# Phyllanthus niruri (stone breaker) herbal therapy for kidney stones; a systematic review and meta-analysis of clinical efficacy, and Google Trends analysis of public interest

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**Introduction:** Phyllanthus niruri (P. niruri) is the most commonly listed active ingredient in commercially available herbal therapies for kidney stones, despite limited supporting clinical evidence. We performed a meta-analysis to evaluate its efficacy in reducing stone burden. We used Google Trends to analyze its relative popularity in internet searches relative to conventional stone therapies.

Materials and methods: A comprehensive literature search for controlled human studies containing data on the effect of P. niruri treatment on stone size and number was performed. Pooled analysis of change in mean stone size and number with P. niruri was performed using a fixed-effects model. Standardized mean difference (SMD) and 95% CI were reported. Google searches in the United States within the "Health" category, for topics "Gale of the wind (P. niruri)", "Extracorporeal shockwave lithotripsy"

# Introduction

Kidney stones currently afflict nearly 1 in 11 adults in the United States, often imparting significant patient morbidity, and resulting in detriment to health-related quality of life and high treatment-related costs.<sup>1-3</sup> Recurrence rates exceed 50% within 10 years of the

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Address correspondence to Dr. Ephrem O. Olweny, Division of Urology, Rutgers Robert Wood Johnson, 1 Robert Wood Johnson Place, MEB 584-A, New Brunswick, NJ 08901 USA (ESWL), "Ureteroscopy" (URS), "Laser lithotripsy" (URSL) and "Percutaneous nephrolithotomy" (PCNL), conducted between January 2014 and December 2018, were quantified. Annual median relative search volumes (RSV; 0-100 scale) were compared using the Kruskal-Wallis test. Post-hoc pairwise comparisons were performed using the Dunn test with Holm-Sidak adjustment.

**Results:** Two studies met inclusion criteria. P. niruri treatment resulted in significant decreases in mean stone size (SMD -0.39 cm, 95% CI = -0.68 to -0.09, p = 0.01) and number (SMD -0.38, 95% CI = -0.68 to -0.09, p = 0.01). Median RSV for P. niruri was similar to that for ESWL, PCNL and URS through 2015, but was significantly higher than for ESWL and PCNL after 2015, and higher than for URS after 2016 (each p value  $p \le 0.0012$ ).

**Conclusions:** Limited clinical evidence supports modest efficacy of P. niruri in reducing stone burden, pending further study. Public interest in P. niruri is growing within the United States, possibly reflecting a rising demand.

Key Words: urolithiasis, naturopathy, internet

index stone,<sup>4</sup> leading many sufferers to seek preventive management, including dietary and pharmacologic therapy. Additionally, many urolithiasis patients seek out medical chemo-dissolution therapy so as to avoid surgery, but medications for this purpose are limited to date. Currently, the only chemolytic therapies endorsed by the American Urological Association (AUA) are urinary alkalinization for uric acid and cystine stones, cystine-binding drugs for cystine stones, and in rare cases, urease inhibitors for strutvite stones, but no agents for chemolysis of calcium stones are currently recommended.<sup>5</sup> Accordingly, many chronic stone formers seek out non-conventional alternatives, including herbal remedies. Several herbs used in Ayurvedic, Chinese and European herbal medicine have been described for this purpose,<sup>6-12</sup> many with purported claims of ability to dissolve stones despite lack of clinical evidence. Phyllanthus niruri (P. niruri) is a widely available herbal remedy for kidney stones, commonly used in Brazil,<sup>13</sup> and is also widely commercially available in the United States as "Stone Breaker". It is also a key ingredient in numerous other commercially available herbs such as "Chanca Piedra", "Stone Crusher" and "Disolvatol" to name a few. It has been widely evaluated in in vitro and in vivo pre-clinical studies, as well as a handful of clinical trials.<sup>14</sup> However, data on its clinical efficacy with regard to stone elimination or reduction in size and number are conflicting.<sup>13,15</sup> Additionally, quantitative data on the public's demand for *P. niruri* are lacking. We performed a systematic review and meta-analysis of the available clinical literature on *P. niruri*, with the primary goal of evaluating its efficacy in reducing stone burden (size and number). Additionally, using Google Trends methodology, we quantitated the public's interest in P. niruri, by analyzing internet search volume for it relative to search volume for conventional kidney stone surgeries.

# Materials and methods

#### Systematic review and meta-analysis

The systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist whenever possible.<sup>16</sup> PubMed, Google Scholar, the Cochrane Library, and SCOPUS databases were searched, and articles reporting on effects of *P. niruri* on kidney stones, published through March 31, 2019 were selected for further screening. We included controlled studies performed in humans, reporting data on the effect of P. niruri treatment on stone size and number, published in English. We excluded pre-clinical in vitro and in vivo studies, review articles, toxicity studies and studies reporting on effects of *P. niruri* other than for kidney stone treatment. The literature search was independently performed by 2 reviewers, with data extracted into identical extraction tables. Pooled analysis of change in mean stone size and number following P. niruri treatment was performed using a fixed-effects model, with standardized mean difference (SMD) and 95% confidence interval (CI) reported. Heterogeneity was assessed by calculating the I<sup>2</sup> value.

#### Google Trends methodology

Google Trends is a free, publically accessible online portal that enables quantitation of the volume of internet searches for a user-specified topic. It is increasingly used in health care to gain insights into disease epidemiology and population health behaviors.<sup>17,18</sup> Search words can be defined as "terms" or "topics"; "term" searches return matches on all terms entered in the language given, while "topics" searches group together several terms that share a common concept, in any language. Absolute number of internet searches on a specified subject is divided by the total volume of searches on all topics conducted during the same specified time period within a specified geographic region. Relative search volume (RSV) for each search subject, a measure of its relative popularity, is reported on a 0-100 scale.<sup>19</sup>

We determined RSV for the following topics: "Gale of the wind" (*P. niruri*), "Extracorporeal shockwave lithotripsy" (ESWL), "Ureteroscopy" (URS), "Laser lithotripsy" (URSL) and "Percutaneous nephrolithotomy" (PCNL), for searches performed in the United States between January 1, 2014 and December 31, 2018, under the query category "Health". Search data were downloaded on February 3, 2019. Median RSV values in each year were compared across the above 'topic' categories using the Kruskal-Wallis test. Posthoc pairwise comparisons of RSVs for the treatment modalities were performed using the Dunn test with Holm-Sidak adjustment for multiple comparisons. Stata version 15 (StataCorp LP, College Station, TX, USA) statistical software was used for statistical analyses.

# Results

# Study selection

A total of 21 articles of interest were retrieved from the database searches. Of these, 10 were review articles, 4 were in vivo animal studies and 4 were in vitro studies, resulting in exclusion. Only 3 clinical studies were identified, including 2 randomized controlled trials (RCTs)<sup>13,20</sup> and one prospective controlled study.<sup>15</sup> Of the RCTs, one reported on the effect of P. niruri on stone clearance rates following ESWL, but did not contain data on stone size and number<sup>20</sup> and was therefore excluded from the final analysis. Only two studies, one with 56 patients<sup>15</sup> and the other with 69 patients,13 contained data on changes in stone size and number following treatment with P. niruri, in both cases as secondary endpoints, Figure 1. The pooled data from these studies included 89 patients treated with P. niruri versus 92 controls who received placebo or no treatment.

# Effect on stone size and number

In study by Pucci et al 56 patients with radiographically confirmed stones, underwent 12 weeks of treatment with *P. niruri* followed by a 12-week washout. Each

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Figure 1. Study flow diagram.

patient served as their own control. Twenty-four hour urines and renal ultrasounds were obtained at baseline, immediately after *P. niruri*, and at the end of the washout phase,<sup>15</sup> and kidney stone size and number were documented for each phase. Compared with baseline, treatment with *P. niruri* resulted in significant reduction in mean (SD) number of stones from  $3.2 \pm 2.0$  to  $2.0 \pm 2.1$  (p = 0.0005), as well in reduction in mean stone size from  $1.56 \pm 1.06$  cm to  $0.94 \pm 0.89$  cm



Figure 2. Meta-analysis of *P. niruri* effect on size of stones.



Figure 3. Meta-analysis of *P. niruri* effect on number of stones.

(p = 0.0002). These effects were maintained during the washout phase. In study by Nishiura et al, 69 calcium stone formers were randomized to receive *P. niruri* (n = 33) versus placebo (n = 36) for a period of 3 months. Serum and 24 hr urine chemistries, as well renal ultrasonography were obtained at baseline and at the end of the study. In the *P. niruri* group, mean (SD) stone size and number post-treatment (0.6 ± 0.2 cm and 1.5 ± 1.4 respectively) did not significantly differ from pre-treatment values (0.6 ± 0.2 cm and 1.8 ± 0.9 respectively) or from placebo.<sup>13</sup>

In the pooled analysis, data for a total of 89 patients exposed *P. niruri* versus 92 controls were compared. Treatment with *P. niruri* was found to result in a significant decrease in mean stone size compared with placebo or no treatment (SMD -0.39 cm, 95% CI = -0.68 to -0.09, p = 0.01; I<sup>2</sup>=76%), Figure 2. *P. niruri* treatment also resulted in a significant decrease in number of stones compared with placebo or no treatment (SMD -0.38, 95% CI = -0.68 to -0.09, p = 0.01; I<sup>2</sup>=64%), Figure 3.



**Figure 4.** Internet search volume for *P. niruri* in comparison with conventional surgical therapies for kidney stones.

#### Google Trends data

Median RSV for *P. niruri*, ESWL, URS and PCNL was significantly higher than that for URSL in each year between 2014 and 2018 (p < 0.0001 in each case). For 2014 and 2015, median RSV for *P. niruri* was similar to that for ESWL and PCNL (p > 0.05 in each case), but for 2016 to 2018, median RSV for *P. niruri* significantly exceeded that for ESWL and PCNL in each year (p ≤ 0.0004 in each case). Median RSV for *P. niruri* was similar to that for URS during 2014-2016 (p > 0.05), but significantly higher than for URS in 2017 and 2018 (p ≤ 0.0012 in each case), Figure 4.

#### Discussion

Data from a 2007 National Health Interview Survey (NHIS), conducted by the National Center for Complementary and Integrative Health (NCCIH), a branch of the National Institutes of Health (NIH) reveal that approximately 38% of adults in the United States use some form of complementary and alternative medicine for a wide range of health conditions . Estimated expenditures for these therapies among United States adults totaled \$13 billion in 1993, majority paid outof-pocket.<sup>21</sup> *P. niruri* is the main ingredient of several naturopathic formulations for kidney stone treatment in commercial use in the United States. It is native to tropical areas and has been widely used worldwide for more than 2000 years in treating kidney stones.<sup>22</sup> In a recent review, Boim et al outlined much of the pre-clinical evidence supporting the possible beneficial role of P. niruri in kidney stone treatment.<sup>14</sup> In vitro, it was found to decrease calcium oxalate (CaOx) crystal size and aggregation, inhibit crystal adhesion and endocytosis, and to inhibit xanthine oxidase activity. In vivo, it was found to reduce the rate of CaOx stone growth independently of modifying other lithogenic factors, and to disrupt crystalmatrix interactions, resulting in smoothing of the surface of already formed CaOx stones.14

Anecdotally, many stone formers who use "stone breaker" believe that it is effective in dissolving kidney stones. In the present study, we analyzed the available clinical evidence for the efficacy of *P. niruri* in reducing stone burden. We found that although clinical studies are lacking overall, two prospective controlled studies, including one RCT, analyzed the effects of *P. niruri* on stone size and number as a secondary outcome.<sup>13,15</sup> In the pooled analysis of the data from these trials, *P. niruri* treatment over at least 3 months resulted in modest, statistically significant reductions in the size and number of calcium stones. However, the pooled comparisons were characterized by significant heterogeneity (I<sup>2</sup> = 76% for stone size and 64% for stone number), which we believe

is partly due to the fact that the outcomes evaluated in our analysis were not the primary outcomes assessed in the individual studies, and the selection of control groups varied between the trials. Nonetheless we believe that the use of a fixed effects meta-analysis was justified, in that the two trials both sought to measure near-identical primary and secondary endpoints, each used P. niruri in the intervention arms for a period of 3 months, and each obtained P. niruri using near-identical extraction methods from the natural plant i.e. tea prepared from the dry plant extract, which was delivered using different modalities (tea capsule versus infusion tea). In a separate RCT comparing stone clearance rates post-ESWL for those receiving adjuvant P. niruri versus no additional therapy, Micali et al observed that although there was no overall difference between the groups in the overall stone free rate, stone free rates for patients with lower pole stones were significantly higher for those who received P. niruri therapy.<sup>20</sup> Collectively the above findings suggest that P. niruri may have a clinically significant role in reducing stone burden, but additional larger clinical studies are needed to better explore its efficacy.

Our analysis of search data available through Google Trends revealed that searches for P. niruri were as popular, and in more recent years significantly more popular than searches for conventional kidney stone treatments performed during the corresponding time period in the United States. Google Trends is a relatively novel tool which is increasingly used in epidemiological research to gain insights into health information seeking behavior of populations, methodology sometimes referred to as "infodemiology".18,23 Use of internetbased data is recognized by the Institute of Medicine as an emerging tool that has the potential to complement and extend more traditional epidemiologic surveillance methods.<sup>24</sup> In the setting of nephrolithiasis, Google search data have been found to strongly correlate with data for kidney stone hospitalizations available through the National (Nationwide) Inpatient Sample (NIS) database.<sup>25</sup> Our findings point to growing information seeking behavior within the United States public for *P. niruri* in recent years. Considering that subjects who seek information about a personal health problem are 60% more likely to contact a health professional following search,<sup>26</sup> we postulate that for a large proportion of people, seeking information about P. niruri will likely translate towards future efforts to acquire it for therapeutic purposes, suggesting a growing public demand despite limited supporting clinical evidence.

Although to our knowledge our study is the first to evaluate the clinical efficacy of *P. niruri* by pooled analysis of the available evidence, and also the first to examine

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the public's information seeking behavior for this herb relative to conventional treatments for stone disease, it is not without its limitations. Firstly, the number of clinical studies and treated patients is small, limiting the power to estimate its true clinical impact. Nonetheless we believe that the totality of the evidence from completed studies to date points to a potential benefit, and that further largerscale studies are warranted. Secondly, search results for P. niruri on the Google Trends platform could have included searches for its use in health conditions other than kidney stones, resulting in overestimation. However, P. niruri is most commonly used worldwide for kidney stone treatment, having been used for this purpose for over 2000 years,<sup>22</sup> and we therefore believe that a majority of the searches were with regard to its use for kidney stones. Third, although insights into the public's demand for *P*. niruri were obtained by analysis of internet search data, its actual utilization as a treatment alternative in stone disease was not directly measurable. Nonetheless taking into consideration the observations regarding trends in internet search behaviors, the widespread, centuries-long use of *P. niruri* for kidney stone treatment, and anecdotal evidence, we believe there is a potentially high and growing demand for it, which could likely continue to rise.

#### Conclusion

Based on limited clinical evidence, *Phyllanthus niruri* (stone breaker) appears to have some efficacy in reducing stone burden in kidney stone patients, but it needs reevaluation in larger-scale clinical studies to better assess its true efficacy in this regard. Analysis of internet search behaviors suggests that public interest for it within the United States is growing, exceeding that for conventional surgical interventions for stone disease in recent years, possibly suggesting a growing public demand. A better understanding of its current and projected utilization in kidney stone treatment is needed.

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