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Chemical Constituents and Pharmacological Effects of *Melilotus Officinalis*- A Review

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Abstract: *Melilotus officinalis* contained coumarins, melilotin, phenolic acids, flavonoids, steroids, saponins, volatile oils, fats, triterpenes, carbohydrates, sugar, anthraquinone glycosides, mucilage, tannin, bis hydroxycoumarin, choline, alcohols, uric acid and many other chemical groups. Antimicrobial, antioxidant, anticancer, anti-inflammatory, neural, protective, sedative, anxiolytic, smooth muscle relaxant, hypotensive and manyother pharmacological effects. The current review highlighted the chemical constituents and pharmacological effects of *Melilotus* officinalis.
Keywords: chemical constituents, pharmacology, *Melilotus officinalis*.

I. INTRODUCTION:

In the last few decades there has been an exponential growth in the field of herbal medicine. It is getting popularized in developing and developed countries owing to its natural origin and lesser side effects. Plants generally produce many secondary metabolites which are bio-synthetically derived from primary metabolites and constitute an important source of chemicals which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives[1-35]. The phytochemical analysis showed that *Melilotus officinalis* contained coumarins, melilotin, phenolic acids, flavonoids, steroids, saponins, volatile oils, fats, triterpenes, carbohydrates, sugar, anthraquinone glycosides, mucilage, tannin, bis hydroxycoumarin, choline, alcohols, uric acid and many other chemical groups. Antimicrobial, antioxidant, anticancer, anti-inflammatory, neural, protective, sedative, anxiolytic, smooth muscle relaxant, hypotensive and manyother pharmacological effects. The current review will highlight the chemical constituents and pharmacological effects of *Melilotus officinalis*.

Plant profile:
Synonyms:
Medicago officinalis, Melilotus arenarius, Melilotus arvensis, Melilotus melilotus-officinalis, Melilotus neglectus, Melilotus pallidus, Melilotus petitpierreanus, Trifolium melilotus, Trifolium melilotus-officinalis, Trifolium officinale[36].

Taxonomic classification:
Kingdom: Plantae, **Subkingdom**: Viridiplantae, **Infrakingdom**: Streptophyta, **Superdivision**: Embryophyta, **Division**: Tracheophyta, **Subdivision**: Spermatophytina, **Class**: Magnoliopsida, **Superorder**: Rosanae, **Order**: Fabales, **Family**: Fabaceae, **Genus**: Melilotus, **Species**: *Melilotus officinalis*[37].
Common names:
Arabic: Nafal; Melesa, Hahaq, Handikok hakli, Ghsin El-ban; **Canada**: Yellow sweet clover; **Chinese**: cao mu xi; **Cuba**: Torongil For; **English**: common melilot, field melilot, ribbed melilot, yellow melilot, yellow sweetclover, yellow sweet-clover; yellow trefoil; **French**: melilot des champs, melilot jaune, melilot officinal; **Germany**: Acker- Honigklee, Echter Steinklee, gelber Steinklee; **Italy:** meliloto giallo; **Japan**: seiyō-ebira-hagi; **Netherlands**: Akkerhoningklaver; **Portugal**: trevo-cheiroso; **Spanish**: cornilla real, meliloto Amarillo, meliloto de los campos, trébol de olor, trebol de olor amarillo; **Sweden**: Gulmelot[38-39].

Distribution:
It was distributed in **Africa** (Egypt, Libya, South Africa); **Asia** (Oman, Saudi Arabia, Qatar, United Arab Emirates, Yemen, Afghanistan, Cyprus, Iran, Iraq, Palestine, Jordan, Lebanon, Turkey, Armenia, Azerbaijan, Georgia, Russian federation, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, China, Bhutan, India, Pakistan, Myanmar), **Europe** (Austria, Czechoslovakia, Germany, Hungary, Poland, Belarus, Estonia, Latvia, Lithuania, Moldova, Russian Federation-European part, Albania, Bulgaria, Former Yugoslavia, Greece, United Kingdom, Italy, Romania, France, Spain), **Australasia** (Australia, New

Zealand), **Northern America** (United states and Canada) and **Southern America** (Argentina, Chile, Bolivia, Paraguay, Uruguay)[38].

Description:

It is annual to biennial, erect or decumbent plant. Stems erect, 40-100(-250) cm, longitudinally ridged. Stipules linear-falcate, 3-5(-7) mm, entire or with 1 tooth at base; petiole slender; leaflets obovate, broadly ovate, oblanceolate, to linear, 15-25(-30) × 5-15 mm, lateral veins running into teeth, 8-12 pairs, margins shallowly serrate. Racemes 6-15(-20) mm, 30-70-flowered, dense at first, becoming lax in anthesis; bracts equal to pedicels, 1.5-2 mm. Corolla yellow, 4.5-7 mm; standard ± equal to wings and keel. Ovary narrowly ovate; ovules (4-)6(-8). Legume ovoid, 3-5 × ca. 2 mm, veins transversely reticulate, dark brown, apex with persistent style. Seeds 1 or 2, yellowish brown, ovoid, ca. 2.5 mm, smooth[40-41].

Traditional uses:

The plant was used as aromatic, emollient, demulcent, maturant, tonic, aphrodisiac, carminative to relieve flatulence and externally applied as poultice for pains and aches. The small fruits were used as demulcent, maturant, tonic, aphrodisiac and in leucoderma[42].

Herbal tea was used as a wash and rinse for swelling and swollen glands, abscesses, and swelling of the lymph nodes. Tea herbs, or the flowers themselves, were applied in cases of cold, mucosity, and respiratory and gastrointestinal disorders[43].

It was also used in idiopathic headaches, long-standing neuralgias, coldness, tenderness, lameness or marked soreness of joints, cold, menstrual colic, ovarian neuralgia, colic with diarrhoea and much[44].

Parts used medicinally:

The whole herb and flowering shoots and fruits were used medicinally[45].

Physicochemical parameters:

Physicochemical parameters of powdered *Melilotus officinalis* (% w/w) were: total ash: 11.25±0.25, acid insoluble: 2.11±0.12, water soluble: 6.86±0.19, methanol extractive value 3.96, aqueous extractive value 13.27, volatile oil 0.59±0.02 and loss on drying 6.69±0.12[46].

Chemical constituents:

The preliminary phytochemical analysis showed that *Melilotus officinalis* contained coumarins, melilotin, phenolic acids, flavonoids, steroids, saponins, volatile oils, fats, triterpenes, carbohydrates, sugar, anthraquinone glycosides, mucilage, tannin, bis hydroxycoumarin, choline, alcohols and uric acid[46-50].

The dominant components in total lipophilic compounds of the chloroform extract of *Melilotus officinalis* were 1,3- di-o-methylmyo-inositol (75.503%), acetal (5.874%), palmitic acid (2.252%) and linoleic acid (1.958%)[51].

Twenty six constituents were identified in the *Melilotus officinalis* essential oil from Borispol (Ukraine), hexahydrofarnesylacetone (16.64%), β-eudesmol (11.49%) and globulol (8.65%) represented the main constituents. However, the identified compounds and their percentage were: para-hydroxybenzaldehyde 1.96, camphor 3.15, terpinene-4-ol 4.17, 2-methylbenzaldehyde 2.70, aromadendrene 1.38, geranylacetone 1.21, 2,6,10-trimethyldodecane (farnesane) 5.68, β-ionone 0.93, β -ionone-5,6-epoxide 2.08, epi-globulol 3.05, isophytol 1.47, spathulenol 4.27, globulol 8.65, viridiflorol 2.98, epi- eudesmol 2.50, ϒ- eudesmol 1.98, β-eudesmol 11.49, bisabolon oxide 7.43, hexahydrofarnesylacetone 16.64, methyl palmitate 2.68, methyl linoleate 1.77, methyl linolenate 5.19, phytol 4.52, ethyl linoleate 0.96 and Phytyl acetate 1.12%[52] .

The main compounds identified in the volatile oils of the methanol extract of the leaves of *Melilotus officinalis* from Syria were: n-docosane (39.82%), hydrocoumarin (15.39%) and methyl 3-(2-hydroxyphenyl) propionate) (14.29%)**,** while, the main compounds identified in the volatile oils of the hexane extract of the leaves of *Melilotus officinalis* from Syria were: palatinol (17.77%), 9,12,15-octadecatrienoic acid, methyl ester (12.85%), 1-(dimethylamino)-5-[(4'-ethynylphenyl) ethynyl] naphthalene (12.59%), 2,4-dioctylphenol (9.73%), hexadecanoic acid, methyl ester (8.99%) and ecosane(8.53%)[53].

Hexadecanoic acid, lupanone, lupeol, betulinic acid, oleanolic acid, kaempferol-3-O-β-glucopyranoside were isolated from the methanol extract of whole *Melilotus officinalis*[50].

Oleanene glucuronide (melilotus-saponin O1), together with soyasaponin, dehydrosoyasaponin, acetyl-soyasaponin were isolated from the roots of *Melilotus officinalis*[54], while, soyasapogenols B and E were isolated from the aerial parts[55].

P-hydroxybenzoic acid glycosides [p-hydroxybenzoic acid-4-*O*-α-D-manopyranosyl-(1→3)-α-L-rhamnopyranoside and -*O*-α-L-rhamnopyran-osyl-(1→6)-α-D-mano pyranosyl -(1 → 3)-α-L-rhamnopyranoside], salicylic acid, coumarin, betaine, fumalic acid, caffeic acid, luteolin, quercetin were isolated from the 70% ethanol extract of of the aerial parts of *Melilotus officinalis*[56].

Coumarin concentration in whole *Melilotus officinalis* hexane extract was 8.86 ± 0.67 mg/100 g, in ethanol 96% extract 316.37 ± 8.10 mg/100 g, and in ethanol 50% extract 146.43 ± 9.15 mg/100 g[57].

HPLC analysis revealed that five grams of the flower powder contained 9.7 mg gallic acid, 99 mg catechin, 21.9 mg caffeic acid, 0.86 mg chlorogenic acid, 1.13 mg quercetin, 548.9 mg cinnamic acid, 289 mg coumarin and 126 mg p-coumaric acid[58].

The concentrations of total phenols (mg RU/g extract), flavonoids (mgGA/g extract), tannins (mgGA/g extract) and proanthocyanidins (CChE/g extract) in *M. officinalis* aerial parts were (19.66 ± 0.23, 36.25 ± 0.79, 21.25 ± 1.32 and undetected, respectively, in the water extract), (53.09 ± 1.67, 27.12 ± 0.49, 11.87 ± 0.12 and 3.77 ± 0.03, respectively, in the acetone extract) (33.52 ± 0.22, 16.37 ± 0.59, 6.12 ± 0.16 and 1 ± 0.13, respectively, in the diethyl ether extract) and (34.19 ± 0.06, 21.37 ± 1.09, 1.37 ± 1.08 and 0.77 ± 0.59, respectively, in the ethanol extract)[59].

However, the total phenolic concentration in whole *Melilotus officinalis* hexane extract was: 10.5 ± 0.6 mg gallic acid equivalent/ g, in ethanol 96% extract: 47.1±3.6 mg gallic acid equivalent/ g, and in ethanol 50% extract: 46.3 ± 7.4 mg gallic acid equivalent/ g[57].

The plant contained many flavonoids included: robinin, rutin, kaempferol-3-O-β-glycopyranoside and kaempferol-7-O-glycosides[60-61].

Pharmacological effects:

Antimicrobial effect:

The antimicrobial effect of the methanolic extract of *Melilotus officinalis* was investigated against Gram positive and Gram negative bacteria. MIC against *Escherchia coli*: 15mg, *Klebsiella pneumonia*: 18mg, *Proteus mirabilis*: 20mg, *Pseudomonas aeruginosa*: 25mg, *Staphyliococcus aureus*: 25mg, *Streptococcus pyogenes*: 30mg, *Bacillus subtilis*: 25mg , *Bacilluscereus*: 25 mg and *Candida albicans* 35mg[53].

The antibacterial activity of the water, acetone, diethyl ether and ethanol extracts of *Melilotus officinalis* was studied against *Klebsiella pneumonia, Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Salmonella typhimurium, Salmonella enteric, Enterococcus faecalis, Staphylococcus aureus, Sarcina lutea, Bacillus suptilis, Bacillus cereus, Bifidobacterium animalis* subsp. *lactis* and *Lactobacillus rhamnosus*. The values of MIC and MMC were in a range of <0.156 mg/ml to >20 mg/ml. The intensity of antibacterial activity depended on the type of extract and the type of bacteria. The extracts were active in the following ascending order: water < ethanol < diethyl ether < acetone. The acetone and the diethyl ether were the most active extracts, while water and ethanol extracts showed significantly lower activity. Gram negative bacteria showed higher sensitivity to the acetone and diethyl ether extracts, but never in concentrations less than 10 mg/ml for MIC and MMC, except for *Escherichia coli* which was sensitive in the concentration of 5 mg/ml of the ether extract for MIC[59].

The antibacterial effect of the aqueous, methanolic and ethanolic extract of *Melilotus officinalis* was investigated against Gam negative bacteria (*Escherichia coli, Pseudomonas aeruginosa, Salmonella typhimurium, Serratia marcescens, Proteus vulgaris, Enterobacter cloacae* and *Klebsiella pneumonia*) and Gram positive bacteria (*Streptococcus pyogenes, Staphylococcus aureus* and *Staphylococcus epidermidis*). The ethanolic extract of *Melilotus officinalis* showed more antibacterial effect than aqueous and methanolic extracts against *S. marcescens* and *S. typhimurium*. *P. vulgaris*, *E. cloacae*, and *E. coli* were susceptible to aqueous extract of *Melilotus officinalis*. However, all the tested bacteria were not susceptible to methanolic extracts[62].

In vitro antifungal activities of *Melilotus officinalis* extracts were evaluated against *C. inconspicua*, *C. guilliermondii*, *C. albicans*, C. *krusei*, C. *lusitaniae*, *C. glabrata, C. parapsilosis*, *C. methapsilosis*, and *C. ortopsilosis*. The results showed that *Melilotus officinalis* extracts were active antimycotic agents against wide range of *Candida* species. *C. guilliermondii* and *C. parapsilosis* were the most sensitive[63].

The antifungal activity of *Melilotus officinalis* was studied against *Microsporum canis*, *Trichophyton mentagrophytes* var. *interdigitale*, *Trichophyton mentagrophytes* var. *mentagrophytes*, *Trichophyton rubrum* and *Tricophyton violaceum*. It caused partial growth inhibition at 0.5% and 0.25% concentration of ethanol extract. It appeared that *Trichophytom mentogrophytes* was the more sensitive fungi[64].

The anti-candidal effect of ethanol (30%v/v) *Melilotus officinalis* extracts was studied *in vitro*. *Melilotus officinalis* extract possessed potent anti-candidal activity with minimum inhibitory concentration of 19.3 mg/ml against *C. norvegica*, *C. pulcherrima* and *C. guilliermondii*[65].

The therapeutic activity of cumarinic extract of *Melilotus officinalis* was studied clinically in fourteen patients with chronic upper arm lymphedema due to post-lymphadenectomy of the axilla for breast cancer. Patients were receive 400 mg of cumarinic extract containing 8 mg of cumarine in a sole daily administration for 6 months. Of the fourteen treated patients, 11 patients (52.3%) showed reduction of the circumference of the affected arm of 5% with respect to base values. Three patients (14.2%) had no change. In 12 patients (57.1%), the symptoms were improved. Regarding tolerability: 3 patients (14.2%) had transitory

gastrointestinal side effects. The authors concluded that cumarinic extract of *Melilotus officinalis* was effective in reducing lymphedema in 79% of the patients treated for a period of six months[66].

Dermatological effect:

In studying the beneficial effect of the extract of *Melilotus officinalis* in skin care applications, the extract showed an ability of stimulating skin cells and promoting tissue regeneration, preventing skin aging, and reducing fat deposition. The effects of ethanolic extract at doses ranging from 0.25 to 50 µg/ml (from 1 to 5000 µg/ml in cell viability assays) were evaluated using *in vitro* tests on HaCaT human keratinocytes, 46BR 1N fibroblasts, and adipocyte cell cultures, and on matrix-degrading enzymes. MTT assay revealed weak effects on cell viability (IC_{50} > 1000 µg/ml) and significant increase of fibroblast growth rate. Cell-free enzymatic assays showed collagenase inhibition, while an ELISA assay revealed efficient stimulation of fibroblast collagen production. Oil-Red-O adipocyte staining showed pronounced lipolytic effect[67].

The effects of *Melilotus officinalis* ointment in the healing of burn wounds were studied in burn ulcers produced on the back of rats. Wound healing contraction and histopathological examination were evaluated at the end of 7, 14, and 21 days. *Melilotus officinalis* preparations significantly improved the quality of wound healing and scar formation and also they were more appropriate treatment choices than silver sulfadiazine[68].

The effect of melilotus extract on the thermal edema was studied in rats. The intraperitoneal injection of melilotus extract immediately after burn greatly reduced the amount of swelling and effectively inhibited the occurrence of necrosis and induration in the injured leg-skin as compared with the saline controls in which a 3rd degree of thermal injury was observed. Intraperitoneal or subcutaneous local injection of melilotus extract, 4 hr before burn was effective in reducing the edema and thermal injury. No increase of the lymph flow and output of lymphocytes and protein from the thoracic duct lymph was observed in thermally injured rats given an injection of melilotus extract. Massive infiltration of neutrophils and macrophages 6 to 24 hr after the subcutaneous injection of melilotus extract was histologically observed in the dermal lesion of normal rats. Twenty-four hr later, macrophages, fibroblasts, and lymphocytes became predominant[69].

Hypotensive effect:

Melilotus officinalis extract caused hypotensive and vaso-dilating actions due to the vascular smooth muscle relaxation in rabbits[70].

The hypotensive effect of *Melilotus officinalis* butanolic fraction (20-100 mg/kg, iv) was investigated in anaesthetized normotensive rats. The doses of 20 and 40 mg/kg iv, produced non-significant reduction in the blood pressure, but 60, 80 and 100 mg/kg, iv, significantly ($p<0.05$) decreased blood pressure[71].

Antioxidant effect:

The antiradical activity of the whole *Melilotus officinalis* hexane, 96 and 50% ethanol extracts was determined using DPPH. Their DPPH scavenging activity was 9.0±0.28, 35.6±0.65 and 30.2±0.98% respectively[22]. The free radical scavenging activity of *Melilotus officinalis* was studied using DPPH assay at different temperatures. The results demonstrated that with increasing temperature, the free radical scavenging activity was decreased, it gave the highest free radical scavenging activity at 25^{o}C[72].

The antioxidant activity of the water, acetone, diethyl ether and ethanol extracts of *Melilotus officinalis* was studied using DPPH method. The water extract demonstrated antioxidant activity in the range of 21.43 to 93.59% %; acetone extract 11.72 to 67.95%, diethyl ether extract 17.94 to 61.28% and ethanol extract 13 to 71.98%. The extent of reducing power in the examined extracts was various. The highest activity was detected with the water extract, while the lowest reducing power was demonstrated in the diethyl ether extract[59].

Nine compounds (2 p-hydroxybenzoic acid glycosides, 3 acid components, 2 flavonoids, 1 coumarin and 1 alkaloid) isolated from the 70% ethanol aqueous extract of the aerial parts of *Melilotus officinalis* were tested for antioxidant activity using ABTS and DPPH. The results showed that [p-hydroxybenzoic acid-4-O-α-D-manopyranosyl-(1 →3)-α-L-rhamnopyranoside 4-O-α-L-rhamnopyran-osyl-(1 → 6)-α-D-manopyranosyl-(1 → 3)-α-L-rhamnopyranoside, caffeic acid, luteolin and quercetin] exhibited better antioxidant activity than other compounds[56].

The antioxidant and anti-inflammatory effects of the aqueous extract of *Melilotus officinalis* were studied in the acetic acid induced ulcerative colitis in rats. The FRAP value of the extract was 2.91 ± 0.14 µM/g. There were significant differences between the groups of rats which received the gel or aqueous extract of the flower compared to the negative control group using normal saline and the base gel, and they had no significant differences with the positive control group using the Asacol, regarding the pathologic, malondialdehyde, and weight improvements[23]. The antioxidant effect of *Melilotus officinalis* aqueous extracts (1000 and 2000 mg/kg bw, orally, for seven days) was studied in colitis induced by intra-rectal acetic acid (3% v/v) in rats. Treatment with *Melilotus officinalis* aqueous extract enhanced colonic antioxidant capacity and

decreased inflammation and acute colonic injury induced by acetic acid, dose-dependent. Furthermore, the extract significantly ($p \leq 0.05$) reduced the colonic level of malondialdehyde and myeloperoxidase, and significantly ($p \leq 0.05$) increased the level of reduced glutathione ($p \leq 0.05$). The extract possessed more effects at the dose of 2000 mg/kg than 1000 mg/kg dosage and prednisolone[73].

The interference of *Melilotus officinalis* leaves extract with ROS and RNS during the course of human PMN respiratory bursts was studied, the lowest concentration at which it still has antioxidant activity by means of luminol amplified chemiluminescence (LACL) and the ability to counteract lipid peroxidation (LPO) in human cells, were also studied. The extract of *Melilotus officinalis* exerted its anti-ROS/RNS activity in a concentration dependent manner, with significant effects being observed for even very low concentration: 20 µg/ml without L-arginine and 10 µg/ml when L-arginine was added to the formyl-methionyl-leucylphenylalanine (fMLP) test. LPO assay confirmed these results, which were paralleled by the electron paramagnetic resonance study[74].

Hepatoprotective effect:

The hepatoprotective effect of methanolic extract of *Melilomus officinalis* (50 mg/kg and 100 mg/kg) was investigated against paracetamol and carbon tetrachloride induced hepatic damage in mice. *Melilotus officinalis* extract showed significant hepatoprotective effects by decreasing the levels of serum markers (total bilirubin, SGOT, SGPT, ALP, albumin and total protein). These effects were further documented by histopathological studies[75].

The hepatoprotective and antioxidant potentials of *Melilotus officinalis* was investigated in hepatotoxicity induced by iron dextran (12.5 mg/100g) in rats. Different fractions of *Melilotus officinalis* were given orally for 30 days. Biochemical parameters were estimated on 15^{th} and 30^{th} day whereas antioxidant parameters on 30^{th} day of treatment. Methanolic fraction of methanolic extract and methanolic fraction of aqueous extract of *Melilotus officinalis* significantly ($p<0.01$) decreased superoxide dismutase, catalase, glutathione, while, increases malondialdehyde as compared to untreated rats[76].

Neuroprotective effect:

The protective effect of *Melilotus officinalis* extract (100, 250 and 500 mg/kg, for 3 days) on the brain tissues in acute cerebral ischemia induced by occlusion of carotid artery, was studied in rats. Cerebral ischemia was confirmed by estimation of infract volume and neurological deficit score, in addition to plasma biochemical parameters such as 6-keto-PGF1α and TXB2 and concentration of cytokine, oxidative stress, apoptosis ratio and protein expressions of Bcl2 & Bax in the brain tissues. The extract significantly ($p<0.01$) decreased the infract volume and neurological deficit score compared with negative control group. It also significantly ($p<0.01$) decreased oxidative stress and cytokine in the brain tissues and increased plasma concentration of 6-keto-PGF1α. Plasma concentration of TXB 2 was significantly enhanced by the extract. Extract was also ameliorated the apoptosis induced by cerebral ischemia[77].

Sedative and anxiolytic effects:

The sedative effect of *Melilotus officinalis* extract was evaluated using a model of prolongation of hypnotic time of pentobarbital sodium in mice. Sedative action was recognized markedly in mice treated by the extract[70].

The antianxiety effect of petroleum ether, chloroform, ethanol, and water extracts (50, 100, and 200 mg/kg, po) of roots and aerial parts of *Melilotus officinalis* was studied in mice, using elevated plus maze (EPM) and mirror-chamber models of anxiety. The ethanol extract prepared from aerial parts at 100 and 200 mg/kg showed a significant anxiolytic effect as compared to control and standard treatment group. The petroleum ether, chloroform, and water extracts (50, 100, and 200 mg/kg) of the aerial parts of the plant did not produce antianxiety effect[78].

For the treatment of Alzheimer Disease:

The effect of *Melilotus officinalis* extract in Alzheimer disease was studied, regarding its possible role as anti-inflammatory, anti-oxidant agent and its effect on the expression of many genes including *DAXX*, *NFkB* and *VEGF*. The results revealed that the extract caused significant decreased the expression of *Daxx*, *Nfkb* and *Vegf* genes in the sporadic Alzheimer disease rat's model compared to the streptozotocin (STZ)-induced rats. Furthermore, no significant changes were seen in swimming distance and time for finding the hidden platform in the extract- treated compared to the STZ-induced group. No significant changes were observed in the memory level among treated and untreated groups[79].

Smooth muscle relaxant effect:

Melilotus officinalis flowers and leaves extract caused relaxing action on the isolated ileum in mice and antagonized barium chloride induced contraction of the ileum[70].

Management of iron overload:

The beneficial effects of different fractions of *Melilotus officinalis* in management of iron overload disease and its complications (free radicals generation and organ damage) were studied in rats. Iron overload was induced by 6 ip, injections of iron dextran (12.5 mg/100 g) over the period of 30 days. The different fractions of *Melilotus officinalis* were given orally for 30 days. The iron chelating and various biochemical parameters were estimated on 15th and 30th day. Methanolic fraction of methanolic extract and methanolic fraction of aqueous extract of *Melilotus officinalis* caused significant ($p<0.01$) iron chelating potential and significant ($p<0.01$) antioxidant effects in rats. Better iron chelation was observed on 30th day and at higher dose (300 mg/kg) as compared to 15th day and at lower dose (150 mg/kg)[80].

Anticoagulant effect:

The anticoagulation effect of crud coumarin extract of yellow clover *Melilotus officinalis* was investigated by prothrombin time, it showed concentration dependent anticoagulation activity[81].

Antiinflammatory effect:

The anti-inflammatory effect of *Melilotus officinalis* extract was recorded in mice[70]. Nine compounds (2 p-hydroxybenzoic acid glycosides, 3 acid components, 2 flavonoids, 1 coumarin and 1 alkaloid) isolated from the 70% ethanol aqueous extract of the aerial parts of *Melilotus officinalis* were tested for anti-inflammatory effects in lipopolysaccharide (LPS)- stimulated RAW 264.7 macrophages. All compounds inhibited LPS-induced nitric oxide (NO) and prostaglandin E2 production by suppressing the expression of inducible NO synthase (iNOS) and cyclooxygenase-2, in LPS-stimulated RAW 264.7 cells [56].

The effect of *Melilotus officinalis* extract (contained 0.25% coumarin), on acute inflammation induced by oil of turpentine was investigated in male rabbits. The effects were evaluated by measuring serum citrulline, a test of *in vitro* phagocytosis, total leukocyte count and differential leukocyte count. *Melilotus officinalis* possessed antiinflammatory effects, it reduced the activation of circulating phagocytes and lowered citrulline production similar to hydrocortisone sodium hemisuccinate and coumarin. In the bone marrow acute phase response, *Melilotus officinalis* had an inhibitory action that was lower than that of hydrocortisone sodium hemisuccinate and similar to coumarin[82].

The mechanisms by which melilotus extract interferes with inflammation-associated and oxidative stress pathways during sepsis were investigated in cecal ligation- perforation (CLP)- induced sepsis in mice. Melilotus extract possessed marked effect on the pathological manifestation of lung tissue and lung inflammatory response, it up regulated TIPE2, heme oxygenase-1 and IκB expression, and inhibited TLR4 and NF-κB activities. In addition, melilotus extract, treated mice showed decreased levels of MPO and MDA as well as increased levels of SOD[83].

Antidiabetic effect:

The therapeutic efficacy of oral use of a combination of [desmin (300 mg/day) and troxerutin (300 mg/day) with *Centella asiatica* (30 mg/die) and *Melilotus officinalis* (160 mg/die) for 14 months] was evaluated in diabetic patients with diabetic cystoid macular edema without macular thickening. The orally administered combination preserved retinal sensitivity in diabetic patients[84].

Melilotus officinalis was introduced as a component of a new drug by trade name of Semilil (Angipars). The effects of Angipars (ip, 5, 10, and 20mg/kg for 2 weeks) on nerve conduction velocity, histological alterations, and behavioral indices were investigated in streptozotocin (STZ) induced diabetic rats. Intraperitoneal injection of Angipars, significantly improved nerve conduction velocity in neuropathic rats. It also reduced the physiologic symptoms and improved sciatic morphological injuries in neuropathic rats[85].

Furthermore, the investigations also revealed that Semilil (Angipars) was safe with therapeutic efficacy in focal cerebral ischemia in rats, wound healing in rodents, human diabetic foot ulcer and pressure ulcers[86-89].

Management of venous insufficiency:

The therapeutic efficacy and the clinical tolerability of an association of alphatocopherol, rutin, *Melilotus officinalis*, and *Centella asiatica* was evaluated in patients with chronic venous insufficiency after 15 and 30 days treatment. A significant improvement of the clinical simptomatology was obtained, characterised by a diminution of the soprafascial edema after the treatment period[90].

Antitumor effect:

The antitumor activity of the aqueous, methanolic and ethanolic extract of *Melilotus officinalis* were investigated with *Agrobacterium tumefaciens*-induced potato disk tumor assay. Methanolic and ethanolic extract caused 33.8, 5.0 and 20.0% tumor growth inhibition respectively[(62)].

Toxicity and side effects:

During the process of spoiling, the coumarins in sweet clover are converted to toxic dicumarol, a potent vitamin K antagonist and anticoagulant. Any method of hay storage that allows molding of sweet clover promotes the likelihood of formation of dicumarol in the hay. When toxic hay or silage is consumed for several weeks, dicumarol alters proenzymes required for synthesis of prothrombin, resulting in hypoprothrombinemia (by preventing formation of the active enzyme). It probably also interferes with synthesis of factor VII and other vitamin K–dependent coagulation factors**.** Dicumarol concentrations of 20–30 mg/kg of hay ingested throughout several weeks are usually required to cause poisoning in cattle. However, all species of animals are susceptible, it mostly occurred in cattle, to a limited extent in pigs, and horses, while sheep are quite resistant. The time between consumption of toxic sweet clover and appearance of clinical disease varies greatly and depends on the dicumarol content of the particular sweet clover variety being fed, age of the animals, and amount of feed consumed. If the dicumarol content of the ration is low or variable, animals may consume it for months before signs of disease appear. Hay containing dicoumarol levels of 10-20 mg/kg of feed can be fed for 100 days before poisoning develops. Feeds containing 60-70 mg/kg of feed can cause poisoning in 21 days. The first indication of dicumarol poisoning in cattle, may be the death of one or more animals. In intoxicated animals, the first signs may be stiffness and lameness, due to bleeding into the muscles and joints. Cardiovascular signs (severe hemorrhaging will cause anemia, pale mucous membranes, rapid heart rate and death), respiratory signs (epistaxis), renal signs (hematuria), reproductive signs (excessive hemorrhaging during calving) and ocular signs (hemorrhaging into the anterior chamber of the eye). Death is generally caused by massive hemorrhage or bleeding. In horses poisoning manifested by excessive blood loss, pale mucous membranes and weakness. Prothrombin times above 40 seconds are suggestive of decreased clotting ability. Blood prothrombin, activated partial thromboplastin times, and clotting times are markedly increased[(91-94)].

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