

# Prevalence of COVID-19 Complications during a Program of Homeopathic *Camphora Officinalis* Distribution to City Populations of Santa Catarina, Brazil: An Ecological Study

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## Abstract

**Background** Coronavirus disease 2019 (COVID-19), a disease caused by the SARS-CoV-2 coronavirus, was declared a pandemic in March 2020, posing significant challenges globally. Homeopathy has historical relevance in epidemic management. In response, the government of the state of Santa Catarina, Brazil, distributed *Camphora* 1M as a potential prophylactic intervention for COVID-19.

**Objective** This study aimed to investigate the possible effects of *Camphora* 1M as an adjunctive prophylactic measure in managing COVID-19, focusing on mortality and hospitalization rates, during the period April 28 to July 31, 2020, within designated COVID-19 in-patient units in Santa Catarina.

**Methods** An ecological study design was applied to this epidemiological research. Five case municipalities (Itajaí, Atalanta, Entre Rios, Rio do Campo, Trombudo Central) were compared with five control municipalities (São José, Galvão, Pedras Grandes, Grão-Pará, Ascurra).

**Results** No statistically significant differences were observed in predictor variables between municipalities that received *Camphora* 1M and the respective controls. Similarly, no statistically significant differences were observed in outcomes: deaths ( $p = 0.879$ ), hospitalized cases ( $p = 0.537$ ), daily ward admissions ( $p = 0.730$ ) and ICU admissions ( $p = 0.072$ ).

**Conclusion** For the first wave of the pandemic in the state of Santa Catarina, Brazil, city-wide distribution of *Camphora* 1M was not associated with reduced numbers, severity or mortality among the population hospitalized in designated public hospitals for COVID-19.

## Keywords

- ▶ *Camphora*
- ▶ COVID-19
- ▶ homeopathy
- ▶ pandemic

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## Introduction

Since December 2019, reports of several cases of pneumonia, initially emerging in Wuhan, China, and associated with an RNA virus identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been designated as “coronavirus disease 2019” (COVID-19), with its pandemic status declared in March 2020.<sup>1</sup> This pathogen primarily targets the human respiratory tract, often leading to a syndrome that can progress to critical respiratory conditions, systemic hyperinflammation, acute respiratory distress syndrome and disseminated intravascular coagulation, necessitating intensive care unit (ICU) management.<sup>2</sup> Hospitalized patients with underlying health conditions, comprising approximately 20% of cases, require ICU admission.<sup>3</sup>

In this context, several variables have been studied in relation to the severity of COVID-19. Ecological studies outline these variables,<sup>4</sup> yet a more meticulous examination is essential to prevent biased diagnoses associated with COVID-19. For instance, factors such as the following warrant thorough investigation: previous or concurrent BCG vaccination<sup>5,6</sup>; the adequacy of health systems<sup>7</sup>; influenza as co-morbidity or the effect of influenza vaccination; prevalence rates of cardiovascular diseases, Kawasaki disease and other co-morbidities; population size and density; the proportion of elderly individuals; consumption of alcohol-based sanitizers; utilization of imaging tests<sup>8–11</sup>; household density and social inequalities<sup>12–14</sup>; ethical and legal considerations related to isolation protocols<sup>15</sup>; gender disparities<sup>16</sup>; adherence to mask-wearing guidelines<sup>17</sup>; mobility patterns and gatherings<sup>18</sup>; and the prevalence of undiagnosed cases.<sup>19</sup> Although these studies offer valuable insights into the severity of COVID-19, it is essential to be wary of the ecological fallacy of making any link to the diagnosis of an individual.<sup>4</sup> Nonetheless, an integrated analysis suggests that COVID-19 prevalence tends to be higher among vulnerable demographic groups.<sup>7–14</sup>

The utilization of homeopathy in addressing epidemics traces back to the era of its founder, Dr. Samuel Hahnemann, who employed *Belladonna* as a prophylactic agent during a scarlet fever epidemic in Europe. Throughout the 19th century, homeopathy was frequently applied in various outbreaks, including cholera, yellow fever, influenza and typhus.<sup>20–23</sup> Different methods exist for employing homeopathic medicines in epidemic scenarios, which may involve individual administration, combination of remedies in complexes, preparation from the etiological agent itself (isotherapy or biotherapy) or identification of the so-called *genus epidemicus*<sup>23–25</sup> in which prevailing clinical manifestations in the majority of individuals afflicted by a specific infectious disease are considered to establish treatment protocols.<sup>21</sup> Presently, several reports suggest some efficacy of homeopathy in epidemic management,<sup>24–29</sup> yet uncertainties persist regarding SARS-CoV-2 due to its pleomorphism and significant mutational potential.<sup>30–32</sup>

Among the medications proposed by the international homeopathy community for prophylactic use in COVID-19 was *Camphora officinalis* 1M, which is derived from the *Cinnamomum camphora* plant, a remedy with historical origins dating back to Hahnemann’s era, initially described in

1805.<sup>33,34</sup> *Camphora* is listed in the Brazilian Homeopathic Pharmacopeia.<sup>35</sup> The proposed single dose of *Camphora* 1M as a possible mitigating agent for the disease prompted the government of the state of Santa Catarina to authorize the deployment of homeopathy as an adjunctive practice alongside the standard recommendations of the Ministry of Health/World Health Organization<sup>36</sup> for the prevention and treatment of COVID-19 in 2020. This decision followed the release of two significant documents: (1) a technical note issued by the Santa Catarina State Health Department outlining various guidelines regarding the use of integrative and complementary practices for the COVID-19 pandemic<sup>37</sup>; (2) guidelines published by the Medical Homeopathic Association in Santa Catarina state, Brazil, and the Brazilian Pharmaceutical Homeopathy Association regarding the application of homeopathy in COVID-19 prevention and treatment as an adjuvant intervention.<sup>38</sup>

Prophylactic and therapeutic options for infectious diseases, including COVID-19, were based on the concept of *genus epidemicus*, which received considerable attention during the pandemic,<sup>39,40</sup> emphasizing that these initiatives were implemented during the initial “wave” of the pandemic when vaccines were not yet available. Herein we report an epidemiological study following the ecological model<sup>4,41</sup> that was designed to evaluate the association between the use of *Camphora* 1M as an adjunctive attenuating and prophylactic agent—in tandem with other official measures—and the prevalence of COVID-19 complications in the five municipalities participating in the campaign, which lasted until July 31st, 2020.

## Objectives

To assess the association between the utilization of *Camphora* 1M as a prophylactic adjunctive intervention to mitigate the impact of COVID-19 on (1) the number of COVID-19-related deaths (primary objective), as well as (2) the number of hospitalized patients due to COVID-19, including the daily ward rates and the daily ICU rates for all municipalities in this study (secondary objectives), prioritized in that order of significance. Reference public hospitals designated for COVID-19 admissions in each municipality participating in the *Camphora* 1M campaign were consulted, alongside the respective control municipalities (cities in Santa Catarina State with similar demographic characteristics but not adhering to the campaign).

## Methods

### Study Design

Given the interest in determining prevalence at the population level, an ecological study design was employed as the most appropriate epidemiological model for analyzing aggregated data.

### Ethical Considerations

The research project, which followed that outlined by the World Medical Association in the Declaration of Helsinki,<sup>42</sup> received approval from the ethics committee of Universidade

Paulista (approval number 4.326.088), as documented in *Plataforma Brasil*—CAAE: 36429720.9.1001.5512. The proposal did not present ethical restrictions for implementation, given that the study unit comprises municipalities (ecological model), and the data collected are epidemiological in nature and publicly available. Additionally, the research protocol was registered in compliance with ReBEC (Brazilian Clinical Trials Registry)—RBR-6bckd5p: <https://ensaiosclinicos.gov.br/rg/RBR-6bckd5p>.

### Exposure Variable

To each volunteer who accepted to participate, *Camphora* 1M, prepared in five globules contained in a microtube, was administered as a single dose by a member of health care personnel from basic health units in municipalities participating in the campaign. Each dosage was overseen by a designated responsible physician in every city.

### Inclusion and Exclusion Criteria for Sample Definition

The study framework is situated within the state of Santa Catarina. The following inclusion criteria were established:

- Municipalities in Santa Catarina that have formally implemented (by decisions of each municipal government) the widespread distribution of *Camphora* 1M.
- Control municipalities in Santa Catarina with demographic and epidemiological profiles most closely resembling those of the test municipality (profiles were rated as 1 or 2 based on the variable type, as detailed below).

The exclusion criteria were defined as follows:

- Municipalities dissimilar to the adherent municipalities in terms of the parameters described in the predictor variables to be used as controls.
- Municipalities outside Santa Catarina, Brazil, regardless of group affiliation.

### Observation Period

The prevalence of the variables related to the “outcome” was assessed 90 days after the beginning of *Camphora* 1M distribution in each participating municipality. The cities and initial distribution dates were as follows: Itajaí, April 28th; Atalanta, February 6th; Entre Rios, May 8th; Rio do Campo, May 4th; and Trombudo Central, May 4th. The assessment period extended from April 28th to July 31st, covering the first and last observation points. Only the above five municipalities adhered to the campaign: that is, Itajaí, Atalanta, Entre Rios, Rio do Campo and Trombudo Central. During this timeframe in 2020, Brazil was experiencing its first wave of the pandemic, and anti-SARS-CoV-2 vaccines were not yet available in any country.

According to the respective official municipal reports (“news” or “transparency platform”) accessible online as of December 2023, Itajaí received 42,917 doses (reported on July 17th, 2020) for a population exceeding 183,373, achieving 23% coverage; Atalanta, 3,100 doses (reported on May 22nd and 28th, 2020) for a population of 3,310, achieving 93% coverage; Entre Rios, 3,100 doses (reported on May 7th, 2020) for a population of 3,332, achieving 93%

coverage; Rio do Campo, 1,500 doses (reported on June 7th, 2020) for a population of 6,167, reaching 24% coverage; Trombudo Central, 1,500 doses (reported on May 4th, 2020) for a population of 7,360, reaching 20% coverage.

### Definition of Control Municipalities

The selection of control municipalities occurred in two stages: the first stage involved a preliminary screening based solely on general demographic characteristics (pre-selection). In contrast, the second (final) stage consisted of a detailed comparison of specific demographic and epidemiological traits between case municipalities and pre-selected control candidates.

The following variables were considered for the preliminary screening: population size, land area (km<sup>2</sup>), Global Positioning System coordinates within the state, number of inhabitants, altitude (m), area (km<sup>2</sup>), population density, Human Development Index—average (HDI-A) and Gross Domestic Product (GDP). Data were sourced from the Brazilian Institute of Geography and Statistics (IBGE) website related to the 2010 national census, as available in 2020, and the Technical Report of Santa Catarina state’s Information Centre for Environmental and Hydrometeorological Studies (CIRAM).

The municipalities considered at this stage included: Itajaí, Joinville, Entre Rios, Rio do Campo, Balneário Piçarras, Barra Velha, Trombudo Central, Atalanta, Chapecó, Criciúma, São José, Florianópolis, Blumenau, Arroio Trinta, Galvão, Pedras Grandes, Witmarsum, Braço do Norte, Pomerode, São João Batista, Sombrio, Águas Mornas, Angelina, Bela Vista do Toldo, Campo Belo do Sul, Grão-Pará, José Boiteux, Paulo Lopes, Timbé do Sul, Capinzal, Capivari de Baixo, Garopaba, São João Batista, Sombrio, Antônio Carlos, Ascurra, Balneário Gaivota and Passo de Torres.

The level of similarity in general demographic characteristics between case municipalities and respective control candidates was used to rank the cities for the subsequent evaluation. They were grouped accordingly. Thus, the first group was composed of Itajaí (case municipality), along with Chapecó, Criciúma and São José (potential control municipalities). The second group included Atalanta (case municipality), along with Arroio Trinta, Galvão, Pedras Grandes and Witmarsum (potential control municipalities). The third group corresponded to Entre Rios (case municipality), along with Arroio Trinta, Galvão, Pedras Grandes and Witmarsum (potential control municipalities). The fourth group consisted of Rio do Campo (case municipality), along with Águas Mornas, Angelina, Bela Vista do Toldo, Campo Belo do Sul, Grão-Pará, José Boiteux, Paulo Lopes and Timbé do Sul (potential control municipalities). Finally, the fifth group included Trombudo Central (case municipality), along with Antonio Carlos, Ascurra, Balneário Gaivota and Passo de Torres (potential control municipalities).

For the final selection, the pre-selected municipalities underwent analysis based on each case’s specific demographic and epidemiological characteristics. Data were provided from the following entities: (1) the IBGE website about the 2010 national census, as available in 2020; (2) the

technical report of CIRAM; (3) the health department of participating municipalities; (4) the Superintendence of Planning and Management of the Health Department, Santa Catarina state; (5) the Epidemiological Bulletins of Santa Catarina state and its municipalities; and (6) data from the Unified Health System in Brazil (DATASUS; <http://tabnet.datasus.gov.br/tabdata/livroidb/2ed/indicadores.pdf>).

Next, scores 1 or 2 were assigned based on the relevance of variables, with demographic variables receiving a score of 1 and epidemiological variables receiving a score of 2, considering their resemblance to the corresponding case municipality. For instance, a score of 2 was given to epidemiological variables closely aligned with those of the respective case municipality in accordance with the groups generated in the initial step. Ultimately, the ranking of each pre-selected city was defined by the sum of scores. The municipalities with the highest scores were selected as the respective controls for the five case municipalities. The parameters used to determine scores 1 or 2 are detailed as follows:

- **Score 1 predictive variables:** gross domestic product per capita in 2019 (updated by Google); average income based on minimum wages as a reference of formal workers; percentage of males; percentage of females; predominant age group in 2010; urban population rate in 2010; rural population percentage in 2010; religious population percentage in 2010; predominant religion; percentage of married individuals; percentage of individuals with higher education; percentage of individuals with primary education; percentage of individuals with secondary education; main economic activity of the city; average temperature and rainfall for April to July 2017, 2018 and 2019.
- **Score 2 predictive variables:** date of the first COVID-19 case occurrence; date of social isolation decree during the period; date of the mandatory mask-wearing decree; percentage of basic sanitation coverage during the period; percentage of coverage of the family health program in April, May and June of 2020; the average number of outpatient consultations between April and July 2019; average number of hospitalizations per month between April and July 2019; vaccination rate (dose/inhabitant) for influenza in 2020 (influenza [INF, Campaign, pregnant women]; influenza A—H1N1; influenza A—H1N1 [pregnant women]); vaccination rate (dose/inhabitant) for common childhood diseases in 2019 (BCG; rubella, measles, chickenpox, double infantile [DT], oral poliomyelitis [VOP], triple virus [SCR]). Influenza vaccination data were included as predictive epidemiological variables, representing a source of non-specific antiviral immunity.

The geographic locations of the case and control municipalities are illustrated in ► **Supplementary File 1** (available in the online version).

### Outcomes

The outcomes were derived from the following variables:

- Number of deaths from COVID-19 within the same period and admitted to the same hospital (primary objective).

- Number of confirmed cases of COVID-19 hospitalized in each municipality's reference hospital during the period April 28 to July 31, 2020.
  - Daily ward rates of COVID-19 cases at reference hospitals during the period April 28 to July 31, 2020.
  - Daily ICU rates of COVID-19 cases at reference hospitals during the period April 28 to July 31, 2020.

The public hospitals designated by each municipality for COVID-19 in-patient treatment were outlined in Ordinance GAB/SES No. 246 of April 14, 2020. They are as follows:

- **Itajaí (case):** Marieta Hospital, Pequeno Anjo Hospital/**São José (control):** São José Regional Hospital.
- **Atalanta (case):** Bom Jesus de Ituporanga Hospital/**Galvão (control):** São Lourenço do Oeste Hospital.
- **Entre Rios (case):** São Paulo de Xanxerê Hospital/**Pedras Grandes (control):** Nossa Senhora da Conceição—Tubarão City Hospital.
- **Rio do Campo (case):** OASE Hospital in Timbó—Alto Vale/**Grão-Pará (control):** North Branch Santa Terezinha Hospital, and Nossa Senhora da Conceição—Tubarão City Hospital.
- **Trombudo Central (case):** OEASE Hospital de Timbó/**Ascurra (control):** OASE Hospital de Timbó; Dr. Valdomiro Colantti Hospital in Ibirama.

The epidemiological control sector of each hospital provided data.

### Statistical Analysis

A double correction and double checks of the compiled data were done at different stages to minimize the risk of possible typing errors. Statistical analysis was conducted using SPSS 17.0 software. Descriptive statistics, including frequencies, measures of central tendency and measures of dispersion, were obtained according to the variable type. For continuous variables, the inspection of data for Normality was assessed by Shapiro–Wilk tests and Q–Q plots. Data are reported as mean ± standard deviation, unless otherwise stated. A paired-sample *t*-test was used to determine whether there was a statistically significant mean difference between case and control municipalities when differences were Normally distributed. Otherwise, a Wilcoxon signed-rank test was conducted (for ordinal level or non-Normally distributed continuous variables). A significance level of 5% was adopted in all cases.

### Results

The homogeneity observed between the statistically analyzed groups is noteworthy, indicating a sound strategy in selecting the controls. A score of 1 was assigned to demographic variables. In contrast, a score of 2 was attributed to epidemiological ones, with no significant differences observed between the groups according to the *t*-test (► **Table 1**) and the Wilcoxon signed-rank test (► **Table 2**).

► **Tables 1 and 2** reveal comparable results between the test and control municipalities concerning key variables associated with population vulnerability to infection and

**Table 1** Analysis of differences between case and control municipalities in variables with Normal distribution, using Student's *t*-test for dependent samples

Variable	Mean ± SD		Mean difference	95% CI	p-Value
	Case	Control			
Area (km <sup>2</sup> )	219.10 ± 175.05	177.18 ± 87.70	41.92	[-87.76;171.61]	0.420
Altitude (m)	318.4 ± 246.21	176.80 ± 266.31	141.6	[-128.84;412.04]	0.220
Average temperature (°C) <sup>a</sup>	16.31 ± 2.43	14.73 ± 2.57	1.58	[-1.35;4.52]	0.209
Rainfall index <sup>a</sup>	92.08 ± 52.76	113.83 ± 51.90	-21.75	[-135.71;92.21]	0.624
Influenza vaccinated people rate (%)	6.10 ± 7.50	1.82 ± 2.31	4.28	[-4.34;12.90]	0.240
Municipal HDI	0.738 ± 0.053	0.685 ± 0.144	0.053	[-0.121;0.227]	0.444
Average income <sup>b</sup>	2.34 ± 0.47	2.04 ± 0.27	0.3	[-0.04;0.64]	0.071
Sanitation (%)	76.08 ± 16.14	63.34 ± 32.94	12.74	[-37.71;63.19]	0.522
Urban population (%)	55.07 ± 25.06	66.86 ± 26.88	-11.79	[-26.23;2.65]	0.086
Rural population (%)	44.92 ± 25.06	33.13 ± 26.88	11.79	[-2.65;26.23]	0.086
Religious population (%)	97.66 ± 3.66	97.56 ± 4.18	0.09	[-1.03;1.22]	0.828
Married population (%)	44.33 ± 8.90	43.47 ± 6.17	0.87	[-16.68;18.42]	0.897
First case of COVID-19 <sup>c</sup>	-	-	8.8	[-30.35;47.95]	0.566
Mask-wearing decree <sup>c</sup>	-	-	26.8	[-12.08;65.68]	0.128

Abbreviations: CI, confidence interval; HDI, Human Development Index; SD, standard deviation.

<sup>a</sup>Average between April and July 2017 to 2019.

<sup>b</sup>Minimum wages for formal workers.

<sup>c</sup>Difference in days. A *t*-test was conducted to assess if the mean difference could be considered significantly different from zero.

**Table 2** Analysis of differences between case and control municipalities in variables with non-Normal distribution, using the Wilcoxon signed-rank test

Variable	Median and IQR		z-Score	p-Value
	Case	Control		
N inhabitants	6,167 (4028)	6,278 (3576)	1.888	0.063
Population density <sup>a</sup>	35.01 (31.63)	28.51 (44.89)	1.079	0.313
GDP per capita (R\$)	30,763.79 (51,047.42)	34,444.66 (9,266.36)	0.539	0.625
N outpatient appointments <sup>b</sup>	4,511 (763)	6,485 (388)	1.888	0.063
N average hospitalizations/month	49.25 (32.25)	51.75 (52.00)	1.888	0.063
Vaccinated people rate <sup>c</sup>	16 (9)	13 (4)	1.079	0.313
Family health coverage (%)	100 (6.25)	100 (13.03)	0.894	0.500
Male (%)	50.33 (2.20)	49.64 (1.55)	0.000	1.000
Female (%)	49.66 (1.45)	50.33 (1.54)	1.079	0.313
Prevailing age group	0–14 y	0–14 y	0.000	1.000
Higher education (%)	4.61 (1.17)	5.34 (1.20)	0.270	0.813
High school education (%)	18.39 (5.42)	17.11 (1.69)	0.270	0.813
Primary level education (%)	77.00 (8.32)	77.89 (2.59)	0.270	0.813
Social isolation decree <sup>d</sup>	-	-	0.544	0.500

Abbreviations: GDP, gross domestic product; IQR, inter-quartile range.

<sup>a</sup>Number of inhabitants per square meter.

<sup>b</sup>Average between April and July 2017 to 2019.

<sup>c</sup>BCG, rubella, measles, varicella, infant double, polio and MMR.

<sup>d</sup>Difference in days. A *t*-test was conducted to assess if the mean difference could be considered significantly different from zero.

**Table 3** Analysis of differences between case and control municipalities in number of deaths per 100,000 people, using Student's *t*-test for dependent samples

Municipalities (case and control)	Deaths per 100,000 people		Mean difference	95% CI	<i>p</i> -Value
	Case	Control			
Itajaí and São José	28.36	178.03	−6.38	[−115.82;103.06]	0.879
Entre Rios and Pedras Grandes	90.04	0.00			
Rio do Campo and Grão Pará	0.00	0.00			
Trombudo Central and Ascurra	40.76	13.02			
Atalanta and Galvão	0.00	0.00			
Mean	31.83	38.21			

Abbreviation: CI, confidence index.

**Table 4** Analysis of differences between case and control municipalities in number of cases hospitalized for COVID-19 per 100,000 people, using the Student's *t*-test for dependent samples

Municipalities (case and control)	Number of cases per 100,000 people		Mean difference	95% CI	<i>p</i> -Value
	Case	Control			
Itajaí and São José	99.80	243.32	87.28	[−271.63;446.20]	0.537
Entre Rios and Pedras Grandes	600.24	24.35			
Rio do Campo and Grão Pará	48.65	0.00			
Trombudo Central and Ascurra	95.11	26.03			
Atalanta and Galvão	30.21	143.88			
Mean	174.8	87.52			

Abbreviation: CI, confidence interval.

**Table 5** Analysis of differences between case and control municipalities in daily ward rate per 100,000 people, using Student's *t*-test for dependent samples

Municipalities (case and control)	Daily ward rate per 100,000 people		Mean difference	95% CI	<i>p</i> -Value
	Case	Control			
Itajaí and São José	468.44	1,346.39	255.02	[−1657.75;2164.78]	0.73
Entre Rios and Pedras Grandes	2,965.19	97.39			
Rio do Campo and Grão Pará	209.18	0.00			
Trombudo Central and Ascurra	43.48	104.13			
Atalanta and Galvão	0.00	863.31			
Mean	737.26	482.24			

Abbreviation: CI, confidence interval.

the advancement of COVID-19. These variables include the average HDI, high school education and coverage of family health and middle-income programs.

For each of three variables, the data consist of records of *dates*. Thus, for the variables “First Case of COVID-19” (►Table 1), “Mask-Wearing Decree” (►Table 1) and “Social Isolation Decree” (►Table 2), the difference in days was estimated between pairs of municipalities, and appropriate analyses were conducted.

Regarding the outcomes analysis, ►Tables 3–6 present statistical comparisons concerning death and hospitalization

parameters between the case and control municipalities. No significant differences were observed.

## Discussion

No statistically significant differences were observed between the case and control units regarding patients admitted to public reference hospitals for COVID-19 in the studied municipalities of the state of Santa Catarina, Brazil. The homogeneity between test and control municipalities confirmed the validity of the methodological selection model.

**Table 6** Analysis of differences between case and control municipalities in daily ICU rate per 100,000 people, using Student's t-test for dependent samples

Municipalities (case and control)	Daily ICU rate per 100,000 people		Mean difference	95% CI	p-Value
	Case	Control			
Itajaí and São José	500.62	91.65	466.55	[-68.67;1001.77]	0.072
Entre Rios and Pedras Grandes	1,109.24	0.00			
Rio do Campo and Grão Pará	0.00	0.00			
Trombudo Central and Ascurra	945.65	312.38			
Atalanta and Galvão	181.27	0.00			
Mean	547.36	80.81			

Abbreviations: CI, confidence interval; ICU, intensive care unit.

Whilst multivariate analyses could be relevant for this type of ecological study, it might not be ideal due to the limited sample size, as seen herein. Indeed, large sample sizes are required for multivariate analysis to yield reliable results.<sup>4,42</sup> Many different “rules of thumb” have been proposed, and a minimum of 5 to 10 cases per variable has been recommended.

According to ►Tables 3–6, based on data disclosed by reference hospitals for COVID-19, no statistical significance was observed between the outcome variables when comparing case and control municipalities. Several interpretations could be inferred: (1) *Camphora* 1M could be inappropriate as a *genus epidemicus*. Later RCT studies have shown positive results with individualized treatment, viral nosode 30cH, *Bryonia* 30cH, *Arsenicum album* 30cH and *Natrum muriaticum* 2LM only,<sup>43–46</sup> though observational studies have pointed to other findings.<sup>47,48</sup> (2) The use of homeopathic medicine in a single dose might not be the most appropriate posology. Single-dose therapy in homeopathy for infectious and contagious diseases has been more successful in patients with individualized treatment.<sup>49</sup> (3) The potential use of different concomitant medications and their interactions with the homeopathic intervention, such as the use of corticosteroids in some cases, could constitute a confounding variable.<sup>50</sup>

Despite the population factors that could be considered as biased variables in ecological studies,<sup>51</sup> *Camphora* 1M was proposed in Iran at the pandemic's outset following a case series report,<sup>48</sup> with varying presentations between different peaks of case numbers,<sup>52</sup> indicating that it might not be the best remedy for the Brazilian population, considering its demographic characteristics and the pleomorphism of COVID-19's clinical evolution.<sup>30</sup> Treating diseases with varied pathogenesis and a wide range of symptoms, which can manifest differently as observed in COVID-19,<sup>30,53</sup> may diminish the alignment between medicine and disease per clinical homeopathic criterion. In Hong Kong, for example, medicines such as *Arsenicum* and *Gelsemium* were more prevalent among COVID-19 cases.<sup>54</sup> For this reason, an individualized homeopathy approach *a priori* could be more appropriate than applying *genus epidemicus*.<sup>44,46</sup>

In less urgent circumstances, conducting controlled clinical trials or long-term observational studies could provide more robust responses to determine clinical effectiveness or lack thereof. Clinical trials conducted later in India and Brazil showed the effectiveness of *Bryonia* 30cH, the isotherapeutic 30cH and *Natrum muriaticum* 2LM.<sup>43–45</sup> *Camphora* was not observed among the prevalent homeopathic medicines for COVID-19 in other countries, with *Arsenicum* and *Bryonia* being the most frequently listed in databases.<sup>40,47</sup> Nevertheless, using *Camphora* as the *genus epidemicus* presents some controversies.<sup>52–55</sup> Moreover, a repurposing of homeopathic medicines during the pandemic crisis was noted in clinical registrations in India, reflecting the heterogeneity of clinical manifestations and the evolution of COVID-19.<sup>56</sup> A recent study using homeopathic medicines as a COVID-19 prophylaxis tool in Kolkata, India, revealed inconclusive results due to the high variability of symptoms and prescriptions.<sup>57</sup>

Another aspect that must be considered is the distribution rate. Entre Rios and Atalanta cities received over 90% of doses/inhabitants, but Itajaí, Rio do Campo and Trombudo Central had only 20% of their inhabitants covered by the campaign. However, the absence of statistically significant differences between hospitalization rates for the cases and controls from the case and control municipalities, with the variance for the case being smaller than for the control municipalities, suggests a low impact of this discrepancy on the conclusion. On the other hand, safety was another point to be observed, since no increase in death or hospitalization ratio was seen.

Additional limitations of the study are related to the experimental model. In terms of outcomes, as an ecological-type survey involves comparing prevalences instead of occurrences, this study lacks analysis of the duration of hospitalizations, which should include days when patients were admitted before and after the observation period (May–July 2020). This could compromise data with more extended hospitalizations due to greater severity, beyond and before the deadlines stipulated for collection. Additionally, these data are restricted to public hospitals listed for the treatment of COVID-19, not representing the entire hospitalized population, which would include those in the partner

or private network, thereby implying a restriction of data sampling.

Individual analyses are not applicable in ecological studies since the unit of data in this type of study is not the individual, but municipalities and their COVID-19 reference hospitals. Although this type of study allows for identifying changes related to norms, it does not inform about prognosis or clinical effectiveness,<sup>41</sup> which is expected from randomized clinical trials.<sup>58</sup> Instead, ecological studies can be a valuable tool for testing health policies in a broad sense.<sup>4</sup>

## Conclusion

The population-level use of *Camphora* 1M showed no association with preventing numbers, severity or mortality of those admitted to reference public hospitals for COVID-19 in the municipalities of the state of Santa Catarina that adhered to the distribution campaign.

### Highlights

- An ecological study was performed in municipalities of the state of Santa Catarina, Brazil.
- *Camphora* 1M as a single dose was distributed but found not to be associated with the prevalence of COVID-19 deaths or hospitalization rates.
- Confounding variables could be present, impacting the epidemiological evaluation.
- A wide range of symptoms described for COVID-19 makes it challenging to define the *genus epidemicus*.

## Supplementary material

**Supplementary file 1.** State of Santa Catarina showing the study's 10 municipalities.

### Authors' contributions

A.P.O.: UFRJ collaborator. Search and analysis of data from Entre Rios and Pedras Grandes.

C.H.: UFRJ collaborator. Search and analysis of data from Rio do Campo and Gão Pará.

E.C.V.: UNIP post-doctoral student responsible for experimental design, compilation, data analysis and discussion.

E.N.C.: UFAL collaborator. Search and analysis of data from Atalanta and Galvão; search of general demographic data.

G.B.P.: UNIP collaborator, responsible for statistics/data analysis.

K.B.D.: ABFH collaborator. Search and analysis of data from Itajaí and São José.

L.V.B.: UNIP supervisor, project coordinator.

N.R.T.C.: UNIP under-graduate student. Search and analysis of data from Atalanta and Galvão.

V.E.B.: UERJ collaborator. Search and analysis of data from Trombudo Central and Ascurra.

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### Conflict of Interest

None declared.

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