International Journal of Botany Studies
www.botanyjournals.com
ISSN: 2455-541X
Received: 10-10-2021, Accepted: 24-10-2021, Published: 11-11-2021
Volume 6, Issue 6, 2021, Page No. 250-254

Marrubium vulgare–A review on pharmacological activity

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Abstract
Marrubium vulgare also called as white horehound or common horehound is a flowering plant in the Lamiaceae family. It contains marrubiin, a labdane diterpene and phenolic compounds. According to various studies *Marrubium vulgare* act as a good antioxidant agent so potentially useful in the treatment of cancer, liver diseases and diabetes mellitus. It has anti-inflammatory, wound healing, antihypertensive, hypolipidemic, sedative and antimicrobial activity. It could be used as chicken lice repellent, herbicide and natural molluscicide. In veterinary medicine *Marrubium vulgare* can be used as anthelmintic. White horehound used for digestion problems including loss of appetite, indigestion, bloating, gas diarrhea, constipation and gallbladder problems. It is also used for lung and breathing problems including cough, whooping cough, asthma, tuberculosis, bronchitis and swollen breathing passages. White horehound is useful for painful menstrual periods. It is applied to the skin damage, ulcers and wounds.

Keywords: biological activity, marrubiin, *Marrubium vulgare*, labdane

Introduction
The name hore is derived from "Horus" the Egyptian god of sky and light. Marrubium is a latin term derived from Maria urbs- ancient town of Italy. The other derives its name from the Hebrew marrob - a bitter juice. *Marrubium vulgare* is an annual perennial herb from Lamiaceae family, with a tough woody, branched taproot or numerous fibrous lateral roots and numerous stem which are quatrangular, erect, very downy and 20-100 cm height. Leaves are roundish, oval shaped usually toothed petiolate ovate, veined and hoary on the surface and they are arranged in opposite pairs on a long stem.

Marrubium vulgare originated in the region between in the Mediterranean sea and Central asia, has become a widespread species, currently inhabiting all continents [1]. It consists of diterpenoids, essential oils including monoterpenes and sesquiterpenes, Flavonoids and their glycosides, Phenylpropanoid and phenylethanolid glycosides [2]. A total fibre content 9.50%, total ash content 10.70%, Acid insoluble ash content1.3% and water soluble ash content 8.90%.

The alcohol soluble extractive value is 8.66% which suggested that most of the plant constituents were soluble in alcohol [3].

Marrubium vulgare possess expectorant, diaphoretic, vasodilator, and diuretic properties. Seeds are carminative, anti-inflammatory, stomachic, deobstruent, lithotriptic, aphrodisiac and strengthen kindney and urinary bladder. The seeds are given with wine to treat haemorrhoids. In Brazilian medicine it is used in the treatment of various diseases, including gastrointestinal disorders. Herbal tea of *Marrubium vulgare* used as a cough suppressant and expels catarrh [4, 5].

Marrubium Vulgare

Fig 1: *Marrubium vulgare L.*

Family: Lamiaceae
Genus: Marrubium
Order: Lamiales
Species: M.vulgare
Scientific name: *Marrubium vulgare L.,*
Commonname: Horehound, Hoarhound, Marrubium

Pharmacological activity
Antioxidant activity
In vitro antioxidant activity of methanolic extract of *Marrubium vulgare* was evaluated by DPPH free radical scavenging assay with IC_{50} values of 8.24-12.42 µg/ml.[6,7] Methanol and acetone extract of *Marrubium vulgare* possess antioxidant activity which was determined by

Photochemiluminescence (PLC) assay while lower activity was observed for marrubium essential oil and marrubin[8]. Dejeridane et al. evaluated the antioxidant potential of *Marrubium vulgare* due to the presence of phenolic compounds. Bouterfas et al [9]. 2016 determined the activity of *M.vulgare* on DPPH radical and concluded this effect varied depending on the type of solvent used for extraction.

Hepatoprotective activity

Ethanol:water (70:30% v/v) , petroleum ether extract of *Marrubium vulgare* on CCl_4 induced hepatotoxicity in mice showed that the liver and kidney function parameters remained normal in *Marrubium vulgare* treated groups [10]. Methanol extracts of *Marrubium vulgare* reduced the level of AST, ALT and LDH. Increases the GPs, GR and GST, GSH activities and decreased the production of MDA level in rat liver treated with CCl_4 [11].

Antiproliferative activity

Zarai et al. [12] reported that essential oil of *M. vulgare* inhibit the proliferation of cervical cancer (HeLa) cell lines with IC50 values of 0.258 µg/ml. Ethanol-water (70:30 % v/v) extract of *Marrubium vulgare* inhibit the viability of melanoma and glioma [13]. The extract induce apoptosis and autophagy the results suggested that this plant could be a good candidate for anti-melanoma and anti-glioma therapy. Methanolic extract of *M.vulgare* exert cytoprotective activity against U87 and LN229 [14]. Alcoholic extract, acacetin, apigenin and acacetin-7-rhamnoside showed anticancer activity against breast carcinoma and Ehrilich tumor cell lines. Labdanein showed moderate effect on human myeloid leukemia (K562), imatinib resistant human myeloid leukemia (K562R) and human B cell precursor leukemia cell lines (697)

Kozyra et al. [15] reported the potential activity of methanolic extract of phenolic acid fractions of *M.vulgare* against human melanoma cancer cell line (A375) and normal human skin fibroblasts using MTT assay. Esterified form of phenolic compound exert cytotoxic effects since *M.vulgare* is abundant in phenylpropcnoid esters and phenylethanoid glycosides.

Anti-Inflammatory activity

Anti-inflammatory activity of the *M.vulgare* was studied against isoproterenol induced myocardial infarction. Decrease number of neutrophil and TNF-α level indicate that the plant extract has anti-inflammatory activity [16, 17].

Methanolic extract of *M.vulgare* at 200 mg/kg orally reduced the inflammation to 87.30% as compared to standard diclofenac which have 85.52% against carrageenan induced inflammation [18]. Marrubiin caused a dose-dependent inhibition of carrageenan, bradykinin and histamine induced extravasation Evans blue in mice ears with inhibition of 63.0%, 70.0%, and 73.7% respectively while the prostaglandin E2 produced less than 50% inhibition. Anti-inflammatory activities against inflammation induced by Carrageenan and prostaglandin E2 and analgesic activity in the p-benzoquinone – induced abdominal constriction test showed that methanolic extracts of *M.vulgare* have similar effects as standard drugs indomethacin and acetylsalicylic acid [19].

Six compounds of *M.vulgare* (luteolin-7-O-β-glucopyranoside, apigenin-7-O-β-glucopyranoside, oleanolic acid, β-sitosterol, luteolin-7-O-rutionside, and rosmarinic acid) inhibit the formation of hormones such as prostaglandins, and peroxasalandine, which involved in the formation of inflammatory mediators evaluated by *in-vitro* anti-inflammatory activity [20].

Sedative activity

Aqueous and ethanolic extracts of *M.vulgare* reduced the morphine withdrawal signs in animals. The result showed that all doses reduced the physical activity of mice and induced muscle relaxation [21].

Antidiabetic activity

Marrubium vulgare ethnomedically used as an antidiabetic agent [22, 23]. Some scientific evidences also supports antidiabetic activity of *Marrubium vulgare* traditionally [24]. Ethanol extract of *Marrubium vulgare* exert moderate effect using α-glucosidase inhibitory activity *in-vitro*. [25] Aqueous extract of *Marrubium vulgare* at 200 mg/kg and 300 mg/kg reduced the sugar level in alloxan induced diabetes model which was comparable with standard Glibenclamide. *M.vulgare* treated groups showed decreased total lipid, triglycerides and cholesterol levels when compared to diabetic group [26]. In Streptozotocin- induced diabetes the methanolic extract of *Marrubium vulgare* reduced the blood sugar level, serum urea, uric acid, creatinine and correction of lipid profiles. Methanolic extract of *Marrubium vulgare* increased the glucose uptake of liver and skeletal muscles reported by chakir et al [27]. Methanol, Aqueous and butanol extract of *M.vulgare* on autoimmune diabetes mellitus induced by cyclosporine and streptozotocin reduced the blood glucose level, IFN-γ and NO also decreased the total cholesterol, Low density lipoprotein cholesterol (LDL) and very low density lipoprotein cholesterol (VLDL) and triglycerides additionally increased the serum insulin level [28]. Alkofahi et al. reported that *M.vulgare* extract at 1g/kg showed neutral effect on blood glucose level [29].

In another study *M.vulgare* treated group showed a lower concentration of KCL and noradrenaline compare to control group. So it was concluded that oral administration of *M.vulgare* for 2 months could attenuate the contractile responsiveness of the vascular system which prevent the development of hypertension in diabetic rats [30]

Immunomodulatory activity

Aqueous extract of *M.vulgare* at different concentration (100, 500 and 1000 mg/kg bodyweight) showed immunomodulatory effect in mice infected with Salmonella typhimurium [31]. *M.vulgare* at 100 mg/kg showed high immunomodulatory effect in the level of T cells, interleukin and interferon-gamma (IFN-γ)

Gastroprotective activity

In ethanol induced ulcer group *M.vulgare* at 50 and 100 mg/kg produced 49.31-74.31% ulcer inhibition, while the indomethacin at 25, 50 and 100 mg/kg produced 50.32%, 66.24% and 82.17% of ulcer inhibition. Marrubiin at 25 mg/kg increased the pH and mucus production. The result indicates that the gastroprotective effect induced by extract and marrubiin related to NO and sulfhydryls which are important gastroprotective factors [32].

Antimicrobial activity

Ethylacetate, diethyl ether, 1-butanol extract of *Marrubium vulgare* was tested on *Staphlococcus aureus*, *Escherichia*

coli, Proteus vulgaris and *Pseudomonas aeruginosa*. The antibacterial activity of different fraction was performed on solid agar medium showed little or no effect [33]. Methanolic extract of *M.vulgare* showed antimicrobial activity against *E.coli, B.subtilis, Staphylococcus aureus, S.epidermidis, Pseudomonas aeruginosa, Proteus vulgaris* and *Candida albicans* [34]. Flavans and flavonols extracted from the *M.vulgare* leaves possess antifungal activity against *Aspergillus niger* ATCC 16,404 and *Candida albicans* ATCC 10,231using solid medium diffusion method. MIC ranged between 6.25 and 100 µg/ml that exceeded the effect of amphotericin, fluconazole, terbinafine and econazole nitrate that indicate *M.vulgare* flavonoids are potent anti-fungal agent [35]. Rezgui et al. [36] reported that *M.vulgare* and marrubiin used for the treatment of skin dermatophyte infection. They evaluate the effect of acetone and methanol extract, essential oil, and marrubiin against dermatophytes fungi. Among these *M.vulgare* essential oil has an effect on Gram + bacteria with inhibition zones and MIC values in the range of 6.6-25.2 mm and 1120-2600 µg/ml where Gram – bacteria [37].

Wound healing

Methanolic extract of *M.vulgare* contain high polyphenolic compounds and marrubiin showed antioxidant and wound-healing properties by promoting cell migration and the proliferation of fibrosis [38]. Hemostatic activity of aqueous extract of *M.vulgare* using plasma recalcification method confirmed the anticoagulant activity of the extract [39].

Antiviral activity

Methanol, chloroform and hexane extract of *M.vulgare* showed antiviral activity with 3.11, 2.8 and 1.28 respectively. Hexane fraction disrupts the early step of cyclic replication including HSV-1 attachment [40].

Antiparasitic activity

Encephalitis and congenital disorders are caused by *Toxoplasma gondii*. It was concluded that *M.vulgare* could be very useful against this parasite by MTT cell viability assay *in vitro* [41].

Antiprotozoal activity

Ethyl acetate, n-hexane, and methanol extract and essential oil of *M.vulgare* have potent antiprotozoal activity against *Trichomonas vaginalis*. Essential oil with MIC value of 291µg/ml showed the highest antiprotozoal activity followed by ethylacetate541 µg/ml, methanol 1000 µg/ml and n-hexane 1500 µg/ml. According to this study the compound of *M.vulgare* have significant effect on *T. vaginalis* [42].

Antiplasmodial activity

Ethanolic extract of *M.vulgare* produced significant curative and suppressive effect in mice infected with chloroquine-sensitive plasmodium berghei- berghei curative, suppressive and prophylactic experimental animal model. The extract prolonged the survival time of treated mice up to 22 days compared to the negative control group 11 days [43].

Veterinary Medicine

Egg hatch assay and larval mortality assay was used to evaluate anthelmintic activity of ethanolic and aqueous extract of *Marrubium vulgare*. After 24 hrs of exposure period mortality observed at 50 mg/ml was found to be 45.8% for the aqueous extract and 51% for the ethanolic extract[44]. Ethanolic extract of *M.vulgare* shows potent antibacterial activity against methicillin-resistant *staphylococci* and *E.coli* strains [45].

Conclusion

Marrubium vulgare contain various secondary metabolites as source of bioactive compounds with health benefits such as antioxidant, antiproliferative, antidiabetic, hepatoprotective, anti-inflammatory, and antimicrobial being the most evaluated. Effects of marrubiin, essential oil and extracts, flavonoids like flavan and flavonol and phenylethyl esters were studied. White horehound is generally safe but well-designed clinical trials are needed to shift from traditional to use of *M.vulgare* herbal preparations for the prevention and treatment of various diseases.

Acknowledgement

I wish to express my sincere gratitude to Department of Pharmacology, Vinayaka Mission's College of Pharmacy, Salem, Tamil Nadu, India for providing necessary facilities to carry out this review work.

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