⁾.

Antiparasitic effects:

The antiparasitic effects of methanolic extracts of the aerial parts of *Lycopus europaeus* (at the concentrations of 227, 113.5, 56.75, 28.37, 14.1 and 7.09 mg/ml after 0, 1, 3, and 6 hours exposure time) were studied on the growth of *T. gallinae* trophozoites. Both extracts decreased the viability of *T. gallinae*, they showed 60% growth inhibition at the highest concentration immediately after exposure. The lowest concentration of *Lycopus europaeus* extract that showed 100% growth inhibition was 28.37 mg/ml that affected trophozoites after 6 hours⁽⁴⁵⁾.

Antioxidant effect:

The antioxidant effects of *Lycopus europaeus* leaves water extract examined by DPPH, ABTS were (11.3 and 9.8 µg/ml, respectively) and by ferric reducing ability of the plasma method were (891 µmol AAE/g dry extract). It appeared that many phenolic compound responsible for the antioxidant activity of the extract⁽²⁹⁾.

Hydroalcoholic extracts of *Lycopus europaeus* showed significant antioxidative activities, by free radical scavenger effect on DPPH. The antioxidative activity was partly related to the rosmarinic acid content⁽⁴⁶⁾.

Analgesic and anti-inflammatory effects:

The extract possessed highly significant ($p < 0.001$) analgesic activity in a dose dependent manner on hot plate method, acetic acid induced writhing test and also on both the early and late phases of formalin test. In the hot plate method, the extract increased the reaction time of heat sensation to 60.81% and 66.52% at the doses of 250 and 500 mg/kg respectively. In acetic acid induced writhing test, the percent inhibition of writhing response by the extract was 62.87% and 70.66% at 250 and 500 mg/kg doses respectively ($p < 0.001$). The extract also significantly inhibited the licking response at the dose of 500 mg/kg in both the early phase (55.11%, $p < 0.01$) and the late phase (66.43%, $p < 0.01$) of formalin test. The oral administration of the extract significantly ($p < 0.001$) inhibited inflammatory response induced by carrageenan in a dose dependent fashion 61.68% (250 mg/kg) and 73.65% (500 mg/kg)⁽⁴⁷⁾.

The antiinflammatory activity of *Lycopus europaeus* was investigated by membrane stabilizing and protein inhibitory methods. The prevention of hypotonicity induced human red blood cells membrane lysis and protein inhibition was taken as a measure of the anti-inflammatory activity. *Lycopus europaeus* showed significant membrane stabilizing activity of 73.81% and protein inhibition activity of 93.01% at concentration of 200 µg/ml⁽⁴⁸⁾.

Antitussive effect:

The antitussive activity of the methanol extract of *Lycopus europaeus* was studied in sulphur dioxide gas and ammonium liquor induced cough in mice. The methanol extract produced significant antitussive activity ($p < 0.001$) when compared with control, codeine phosphate and dextromethorphan in a dose dependent manner. High dose of the extract (500 mg/kg) showed inhibition of cough by 61.21% and 56.63% in sulphur dioxide gas and ammonium liquor induced cough respectively⁽⁴⁹⁾.

The antitussive effect of the methanolic extract of *Lycopus europaeus* was investigated in citric acid induced cough model in mice. The extract has produced 54%, 70% and 75% reduction in cough bouts at the dose level of 1, 2 and 3 ml respectively after 1hr of drug administration. The antitussive activity produced by the herbal formulation in the minimum dose was much better than the standard drug (diphenhydramine HCl)⁽⁵⁰⁾.

Dermatological effects:

There is growing interest to develop NADPH Oxidase 4 (Nox 4) inhibitors, which might be valuable agents for cosmeceutical applications as skin anti-ageing therapy. The methanolic extract of the subaerial parts of *Lycopus europaeus* showed a strong inhibition of Nox 4 (81% chemiluminescence quenching) of HEK cells, and a simultaneously high cell viability (91% vitality). Rosmarinic acid, the major compound isolated from *Lycopus europaeus* extract, showed a dose dependent inhibitory activity on Nox 4 with an IC_{50} of 1 µM. Moreover, it also showed a significant inhibitory activity on Nox 2 in the low micromolar range, whereas no inhibition of Nox 5 was detected⁽⁵¹⁾.

The wound healing activity of topically applied methanol extract (as ointment 5 and 10% w/w) of *Lycopus europaeus* was evaluated in rat using excision wound model for a period of 12 days. Both 5% and 10% w/w ointments promoted the wound-healing activity significantly. High rate of wound contraction, decrease the period for epithelialisation, high skin breaking strength were observed in animals treated with 10% w/w extract ointment⁽⁵²⁾.

Hypnotic effect:

The sedative effect of the methanolic extract (100, 200, 400, and 600 mg/kg, po) of *Lycopus europaeus* was evaluated compared to reference drug (diazepam) in hole board and thiopental-induced sleeping time methods in mice. The hypnotic effect was evaluated at the doses of 800 and 1000 mg/kg, op, via reduction in reestablishment time and number of head dips during the traction and hole-board tests. The methanolic extract of *Lycopus europaeus* produced significant sedative effect at the doses of 200 and 400 mg/kg po. Furthermore, the dose of 100 mg/kg did not decreased the reestablishment time effectively. In the hole-board test, a significant reduction in the number of head dips was recorded at the doses of 200, 400, and 600 mg/kg by oral route administration. The extract induced reduction in the time of onset of sleep induced by

thiopental. The effects of the extract on onset of sleep at 800 and 1000 mg/kg were comparable to that of diazepam at 30 mg/kg⁽⁵³⁾.

Anti-diarrhoeal effect:

The anti-diarrhoeal activity of the aqueous extract (100 and 200 mg/kg bw) of *Lycopus europaeus* was studied in terms of the reduction in the rate of defecation and the consistency of feces in castor oil and MgSO₄ induced diarrhoea. The mechanism of anti-diarrhoeal activity, was further evaluated on the gastro-intestinal transit time with charcoal meal. The extract showed significant ($p < 0.05$) inhibitory activity against castor oil and MgSO₄ induced diarrhoea. There was a significant reduction in the gastro-intestinal motility which was observed by using the charcoal meal test in mice⁽⁵⁴⁾.

Inhibition of xanthine oxidase:

Chinese medicinal plants traditionally used in the treatment of gout and other hyperuricemia-related disorders, were evaluated for the xanthine oxidase inhibitory activity. Among the plant extracts, the leaves extracts of *Lycopus europaeus* showed potent activity (IC₅₀, 26 microg/ml). The IC₅₀ value of allopurinol used as a positive control was 1.06 microg/ml⁽⁵⁵⁾.

Side effects and contraindications:

Intravenous administration of a dose of 3 ml of pressed juice of Virginia bugleweed was lethal in mice, while a dose of 1 ml orally didn't cause any toxic symptoms. Changes in the estrus cycle in mice and rats and a reduction in the number of offspring were caused by European bugleweed⁽⁵⁶⁾.

The use of the plant is contraindicated in pregnant and nursing women, and also in women suffering from hypothyroidism, diabetes, endocrine disorders such as hypopituitarism, pituitary adenoma or hypogonadism and patients with osteoporosis or who are taking oral contraceptives or fertility drugs⁽²⁵⁾.

II. CONCLUSION

This review discusses the traditional uses, chemical constituent, pharmacological and therapeutic effects of *Lycopus europaeus* as promising herbal drug because of its safety and effectiveness.

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