ORIGINAL ARTICLE

# Pharmacologic Activities of *Yerba Buena* (*Mentha x villosa* Huds Fam. Lamiaceae): An Overview

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## ABSTRACT

**Objectives.** The aim of this study is to describe the pharmacologic activities of *Yerba buena* (*Mentha x villosa* Huds).

**Methods.** Data were collected if available from online databases from 1950 to 2023 as well as the Philippine National Library, and unpublished clinical trials.

**Results.** The initial search yielded thirty-seven studies from the different databases. After further screening, eighteen studies met the inclusion criteria. *In vitro/in vivo* studies of *yerba buena* showed antihypertensive, antibacterial, anthelmintic, antitumor, antiviral, and analgesic activities. Safety studies conducted showed that *yerba buena* possesses antimutagenic property. Clinical trial of *yerba buena* showed that oral administration of *yerba buena* and Paracetamol produced comparable analgesic efficacy.

**Conclusion.** The medical benefits of *yerba buena* have been well-documented and thoroughly researched. *Yerba buena* was reported to have analgesic, antibacterial, anthelmintic, anticancer, antiviral, and antihypertensive properties. Among all the different activities, its analgesic activity was the only reported pharmacologic indication to have been clinically tested.

*Keywords: Yerba buena, Mentha x villosa, bioactivity*

## INTRODUCTION

One of the 10 Herbal Medicines promoted by the Department of Health is *Yerba buena* (*Mentha x villosa Huds* Fam. Lamiaceae).[1] *Yerba buena* is also locally known as ablebana (Ifugao), herba Buena (Tagalog), hilbas (Tagalog), karapbo (Sur del Norte), American wild mint, brook mint, corn mint, field mint, tule mint, and pepper mint (England). *Yerba buena* is an aromatic, creeping herb that grows up to 20-40 centimeters high. The leaves are about 1.5-4cm long, oblong-ovate shape, serrate margined and wrinkled, and is thinly hair. Flowers are purple to bluish and are in axillary head-like whorls.[2] It is a native of Europe and is widely cultivated throughout the Philippines. According to the study of Maramba et al., *Yerba buena* in the Philippines does not grow in the wild.[3] The *Yerba buena* used in the clinical trials of Maramba et al. was cultivated in UP Los Baños.[3-8]

*Yerba buena* leaves and subsequent preparations are traditionally used as remedy for cough[9], toothache, colds[10], headache[11,12], migraine[12], dizziness, fainting, hysteria, gaseous distention, arthritis, mouth wash[13], worm, menstrual colic, otalgia[12], influenza[12], pain[12], and fever[12]. According to the Guidebook on the Proper Use of Medicinal Plants, *Yerba buena* is collected fresh, heated over fire then crushed and applied to the forehead or temples as treatment for headaches.[13]



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For arthritis, a poultice of *Yerba buena* is prepared by heating fresh leaves over a small fire and pounding the leaves. This is then applied to the affected joints.[13]

Fresh leaves of *Yerba buena* were subjected to steam distillation using a clavenger apparatus for an average of six hours until a yellowish oil with characteristic odor was obtained.[14] This essential oil together with leaves were checked for the phytochemical constituents. The main constituents found in the essential oil and leaves were carvone[14], limonene[9,14,15], linalool[15], transcarveol, dihydrocarvone, trans-carvyl acetate, piperitenone oxide or rotundifolone (35.4-55.4%)[15-18], and Gamma-muurolene (13.1%)[16]. Other constituents were alpha-pinene[15], beta-pinene[15], cadinene[15], 1,8-cineol[15], trans-ocimene[15], 1,3-carvomenthone[19], isomenthone[19], 4,8-epoxy-p-menthan-3-one[19], 2-isopropylcyclopentanone[19], p-menthan-2,5-diol[19], b-sitosterol[20] and cis-8-pentadecennlylactone [20].

Due to the many traditional uses of this plant, subsequent studies were performed using different preparations to check its antihypertensive, antibacterial, anthelmintic, antitumor, antiviral, and analgesic activities.

## METHODS

### Electronic searches

We used the search terms: (1) *Yerba buena*; (2) *mentha x villosa*; and (3) *mentha cordifolia*. We searched the Health Research and Development Information Network (HERDIN) (2004 to June 2023); PubMed (2004 to June 2023); MEDLINE (1950 to June 2023); Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* 1950 to June 2023); Philippine Index Medicine (1950 to June 2023); and Google Scholar (1950 to June 2023).

### Searching other resources

We visited the Philippine National Library and searched their database. We searched for existing patent applications or patent approval. We obtained permissions from authors of unpublished studies.

### Selection of studies

We independently searched and extracted data using the stated search terms. We screened and selected the studies according to the following criteria: (1) the *Yerba buena* used in the study is confirmed to be *mentha x villosa* or any of its accepted synonyms; (2) the study focuses on any pharmacologic activity of *Yerba buena*; and (3) the methodology must be, at least, an in vitro study. Disagreement on inclusion of a study is resolved by majority voting.

## RESULTS

The initial search yielded thirty-seven studies. After further screening, eighteen studies met the inclusion criteria. It showed that *Yerba buena* was found to have anti-hypertensive, antibacterial, anthelmintic, antitumor, and analgesic activities as summarized in Table 1. Safety studies conducted showed that *Yerba buena* possess antimutagenic property. Clinical trial of *Yerba buena* showed that oral administration of *Yerba buena* and Paracetamol produced comparable analgesic efficacy.

## DISCUSSION

Due to the many traditional uses of this plant, subsequent *in vivo* studies were performed using its crude extract and essential oil to check its antihypertensive, antibacterial, antitumor, and analgesic activities.

### Analgesic Activity

*Yerba buena* fed through orogastric tube among adult male albino rats showed analgesic activity against a control that received 10% starch solution upon electrical stimulation of the contralateral forepaw.[21] Essential oil and Piperitenone

**Table 1.** Summary of in vitro/in vivo Studies of *Yerba buena*

| Pharmacologic Effect | Author, Year | Study Outcomes | Extraction/Constituent | Test Animal/Assay |
|---|---|---|---|---|
| ***Analgesic*** | Sanchez, MG, 1989 | Analgesic activity versus 10% starch solution upon electrical simulation of contralateral forepaw[21] | *Yerba buena* extract/ bolus | Male Albino Rats |
| | Villaseñor, IM, 1995 | Reduction of number of squirms induced by acetic acid by 81.4%, 58.2% and 71%, respectively.[20] | Hexane, Chloroform and Ethyl acetate | Rats |
| | Villaseñor, IM, 1999 | Decreased in squirms by 70% and 73%, respectively at 100 mg/kg mouse [19,22] | B-sitosterol and B-sitosteryl-B-D-glucoside | Mouse<br>Hot plate method |
| | Villaseñor, IM, 1999<br>Villaseñor, IM, 2009 | Reductions in the number of squirms induced by acetic acid[19,22] | Hexane and Ethyl extract | Rats |
| | Villaseñor, IM, 2002 | 300% and 157% increase in pain tolerance compared to mefenamic acid with 171% pain tolerance[23] | B-sitosterol and B-sitosteryl-B-D-glucoside | Mouse<br>Hot plate method |
| | Villaseñor, IM, 2009 | Showed decreased number of squirms by 67.3% at 100 mg/kg mouse[19] | Menthalactone | Mouse |

**Table 1.** Summary of in vitro/in vivo Studies of *Yerba buena (continued)*

| Pharmacologic Effect | Author, Year | Study Outcomes | Extraction/Constituent | Test Animal/Assay |
|---|---|---|---|---|
| ***Antihypertensive*** | Lahlou, S, 2002 | Vasorelaxant activity and dose-dependent decreased blood pressure and bradycardia[24] | IV treatment of Essential oil | DOCA-salt hypertensive rats |
| | Guedes, DN, 2002 | Dose-dependent and bradycardia in non-anaesthetized normotensive rat[17] | Rotundifolone | Normotensive rats |
| | Pakeechote, P, 2011 | Anti-hypertension<br>-restored heart rate and vascular reactivity<br>-reduced systolic BP, diastole BP, and Mean Arterial Pressure (MAP)[25] | Extracts | L-NAME induced hypertensive rats |
| | Pakeechote P., 2014 | MAP, HVR, Wall thickness, cross-sectional area of thoracic aorta, plasma malondialdehyde (MDA) significantly reduced[26] | Aqueous extract | L-NAME induced hypertensive rats |
| ***Antibacterial*** | Ligaya, AT, 1993 | Inhibited the growth of *Staphylococcus epidermidis* but were not significantly different from control (Ampicillin) against the rest of the organism[27] | Plant extract | Microorganisms |
| | Ragasa, CY, 2001 | Activity against *B. subtilis*, *C. albicans*, *T. methagrophytes and A. niger and P. aeruginos*[28] | Dichloromethane extract | Microorganisms |
| | Arruda, TA. 2006 | Activity against *S. aureus*, *C. albicans* but not with *E. coli* and *P. aeruginosa.* Limonene oxide and carvone epoxide did not prevent activity against MRSA (171c) and the Essential oil had the highest zone of inhibition due to synergistic action of different compounds[14] | Essential oil constituents namely rotundifolone, limonene oxide, pulegone oxide, carvone epoxide and (+)-pulegone | Microorganisms |
| ***Anthelmintic*** | Villaseñor, IM, 1999 | Anthelmintic property of Extract[22] | Hexane extract | Ascaris suum |
| | Matos-Rocha TJ, 2020 | Doses of 200 mg/kg (Mv-EO) and ROT (141.9 mg/Kg) resulted in a significant reduction in fluke burden (72.44% and 74.48%, respectively).[29] There was a marked reduction in liver, intestinal, and fecal egg count and a change in oogram pattern of the Mv-EO and ROT treated mice compared to infected, untreated mice. | Essential oil and rotundifolone | Mouse |
| | Bortoluzzi, BB, 2021 | The nanoemulsion of MVEO/2017 at 0.367 mg/mL, inhibited L3 migration by 83.1%, demonstrating to be highly effective (concentration ratio of 1:0.004), ($EC_{50}$ = 0.10 mg/mL), supports its potential to be a candidate to the next-generation therapy to alleviate clinical parasite infections and combat GIN resistant populations.[30] | Essential oil | Gastrointestinal nematodes |
| ***Antitumor*** | Lim-Syllanco, CY, 1995 | Complete inhibition of formation of all types of tumors (liver, skin, and colon tumor) of mice (Dimethylbenzanthracene-induce and croton-promoted tumor)[31] | Decoction | Mice |
| | Villaseñor, IM, 1997 | Antiteratogenic and anticarcinogenic activities using lethal test and mouse skin cancer assay[32] | Chloroform leaf extract | Mice |
| ***Antiviral*** | Zeljkovic, SC, 2022 | Inhibited the SARS-CoV-2 replication in the infected cells<br><br>Carvone-rich essential oil of *M. x villosa* had the greatest activity among all active essential oils ($IC_{50}$ 127.00 ± 4.63 ppm)[33] | Essential oil extracted by hydrodistillation of the dried plant material | Vero 76 cells |
| | de Paz-Silava, SLM, 2022 | In treated cells, viral replication was inhibited in both cell culture supernatant and whole cell lysates. The level of viral production, as measured by the viral p24 protein concentration, was very much inhibited under noncytotoxic concentrations to the similar level without addition of TNFα.[34] | Ammonium sulfate extract | Human cell lines |

oxide significantly reduced writhing induced by acetic acid in mice and also paw-licking time for second phase of formalin test.[12] Hexane, chloroform, and ethyl acetate extracts of *yerba buena* reduced the number of squirms induced by acetic acid by 81.4%, 58.2%, and 71%, respectively. Among the three, hexane extract exhibited the strongest analgesic activity.[20] Two different studies also showed hexane and ethyl acetate extracts reduced the number of squirms induced by acetic acid.[19,22] Menthalactone, a new long chain alkene with bicyclic lactone moiety, is found to have analgesic property. It decreased the number of squirms by 67.3% at a dose of 100mg/kg mouse.[19] Confirmatory bioassay of elucidated extract showed that B-sitosterol and its glucoside also showed analgesic property.[23] B-sitosterol and B-sitosteryl – B – D- glucoside were isolated analgesic constituents from leaves of *Yerba buena* and showed decrease in squirms induced by acetic acid by 70.0% and 73%, respectively at 100mg/kg mouse. Hot plate method further confirmed their analgesic activities as each constituent showed 300% and 157% increase in pain tolerance, respectively as compared to mefenamic acid showing 171% pain tolerance.[23]

## Antihypertensive

Extracts of *Yerba buena* leaves inhibited development of hypertension, restored heart rate and vascular reactivity near normal values in N(ω)-nitro-L-arginine methyl ester (L-NAME) induced hypertensive rats.[25] The essential oil of *Yerba buena* also showed vasorelaxant effects, dose-dependent decrease in blood pressure, and bradycardia among L-NAME induced hypertensive rats but was not involved in the nitric oxide release.[24] Another study showed that aqueous extracts exhibited anti-hypertensive effect via antioxidant capacity, vasodilator property, and reduced vascular remodeling among L-NAME induced hypertensive rats.[21] Rotundifolone, one of the main constituents of the essential oil of *Yerba buena*, showed a significant and dose-dependent hypotension and bradycardia in non-anaesthetized normotensive rat.[17]

## Antibacterial

*Yerba buena* inhibited the growth of *Staphylococcus epidermidis* but was not significantly different from control (Ampicillin) against the rest of the organism.[27] Dichloromethane extract of *Mentha cordifolia* showed activity against *B. subtilis, C. albicans, T. methagrophytes, A. niger and P. aeruginosa*.[28] Essential oil constituents namely rotundifolone, limonene oxide, pulegone oxide, carvone epoxide and (+)-pulegone were effective against *S. aureus, C. albicans* but not with *E.coli* and *P. aeruginosa.* Limonene oxide and carvone epoxide did not prevent activity against MRSA (171c) and the Essential oil had the highest zone of inhibition due to synergistic action of different compounds.[14]

## Anthelminthic

Hexane extracts of the leaves showed anthelminthic property using live *Ascaris suum*.[22]

Doses of 200 mg/kg *Yerba buena* essential oil and rotundifolone (141.9 mg/Kg) resulted in a significant reduction in fluke burden (72.44% and 74.48%, respectively).[29] The study also showed a reduction in liver, intestinal, and fecal egg count and a change in oogram pattern of the mice treated with yerba buena-essential oil and rotundifolone compared to infected, untreated mice.

A nanoemulsion preparation of *Yerba buena* essential oil at 0.367 mg/mL, inhibited L3 migration by 83.1%, demonstrating to be highly effective (concentration ratio of 1:0.004) ($EC_{50}$ = 0.10 mg/mL), supports its potential to be a candidate to the next-generation therapy to alleviate clinical parasite infections and combat GIN resistant populations.[30]

## Antitumor

Decoction of *Yerba buena* leaves was among the Philippine medicinal plants tested that showed complete inhibition of formation of all types of tumors (liver, skin, and colon tumor) of mice (Dimethylbenzanthracene-induce and croton-promoted tumor).[31] Chloroform leaf extract showed antiteratogenic and anticarcinogenic activities using lethal test and mouse skin cancer assay.[32]

## Antiviral

*Yerba buena* essential oil produced by hydrodistillation inhibited the SARS-CoV-2 replication in the infected Vero76 cells. Carvone-rich essential oil of *M. x villosa* had significant activity among essential oils tested (IC50 127.00 ± 4.63 ppm).[33]

In a different study, the ammonium sulfate extract of *Yerba buena* were tested for its antiviral activity. Cells treated with the extract inhibited viral replication in both cell culture supernatant and whole cell lysates.[34]

## Safety Studies

Chloroform extracts of *Yerba buena* were tested using micronucleus tests and displayed antimutagenic properties.[22] *Yerba buena* essential oils presented fetal toxic effect, due to hemorrhagic points viewed at the brain, kidney, liver, and vessel near heart of some fetus of Wistar rats. This is probably due to the vasorelaxant action of the essential oil. However, it did not show toxicity in pregnant rats and it does not promote impairment at gestation of treated pregnant rats.[15]

Tablets of *Yerba buena* were submitted to Rec assay and showed that it does not possess direct DNA damaging capacity. The tablets are not mutagenic before and after metabolic activation as tested by Ames test and host-mediated assay. They also do not show chromosome breaking capacity using micronucleus test. Furthermore, the tablets showed antimutagenic activity by reducing formation of micronucleated polychromatic erythrocytes induced by dimethylnitrosamone, N-nitrosopyrrolidine and tetracycline.[35]

### Clinical Trial

Powdered dried leaves of *Yerba buena* were produced into tablet form and have been indicated as an analgesic and tested in Clinical trials phases I, II and III by the National Integrated Research Program on Medicinal Plants.[3] A Phase I clinical trial by Maramba et al. showed that *Yerba buena* at 500 mg dose was effective in relieving mild to severe post-operative pain in 72% of patients within one hour of taking the drug.[4] A Phase II double-blind comparative controlled study by Maramba et al. showed that over-all pain relief from moderate to severe post-operative pain was highest with paracetamol (92.84%) followed by *Yerba buena* (72.72%) and placebo (55.55%).[5] Maramba et al. also tested *Yerba buena* tablets for Phase III multi-center clinical trial for moderate to severe post-dental extraction pain, moderate to severe post-episiotomy pain, and acute moderate to severe post-circumcision pain against Paracetamol. It showed that oral administration of *Yerba buena* and Paracetamol produced comparable analgesic efficacy based on Total Pain Intensity Difference (PID), Total Analog Pain Intensity Difference (APID), Sum of Pain Intensity Difference (SPID), Sum Analog Pain Intensity Difference (SAPID), and Total Pain Relief (TOTPAR).[7,8]

## CONCLUSION

*Yerba buena* is a well-documented and extensively studied plant for its medicinal property. The review showed that *Yerba buena* was found to have antihypertensive, antibacterial, anthelmintic, antitumor, antiviral, and analgesic activities. Among all the different pharmacological indications, its analgesic property was the most documented. Documentations from traditional use of the plant, as well as its relation to other *Mentha* species are key to its discovery as an analgesic. Analgesic property was found from the crude extracts using solvents like Hexane, Chloroform, and Ethyl acetate as well as the bioassay structure elucidated constituents Menthalactone, B-sitosterol and its glucoside. The potential of *Yerba buena* as an herbal medicine was further supported by safety studies, in particular, its non-mutagenic and antimutagenic properties. Clinical trials were done using the tablet form of the powdered leaves of *Yerba buena* up to Phase III clinical trial and a subsequent registration under the Philippine FDA.

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### Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

### Author Disclosure

All authors declared no conflicts of interest.

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