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
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EVIDENCE SUMMARY

Should Lagundi (*Vitex negundo*) be used as adjunctive treatment for COVID-19 infection?

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RECOMMENDATION

There is no evidence to recommend Lagundi (Vitex negundo) as adjunctive treatment for patients with COVID-19 infection.

Consensus Issues
Considerations of the panel were the lack of completed studies to date and the possibility of misinterpretation, stemming from anecdotal accounts of relief of symptoms, which could lead to its use even without definite benefits.

Key Findings

Lagundi (*Vitex negundo*), a medicinal herbal cough remedy widely used in the Philippines, was considered a potential adjunctive treatment for COVID-19. We found no published studies on *Vitex negundo* on patients with COVID-19 but there is one completed local clinical trial whose full results are not yet available.

Introduction

There has been a resurgence of interest in *Vitex negundo*, already being used for other medical indications, for its potential as adjunctive treatment for COVID-19.

Lagundi is a woody shrub with bluish purple flowers recognized by the Department of Health as a treatment for respiratory complaints like cough and asthma.[1] The in vivo study by Haq et al. showed that the n-butanol fraction of *Vitex negundo* demonstrated inhibition of cough reflex in a dose-dependent manner.[2] The study of Patel et al. also showed that it can inhibit histamine formation through mast cell stabilization.[3] The iridoid and flavonoid fractions of the plant extract exhibited anti-inflammatory effects through inhibition of chemotaxis, phagocytosis and complement activation.[4] *Vitex negundo* also contains papaverine-like phosphopodiesterase inhibitors partly explaining its bronchodilatory effect.[5] Molecular docking studies show its inhibitory activity against papain like protease of SARS-CoV-2 indicating its potential use as an antiviral agent for COVID-19.[6] There was also a double-blind placebo-controlled trial which showed that Lagundi significantly improved the frequency of cough and color of sputum among older children.[7]

Review Methods

We performed a 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”, “Vitex negundo”, “Lagundi”, “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 these two plants.

Our PICO for this review was as follows: Population – patients with COVID-19; Intervention – lagundi; 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.

Communication with a local expert led us to a completed yet unpublished, local study on *Vitex negundo.* We are awaiting the full paper of Lazarte and co-investigators who conducted a two-stage, adaptive, multicenter parallel randomized clinical trial to determine 1) the appropriate dose and 2) the efficacy of Lagundi plus standard of care in patients with COVID-19.[8]

Evidence to Decision

Vitex negundo is available in drugstores and health outlets, as well as online shopping sites, which show one price at Php8.00 per 600mg tablet.[9] The 2020 Philippine Drug Price Reference Index (DPRI) shows the mean price of the same preparation at Php2.90.[10]

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 Guideline, that make a recommendation on the use of Lagundi as adjunctive treatment for COVID 19.

Research Gaps

Randomized controlled trials investigating the efficacy and safety of Lagundi with specific dosing regimen for adult or pediatric patients with COVID-19 are needed.

References

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[8] Lazarte CC. 2-stage, Randomized, double-blind, placebo-controlled clinical trial on the efficacy and safety of Lagundi (Vitex negundo) tablets/syrup (NIRPROMP formulation) with standard treatment compared to placebo with standard treatment in patients with mild COVID-19 disease without comorbidities**.** [Internet]. Health Research and Development Information Network. 2021. Available from: https://www.herdin.ph/index.php/registry?view=research&layout=details&cid=2992

[9] ASCOF Forte Lagundi. Watsons. [homepage on the Internet]. 2021. Available from: https://www.watsons.com.ph/forte-lagundi-for-adults-600-mg-1-capsule/p/BP_10080988

[10] Department of Health Pharmaceutical Division. The Philippine Drug Price Reference Index. [Internet] 2020. Available from: https://dpri.doh.gov.ph/download/2020-DPRI-updated-as-of-03-05.pdf

Appendix 1. Evidence to Decision

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

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS
Problem	No (3)	Yes (5)					
Benefits	Large	Moderate (1)	Small (2)	Uncertain (5)			• No research evidence found. • Experience from a mild case: can relieve symptoms of COVID such as cough, fever, headache and there could be more promising outcomes if studies are continued. (n=1)
Harm	Large	Small (2)	Uncertain (5)	Varies			• No research evidence found.
Certainty of Evidence	High	Moderate (2)	Low (3)	Very low (3)			• None
Balance of effects	Favors drug (1)	Does not favor drug	Uncertain (7)	Varies			• No research evidence found.
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate Cost (2)	Negligible cost (1)	Moderate savings (3)	Large savings (2)	• 1 cap of 600 mg of Lagundi – Php 3.75 to 8 per cap
Certainty of evidence of required resources	No included studies (2)	Very low (2)	Low (1)	Moderate (4)	High		• No cost-effectiveness studies available.
Cost effectiveness	No included studies (5)	Favors the comparison (1)	Does not favor either the intervention or the comparison (1)	Favors the intervention (1)			• No cost-effectiveness studies available.
Equity	Uncertain (3)	Reduced (2)	Probably no impact (1)	Increased (2)			• No cost-effectiveness studies available.
Acceptability	Uncertain (6)	No	Yes (2)	Varies			• *Panel: Lagundi is used for other respiratory diseases.*
Feasibility	Uncertain (1)	No (1)	Yes (6)	Varies			• No local studies available.

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 (Vitex negundo)) OR (Vitex negundo [tiab])) OR (lagundi [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 Lagundi; 3- Other Chinese medicine
Pubmed	((((clinical trial [tiab]) OR (randomized controlled trial [tiab])) OR (randomized controlled trial[Publication Type])) AND (Vitex negundo)) OR (Vitex negundo [tiab])) OR (lagundi [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 Lagundi
HERDIN	Lagundi	2	1
		Completed but not published Dr Cecilia Lazarte	
Google Scholar	Viral infection AND Lagundi vitex negundo	51	0
Google Scholar	Viral infection AND Lagundi	70	0

Appendix 3. Characteristics of Ongoing Studies

Clinical Trial Identifier/ Title	Population	Intervention	Comparator	Outcome
PHRR210126-002992 2-stage, Randomized, double-blind, placebo-controlled clinical trial on the efficacy and safety of Lagundi (Vitex negundo) tablets/syrup (NIRPROMP formulation) with standard treatment compared to placebo with standard treatment in patients with mild COVID disease without comorbidities	Patients diagnosed with Mild COVID 19 aged 19-55 years old (278)	Lagundi (NIRPROMP Formulation tablet or syrup)	Placebo	Primary: Mean clinical recovery time (normalization of fever <37.3C, respiratory rate <25, oxygen saturation >94% on room air and alleviation of cough for 72hours) Secondary: Time to RTPCR negative, Time to defervescence, Time to absent symptoms in days, Number of patients progressing to moderate disease and Type, frequency and severity of adverse effects