Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Should Tawa-tawa *(Euphorbia hirta)* be used as adjunctive treatment for COVID-19 infection?

Evidence Reviewers: Joanna Marie Tan RN, MD, DPPS, Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS Myzelle Anne Infantado, PTRP, MSc (cand.)

RECOMMENDATION

There is no evidence to recommend Tawa-tawa (Euphorbia hirta) as adjunctive treatment for patients with COVID-19 infection.

Consensus Issues
Due to the lack of evidence, the panel decided not to make a recommendation for the use of Tawa-tawa as adjunctive treatment for COVID-19. One panelist opted to abstain from the vote because her inclination was to suggest against the use of Tawa-tawa. While it has been used in the treatment of dengue, it has no proven benefits for COVID-19 infection and may cause harm.

Key Findings

Tawa-tawa (*Euphorbia hirt*a) is a medicinal herb widely used for febrile illness in the Philippines; it is considered as a potential adjunctive treatment for COVID-19. We found no published studies on *Euphorbia hirta* in patients with COVID-19. There is one ongoing local clinical trial.

Introduction

Euphorbia hirta is a common herb in the Philippines characterized by its hairy stem, forked reddish leaves and purple flowers.[1] An ethnographic study done in 2018 showed that *Euphorbia hirta* has been used since the early 1940s for fever.[2] Aqueous extracts of the herb are shown to strongly reduce the release of prostaglandins I2, E2 and D2, explaining its antipyretic property.[3] In spite of only a few formal studies, *Euphorbia hirta* is being used by the residents of the Cordillera Region as adjunctive treatment for Dengue Fever.[4,5,6] The study of Tayone et al. on animals showed significant platelet-increasing activity as well as reduction in plaque formation of dengue virus serotype 1.[7] One in vitro study by Saptawati et al. also demonstrated inhibition of dengue virus serotype 2.[8] Molecular docking studies also showed promising results, wherein the phytochemical components of *Euphorbia hirta* showed binding with dengue targets, indicating its antiviral efficacy.[9]

Review Methods

We performed an exhaustive comprehensive systematic search of related literature from MEDLINE, MedRxiv.org, WHO Clinical Trials Registry, WHO Therapeutics and COVID 19 Living Guidance, WHO Institutional Repository for Information Sharing, HERDIN Plus, and clinicaltrials.gov. Freehand search using Google was also done. There was no limit as to date, language, and country of publication. The search was conducted using the following terms:

"herbal medicine", "*Euphorbia hirta",* "Tawa-tawa", "COVID-19", "severe acute respiratory syndrome coronavirus 2", "2019-nCoV", "viral illness", "cough". We also contacted local specialists for possible information on studies being conducted on this plant.

Our PICO for this review was as follows: Population – patients with COVID-19; Intervention – tawa-tawa; Control – standard treatment, supportive treatment or no treatment; Outcome – mortality, ICU stay, need for ventilation, length of hospital stay, days to recovery, worsening of symptoms and viral load/cycle threshold. We searched for randomized controlled trials, observational studies, systematic reviews and meta-analyses.

Results

We found no published articles that matched our criteria.

Ongoing Trial

We found one ongoing local trial for *Euphorbia hirta* registered at HERDINPLUS by Padilla and co-investigators from the University of the Philippines–Visayas. It is an interventional, randomized controlled phase II dose-finding study design to evaluate the effects of standardized aqueous spray-dried extract of E. hirta (U4bext®) on the progression of and symptom resolution from COVID-19 versus current guidelines for standard of care.[10]

According to the protocol registration information, the primary outcome of interest for the said study is clinical improvement, which the investigators defined as "at least 2 categories of improvement from baseline in the 7-category Ordinal Scale of patient status." Secondary outcomes include time to improvement of at least 2 categories relative to baseline, time to clinical failure (defined as the period measured from first dose to time of death, mechanical ventilation, ICU admission, or study withdrawal), time to resolution of symptoms, time to normalization of biochemical/hematological parameters, time to hospital discharge, duration of time on supplemental oxygen, percentage of participants with adverse events, time to RT-PCR virus negativity, and proportion of participants with post-treatment infection.

Evidence to Decision

Euphorbia hirta is available in drugstores and health outlets, as well as online shopping sites at P 185.00 the price of a bottle that contains 60 pieces of the 500-mg capsule.[11] The Philippine Drug Price Reference Index (DPRI) does not list tawa-tawa or Euphorbia.

Recommendations from Other Groups

Currently there are no clinical practice guidelines listed by the National Institute of Health, American College of Physicians, Center for Disease Control, National Guidelines Clearinghouse and Australian Clinical Practice Guidelines that make a recommendation on the use of *Euphorbia hirta* as adjunctive treatment for COVID 19.

We were able to reach ten pediatric and adult infectious disease specialists whose expert opinion we requested as to the use of *Euphorbia hirta* as an adjunct for COVID-19. Currently none of them use *Euphorbia hirta*. While they recognize the inherent and potential use of the herb for COVID-19, they are currently awaiting further recommendations prior to using it in their practice.

Research Gaps

There is no available literature on the dosing regimen for these herbal preparations in patients with COVID-19. There is also no information on the use in adult versus pediatric patients with COVID-19, or on the adverse effects of such dosing.

References

[1] Webster GL. Synopsis of the genera and suprageneric taxa of Euphorbiaceae. Annals of the Missouri Botanical Garden. 1994;81:33,144.

[2] Lam H, Montano M, Sia I, Heralde F, Tayao L. Ethnomedicinal uses of tawa-tawa in selected communities in the Philippines. Acta Medica Philippina. 2018; 52(5).

[3] Lanhers MC, Fleurentin J, Dorfman P, Mortier F, Pelt JM. Analgesic, antipyretic, and anti-inflammatory properties of Euphorbia hirta. PlantaMedica. 1991;57(3):225-31.

[4] Garcia LL, Herrera CL, Capal TV, Melo CL, Dayap LA, Banal RV. Philippine vegetable drugs in common use: their chemical constants. Part II. Philippine Journal of Science. 2003;132 (2):103-8.

[5] Balangcod T, Balangcod AKD. Ethnomedical knowledge of plants and healthcare practices among the Kalanguya tribe in Tinoc, Ifugao, Luzon, Philippines. Indian Journal of Traditional Knowledge. 2011;10(2):227-38.

[6] Co LL. Common medicinal plants of the Cordillera Region. Respir Med. 2005; 99(11):1377-85.

[7] Tayone WC, Tayone JC, Hashimoto M. Isolation and structure elucidation of potential Anti-Dengue metabolites from Tawa-Tawa (Euphorbia hirta Linn.). Walailak Journal of Science and Technology. 2014; 11(10):825–832.

[8] Saptawati L, Febrinasari RP, Yudhani RD, et al. In vitro study of eight Indonesian plants extracts as anti Dengue virus. Health Science Journal of Indonesia. 2017; 8(1).

[9] Petra S, Javawordena U, Jayasinghe C. (2018). Potential use of Euphorbia hirta for Dengue: A systematic review of scientific evidence. J Trop Med. 2018; 2018:2048530.

[10] Malabad JC, Benedicto JP, Guanzon M, Ubial PR. A randomized controlled clinical trial on the efficacy and safety of Tawa-tawa (*Euphorbia hirta* L.) extract as an adjunctive treatment for mild to moderate COVID-19 patients. [Internet]. Health Research and Development Information Network. 2021. Available from: https://registry.healthresearch.ph/index.php/registry?view=research&layout=details&cid=3475

[11] Tawa-Tawa Plant capsule. Shopee. [homepage on the Internet]. 2021. Available from: https://shopee.ph/Tawa-Tawa-capsule-60-pcs-500-mg-i.24689633.1413509434

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the actual panel meeting (N = 8)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS
Problem	No (4)	Yes (4)					
Benefits	Large	Moderate (1)	Small (2)	Uncertain (5)			• **No research evidence found.** • *There is a need to conduct more studies for tawa-tawa. (n = 1)*
Harm	Large	Small (1)	Uncertain (7)	Varies			• **No research evidence found.** • *There is a need to conduct more studies for tawa-tawa. (n = 1)*
Certainty of Evidence	High (1)	Moderate	Low (1)	Very low (6)			• **No research evidence found.** • *There is a need to conduct more studies for tawa-tawa. (n = 1)*
Balance of effects	Favors drug	Does not favor drug	Uncertain (8)	Varies			• **No research evidence found.** • *There is a need to conduct more studies for tawa-tawa. (n = 1)*
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability (4)			
Resources Required	Uncertain (5)	Large cost (1)	Moderate Cost (1)	Negligible cost (1)	Moderate savings	Large savings	• No synthetic preparation of tawa-tawa
Certainty of evidence of required resources	No included studies (4)	Very low	Low (2)	Moderate (1)	High (1)		• No synthetic preparation of tawa-tawa
Cost effectiveness	No included studies (8)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			• No available evidence to date
Equity	Uncertain (6)	Reduced	Probably no impact (2)	Increased			
Acceptability	Uncertain (6)	No	Yes (2)	Varies			• *Panel: Tawa-tawa is locally available and abundant*
Feasibility	Uncertain (1)	No (1)	Yes (6)	Varies			*Panel: Tawa-tawa is locally available and abundant (n=1)*

Appendix 2. Search Yield and Results

Database	Search terms	Yield	Hits
PubMed	((((((((((((((((((herbal* [tiab]) OR (herbal medicine)) OR (herbal medicine[MeSH Terms])) OR (integrative medicine[MeSH Terms])) OR (chinese medicine, traditional[MeSH Terms])) OR (complementary medicine[MeSH Terms])) OR (complementary therapies[MeSH Terms])) OR (alternative medicine[MeSH Terms])) OR (euphorbia hirta[MeSH Terms])) OR (tawa-tawa [tiab])) OR (integrative medicine [tiab])) OR (chinese medicine [tiab])) OR (complementary medicine)) OR (alternative medicine)) AND ("COVID-19" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2") OR 19[tiab] OR 2019[tiab] OR "2019-nCoV" OR "Beijing" OR "China" OR "Covid-19" OR epidem*[tiab] OR epidemic* OR epidemy OR new[tiab] OR "novel"[tiab] OR "outbreak" OR pandem* OR "SARS-CoV-2" OR "Shanghai" OR "Wuhan" AND ("Coronavirus Infections"[Mesh] OR "coronavirus"[MeSH Terms] OR coronavirus*[all] OR corona-virus*[all] OR cov[tiab] OR pneumonia-virus*[tiab]))) AND ((((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt])	2986	0 Tawa-tawa 3- Other Chinese medicine
Pubmed	((((clinical trial [tiab]) OR (randomized controlled trial [tiab])) OR (randomized controlled trial[Publication Type])) AND (((((((euphorbia hirta[MeSH Terms]) OR (tawa-tawa [tiab])) OR (herbal* [tiab])) OR (herbal medicine)) OR (herbal medicine[MeSH Terms]))) AND ("severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2")	52	0 Tawa-tawa
Google	COVID and Tawa tawa	Ongoing trial Dr. Phillip Padilla Target completion: Sep 2021	
HERDIN	Tawa tawa	22	0
Google Scholar	Viral infection AND Tawa tawa	90	1
		Background purpose only	

Appendix 3. Characteristics of Ongoing Studies

Clinical Trial Identifier/ Title	Population	Intervention	Comparator	Outcome
PHRR210412-003475 **A randomized controlled clinical trial on the efficacy and safety of Tawa-tawa (*Euphorbia hirta* L.) extract as an adjunctive treatment for mild to moderate COVID-19 patients**	Patients with Mild or Moderate COVID-19 patients aged 18 to 59 years	Standardized aqueous spray-dried extract of *E. hirta* (U4bext®)	Current Guidelines for standard of care	Primary: Clinical improvement, defined as at least 2 categories of improvement from baseline Secondary: Time to Improvement of at least 2 Categories Relative to Baseline, Time to Clinical Failure [From first dose to time of death, mechanical ventilation, ICU admission, or study withdrawal], Time to resolution of symptoms, Time to normalization of biochemical/haematological parameters, Time to Hospital Discharge, Duration of Time on Supplemental Oxygen, Percentage of Participants with Adverse Events, Time to Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) Virus Negativity, Proportion of Participants with Post-Treatment Infection