Herbal Therapy and Stable COPD: Delaying Onset and Duration of Acute Exacerbations with Supplementation to Baseline Therapy

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Recommended Citation
Hernandez, Amy M., "Herbal Therapy and Stable COPD: Delaying Onset and Duration of Acute Exacerbations with Supplementation to Baseline Therapy" (2013). School of Physician Assistant Studies. 471.
https://commons.pacificu.edu/pa/471
Herbal Therapy and Stable COPD: Delaying Onset and Duration of Acute Exacerbations with Supplementation to Baseline Therapy

Abstract

Background: Patients with chronic obstructive pulmonary disease (COPD) experience progressive pulmonary decline with each acute exacerbation of disease. Current therapy is focused on treating acute symptoms of COPD, but there are no medications that have been implemented to delay the progression of the disease. Herbal therapies have been developed by researchers to supplement baseline therapy for COPD with the goal of prolonging healthful pulmonary states, thereby slowing disease progression.

Methods: Exhaustive search of available medical literature from Medline, CINAHL, Web of Science, EBMR and NIH websites was conducted using the keywords: COPD, herbal therapy, and treatment outcomes.

Results: The search produced nine articles for evaluation. Two articles were chosen that met the inclusion criteria of this systematic review. Both studies are randomized controlled trials, which support the use of herbal remedies as a supplement to baseline COPD therapy. One study investigated the use of Pelargonium sidoides, an African geranium, for effective supplemental therapy. The second study performed research on the use of three unique traditional Chinese medicine (TCM) formulations as supplemental therapy for stable COPD. While the results of both studies reflect data that indicates that these herbal supplements are effective in extending the length of duration between acute exacerbations, and decreasing the length of acute exacerbations, further research is necessary to increase confidence in their use.

Conclusion: Use of herbal therapies such as P. sidoides and TCM are promising modalities to maintain wellness in patients with stable COPD when used as a supplement to baseline therapy for COPD to delay progression of disease.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

Keywords
Pelargonium sidoides, traditional Chinese medicine, COPD, herbal therapy, treatment outcomes

Subject Categories
Medicine and Health Sciences

This capstone project is available at CommonKnowledge: https://commons.pacificu.edu/pa/471
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Herbal Therapy and Stable COPD
Delaying Onset and Duration of Acute Exacerbations with Supplementation to Baseline Therapy

Amy M. Hernandez

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 9, 2014

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Biography

Amy Hernandez is originally from the High Desert of Southern California. She and her family relocated to Corvallis, Oregon where she earned her BS in Microbiology at Oregon State University. Thereafter, she worked as a clinical laboratory technologist assistant, and invested time with her husband and children. After completion of PA school, she plans to return to Corvallis, where she hopes to practice family medicine with a focus on infectious disease in underserved populations.

Abstract

Background: Patients with chronic obstructive pulmonary disease (COPD) experience progressive pulmonary decline with each acute exacerbation of disease. Current therapy is focused on treating acute symptoms of COPD, but there are no medications that have been implemented to delay the progression of the disease. Herbal therapies have been developed by researchers to supplement baseline therapy for COPD with the goal of prolonging healthful pulmonary states, thereby slowing disease progression.

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Results: The search produced nine articles for evaluation. Two articles were chosen that met the inclusion criteria of this systematic review. Both studies are randomized controlled trials, which support the use of herbal remedies as a supplement to baseline COPD therapy. One study investigated the use of Pelargonium sidoides, an African geranium, for effective supplemental therapy. The second study performed research on the use of three unique traditional Chinese medicine (TCM) formulations as supplemental therapy for stable COPD. While the results of both studies reflect data that indicates that these herbal supplements are effective in extending the length of duration between acute exacerbations, and decreasing the length of acute exacerbations, further research is necessary to increase confidence in their use.

Conclusion: Use of herbal therapies such as P. sidoides and TCM are promising modalities to maintain wellness in patients with stable COPD when used as a supplement to baseline therapy for COPD to delay progression of disease.
Further studies are necessary to evaluate the efficacy of herbal therapy with greater control of concomitant factors as well as those patients with etiologies of COPD that are not related to smoke inhalation.

**Keywords:** *Pelargonium sidoides, traditional Chinese medicine, COPD, herbal therapy, treatment outcomes*
Acknowledgements

[Redacted for privacy]
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List of Abbreviations

COPD.............................................................Chronic Obstructive Pulmonary Disease
AECOPD...............Acute Exacerbation of Chronic Obstructive Pulmonary Disease
TCM.................................................................Traditional Chinese medicine
BFJP..................................................................................Bu-Fei Jian-Pi granules
BFYS...........................................................................................Bu-Fei Yi-Shen granules
YQZS............................................................................................Yi-Qi Zi-Shen granules
P. sidoides............................................................................................Pelargonium sidoides
FEV1..............................................................Forced Expiratory Volume over 1 second
Herbal Therapy and COPD: Delaying Onset and Duration of Acute Exacerbations with Supplementation to Baseline Therapy

BACKGROUND

Herbal supplements have been vigorously researched for solutions to countless medical ailments and conditions, yet many have weak evidence to support their efficacy and safety. Recent studies \(^1\text{-}^4\) with the use of herbal therapies for URI’s and acute bronchitis have had promising results. It is with these results that research has recently been focused at not only combatting acute illness in patients with COPD, but also their use and efficacy for the protection of patients with stable COPD. The use of \(P. \text{sidoides}\) and TCM are two such therapies that have promising evidence that herbal therapies are effective as supplemental therapy to baseline medical treatments for better maintenance of stable COPD.

COPD is the fourth leading cause of death worldwide, claiming 2.9 million people annually, and 40.8 deaths per 100,000 in the US as of 2010. \(^5\text{-}^6\) Patients with stable COPD experience decreased lung function with each acute exacerbation of the disease. \(^7\text{-}^9\) The use of herbal therapies for treatment of acute respiratory infections has had promising outcomes in recent clinical trials. \(^1\text{-}^4\)

However, there have been no reviews that evaluate the efficacy of herbal therapy
for maintenance of stable COPD in the context of intervals between and duration of acute exacerbations.

Patients with stable COPD have a variety of causes for their conditions. Smoking, pollution and dusty workplace environments are the most widely acknowledged causes of obstructive respiratory damage. However, there are populations of patients who have developed COPD simply due to frequent, severe respiratory infections during childhood, and still others are afflicted due to a systemic deficiency of alpha-1 antitrypsin. Inasmuch as there is progressive research to combat the progression of COPD through pharmaceuticals, it is imperative that patients who suffer from COPD protect their lungs from any further damage, namely through the discontinuation of tobacco inhalation and avoidance of pollutants in the air and dusty work environments. Additionally, these patients greatly benefit from regular vaccinations for influenza and pneumococcal infections. Patients afflicted with alpha-1 antitrypsin disease do have the option of IV augmentation therapy of alpha-1 proteinase; however, this therapy option is invasive, carries with it exorbitant costs and is oftentimes not a feasible treatment option.

COPD, even in its stable state, presents with ongoing symptoms of cough, dyspnea, shortness of breath, and sputum production. When affected with an acute exacerbation of the disease, patients relate that they experience an
amplification of these same symptoms, which can be devastating to their quality of life, oftentimes leading to pneumonia, extended hospitalizations and ultimately death.⁷

There is evidence that the use of herbal supplements such as *Echinacea*, *Baptisia*, *Thuja* and *P. sidoides* are effective as stand-alone treatments or in combination with vitamin and mineral supplements such as zinc, selenium, and vitamin C in the treatment of acute bronchitis, the common cold, and asthma.¹⁴ There is some consideration that these herbal therapies may have a role to play in managing stable COPD.

The use of *Pelargonium sidoides*¹⁴ and traditional Chinese medicine¹⁵ preparations are showing protective benefits of the respiratory tract as well as increasing the functions of the lungs.

Many view herbal supplementation as a more natural option for their medical conditions, and that it is safer to augment their modern drug therapies with natural products rather than adding an additional drug to their health regimen.

Current drug therapy offered to patients with COPD is a combination of medications that are designed to relax airway smooth muscle (SABA’s and LABA’s), dilate bronchioles (ipratropium bromide) and reduce pulmonary inflammation (roflumilast, budesonide, theophylline). Hypercapneic and
hypoxic patients who have decreased lung compliance receive additional relief through the administration of cannulated O₂. ¹²,¹⁶

Recommended drug therapies carry with them multiple adverse affects that can cause co-morbidities such as heart palpitations, new onset arrhythmias, vocal cord changes, candida infections and narrow therapeutic indices can cause drug levels to quickly become toxic. These medications are also implicated in exacerbating pre-existing conditions such as diabetes, cardiac dysrhythmias and interfere with treatment of other immune system diseases.¹¹ For those patients who have exhausted all medical treatment options, the final treatment option is lung transplant,¹² a highly effective, yet risky and extremely invasive procedure that is pursued by few patients for resolution of COPD.

The purpose of researching additional layers of control over COPD is due to the importance of protecting existing pulmonary function. Better control of acute exacerbations delays deterioration of respiratory function, prolongs higher scores of quality of life, reduces higher costs associated with hospitalizations and decreases the possibility of developing antibiotic resistance in afflicted patients due to frequent antibiotic prescription.⁷ In essence, better control of COPD reduces the burden of disease in individuals as well as the healthcare community.⁵,⁷,⁸,¹⁷
Current guidelines have been designed to maintain a stable disease state and decrease symptoms that interfere with everyday activities in patients with COPD. Additionally, patients are encouraged to employ lifestyle modification and encourage healthier practices such as smoking cessation, annual influenza vaccinations and pneumococcal vaccines every 5 years, employing safety measures in the home and workplace to protect the lungs from further damage (eg discontinuing use of solid fuel indoors for cooking, protecting miners’ respiratory tracts while working, etc.) and environmental modifications such as relocating to a region where air pollution is less severe.

Unfortunately, there are patients who are not able to modify their lifestyles, such as patients with alpha-1 antitrypsin deficiencies who require specialized therapy which includes invasive IV augmentation weekly for the rest of the patient’s life, and those who have COPD due to damage caused by recurrent childhood respiratory infections. Others who are unable to modify their lifestyles live in regions where relocating away from pollution or environmental causes is not possible (eg patients in polluted urban areas, with no place to move) and still others who have a long history of nicotine addiction who are unable to comply with measures offered to discontinue smoking. All of these patients are individuals who need to have an additional measure of
protection over their respiratory systems, to offset or even curtail the onset of acute exacerbations from their chronic disease.

Does the addition of herbal therapy to baseline treatment of stable COPD patients delay the onset of acute exacerbations compared to baseline therapy alone?

METHODS

An Exhaustive literature search was conducted using the following search engines: Medline, CINHAL, EBMR, Web of Science, NIH and UpToDate. The searches were conducted on the other aforementioned databases with the keywords COPD, herbal therapy and treatment outcomes.

Criteria used to assess the quality of evidence was conducted through the GRADE system. Biases and quality of evidence were evaluated for each of the following study outcomes: Extension of time between exacerbations, decrease in duration of AECOPD (see figure I), FEV₁ measurement, and improvement of quality of life pertaining to health/pulmonary symptoms. Each of the aforementioned outcomes was evaluated for limitations, indirectness, imprecision and inconsistency in the studies’ methodologies, documentation and evaluation of data and reporting of results of each study. Scores assigned for each outcome of interest ranged from high to very low, and the culmination of
the evidence was then interpreted to generate an overall grade of evidence produced by the studies that were conducted and evaluated.

**Eligibility criteria**

Eligibility criteria for this review were studies conducted on male and female adult patients ≥18 years old, on patients clinically diagnosed with COPD, on the use of herbal therapy as augmentation to baseline treatment of stable COPD, evaluating of pulmonary function through spirometry, in the English language, on research sample size >30 participants and as a randomized controlled trial study design.

**Exclusion criteria**

Exclusion criteria included patients suffering from asthma, acute bronchitis/acute exacerbation of COPD, studies that included acupoint and acupuncture methods, and studies that evaluated pulmonary function through biomarkers found in blood.

**RESULTS**

A total of nine studies were included in the original search for studies that were relevant to this review. Two studies were identified that applied supplemental herbal therapy to recommended baseline medications in male and
female human adult patients with stable COPD (See Figure II)\textsuperscript{20}. Both studies are randomized controlled trials and are available in the English language.

\textit{Pelargonium sidoides} trial

Researchers recruited 200 male and female patients over the age of 18 years in 18 medical centers from the regions of Kiev and Lugansk in Ukraine who were suffering from stage II or stage III COPD (\(FEV_1 < 80\%\) and \(> 30\%\)) for a twenty-four-week treatment study.

Researchers screened all volunteers with initial measurements of \(FEV_1\) before the use of ipratropium bromide/fenoterol, and again at least 6 hours post dose. Chest x-rays and common COPD symptoms such as cough, sputum production and chest pain were also assessed before acceptance into the study. Patients were considered eligible at the time of the trial’s initiation only if their rise in \(FEV_1\) was less than or equal to 0.31 after 2 puffs of ipratropium bromide/fenoterol inhalation dosed at least 6 hours earlier. Patients were also required to be free from concomitant respiratory infections, and had been free from AECOPD over the past 4 weeks, were free of other systemic chronic diseases and had not used concomitant medications that could interfere with the baseline therapy that was to be offered.\textsuperscript{14}

Patients included were randomized into double-blind controlled groups to evaluate the efficacy of supplementation of \textit{P. sidoides} to baseline COPD
therapy of salmeterol and ipratropium bromide/fenoterol for patients with COPD II and budesonide was added for patients who were diagnosed with COPD III.  

Randomization software generated the medication number lists as well as the patient allocation lists by a researcher not involved with the clinical aspect of the study. All patients received their medications in a prospective manner from a pharmacist who allocated the medications according to the numbered list provided for the study.  

Baseline therapy was distributed to all patients in the study according to their stage of COPD outlined by GOLD criteria. Patients allocated to the herbal therapy group were instructed to ingest 30 drops of *P. sidoides* suspension three times daily for 24 weeks in addition to baseline therapy. The therapeutic preparation was a combination of *P. sidoides* root extract, suspension fluid (1:8-10) and 11% ethanol. Patients in the placebo group also received baseline therapy and were provided a matched preparation that was to be orally ingested three times daily for 24 weeks.  

Patients were instructed to return for screening at weeks 4, 8, 12, 16, 20, and 24. The investigators prescribed supplemental prednisolone and augmentin or ofloxacin if patients in either group presented with symptoms that required aggressive therapy for bacterial infections throughout the course of the study.
The primary endpoint of this research was to observe an increase in time to the first exacerbation of COPD after therapy had ensued. Patients were directed to record their use of medications and symptoms in a daily diary to track compliance and features of their health status. The authors acknowledged that it is difficult for patients to recall the date of their last exacerbation before the trial therapy began, and it is common for patients to fail to report to a physician for each exacerbation of their disease. Therefore, the researchers performed an adaptive interim analysis that allowed for a sample size of 200 or more patients to provide sufficient power to achieve the study aim.\textsuperscript{14}

Secondary endpoints of interest were number and duration of mild and moderate exacerbations during treatment, as well as a comprehensive health status score from the St. George’s Respiratory Questionnaire\textsuperscript{21} and patient satisfaction scores.\textsuperscript{14}

Use of \textit{P. sidoides} as baseline supplemental treatment led to an average of 57 days between AECOPD, as compared to the average of 43 days experienced by patients receiving placebo therapy. Furthermore, patients in the treatment group saw a decrease in length of exacerbations by one day; herbal therapy patients had an average of 11 days of AECOPD, whereas patients receiving placebo experienced 12 days of AECOPD. Measurement of FEV\textsubscript{1} in the treatment group reflected an increase in baseline values that were approximately 3\% higher
than those of patients in the placebo group who received baseline COPD therapy alone.¹⁴

Adverse events identified with the use of *P. sidoides* were primarily minor gastrointestinal discomfort, which was reported by fifty-one patients in the therapy group who experienced seventy-nine events of minor gastrointestinal disorders. The placebo group reflects that forty-six patients reported forty adverse events.¹⁴

Mean duration of treatment was 168 days and compliance to the trial was nearly 100% in both groups. One patient was lost to follow up from the herbal therapy group. Each patient’s allocation to the different analysis populations was defined prior to unblinding. This allowed for further evaluation of any data that may have skewed results due to non-compliance of study subjects.¹⁴

**Traditional Chinese Medicine therapy**

Researchers conducted a randomized controlled trial with a total of 352 male and female patients between the ages of 40-80 years in 4 separate medical centers in China over the course of 18 months who had been diagnosed with mild to severe COPD, as determined by GOLD guidelines and Chinese Treatment Guidelines of COPD.¹⁵

Patients who met the above demographics were screened and included in the study if diagnostic criteria of both GOLD and Chinese Treatment Guidelines
of COPD were met as well as the following inclusion criteria: the patient underwent a 2 week washout period prior to the commencement of therapy, had not participated in any other interventional trials within the past month, and were amenable to treatment as volunteers who were able to sign informed consent. Blood, urine and stool specimens were obtained for routine screening. Further testing was also employed for liver and kidney function, and an EKG was also performed at the onset of therapy as well as at the six-month evaluation.  

By applying Traditional Chinese medicine theory to the evaluation of patients, further exploration of each patient’s physical symptoms was required for allocation to subsets of the herbal therapy group. Patients were defined as having lung-spleen qi deficiency, lung-kidney qi deficiency, or lung-kidney and yin deficiency.  

Each subset of lung deficiencies were defined through evaluation of the patient’s respiratory symptoms, energy levels, gastrointestinal symptoms, weight changes, characteristics of pulses, musculoskeletal symptoms, hearing and balance issues, genitourinary symptoms, varying levels of diaphoresis, and the appearance of their tongues.  

Jiang Yin Tian Jiang Pharmaceutical Company produced the three TCM formulations following appropriate protocols, which were tested against
required quality standards. Bu-Fei Jian-Pi (BFJP) granules were formulated and packaged for patients suffering from lung-spleen qi deficiency. Bu-Fei Yi-Shen (BFYS) granules were formulated and packaged for patients suffering from lung-kidney qi deficiency. Yi-Qi Zi-Shen (YQZS) granules were formulated and packaged for patients suffering from lung-kidney and yin deficiency.¹⁵

Randomization software was used to allocate patients to treatment and placebo groups. Allocation was documented, sealed and held by an independent clinical statistician. Patients were assigned on a one to one ratio to the control group or experimental group to which their condition matched. Each of these patients was also supplied with baseline medications for COPD according to GOLD guidelines. Those patients in the placebo group were provided with baseline therapy alone. There were 176 patients in the control group who received baseline medication as placebo and 176 total patients receiving TCM and baseline medication.¹⁵

Baseline therapy was supplied to all participants in the study. The researchers revealed that this was an open-label trial; however, several measures were employed to strengthen the quality of the study. Such measures involved appointing an investigator who was separate from the research team at each research center to preserve and record the randomization information for the study, the clinical researchers had no effect on enrollment or randomization, and
outcome assessments of the patient’s health were performed by independent clinical statisticians who were blinded to group allocation and were uninvolved in providing intervention or management of patient’s health outcomes. \(^{15}\)

The dosing of baseline therapies was assigned according to the stage of COPD outlined by GOLD criteria. Those patients who also received herbal supplementation were issued bags of TMC granules ranging in weights from 3.83g to 5.16g. The variation in weights corresponds to the TCM subsets to which each patient was assigned (ie BFJP for lung-spleen qi deficiency, BFYS for lung-kidney deficiency, and YQZS for lung-kidney qi and yin deficiency). Each patient in the TCM therapy group was instructed to ingest three bags of granules orally twice daily for six months in addition to baseline medical therapy. \(^{15}\)

Patients presented at 0, 6 months, 12 months and again at 18 months in order that exacerbation frequency, exacerbation duration, lung health (measured by FEV\(_1\) and FVC) and symptomatology might be assessed and evaluated by a clinician. The party responsible for recording AECOPD duration and frequency between study visits were not clearly identified if performed by a researcher or the patients themselves.

Primary endpoints for this study were AECOPD, measured as an average number of exacerbations over the course of 6 months, duration of AECOPD, and lung function measured as FEV\(_1\). \(^{15}\)
Secondary endpoints were evaluated on a point scale of symptoms, exercise tolerance, and health status outcomes. There was a large group (44 patients) who did not complete the full course of the trial; however, the researchers employed two data sets to reflect the results of those patients who were compliant to the study’s design, and those who were exposed to one or more treatments of therapy. In this way, the researchers of the TCM trial were fully aware of the risk of publication bias and addressed this issue directly through additional data sets that represented all patients involved.

The data collected reveals that the patients in the treatment groups who received any one of the three granular formulations as a supplement to baseline medical therapy experienced an average of 0.54 exacerbations over the course of 6 months as compared to placebo, which experienced an average of 1.06 exacerbations over the same time frame.

Additionally, patients in the treatment group saw a decrease in average days of exacerbations (4.39 therapy, 6.37 placebo). At the 18 month re-evaluation, patients in the treatment group continued to show healthier FEV1 values on average (+4.16ml/year therapy, -52.54ml/year placebo), longer 6MWD on average (31.84meters therapy, 14.07meters placebo), and a greater average in quality of
life (13.26% therapy, 6.13% placebo), which was measured with the WHOQOL-BREF questionnaire.

Patients in the trial did report 5 adverse events associated with the combination of baseline treatment and herbal therapy. All five patients experienced different adverse events including: abdominal distention, palpitations, constipation, thirst, and insomnia.

The control group also reported 8 adverse events associated with therapy. Each patient also experienced different adverse events including: abdominal distention, palpitations, constipation, thirst, insomnia, stomach discomfort and dry throat.

Three hundred-six patients completed the experiment, with 46 patients being released from the study due to poor compliance or loss to follow up. The researchers developed a Per protocol analysis set of results for those patients who were the most compliant to therapy. Additionally, a full analysis set was constructed to evaluate those patients who were included into the study and were observed on at least one record point during the trial. For those clinical visits where information was partially missing, the principle of last visit carried out was applied. A safety set was also developed for those patients who took the trial medicine at least once.
DISCUSSION

Patients with stable COPD are faced with the stark reality that the disease they are plagued with is progressive and mostly irreversible. While there are baseline therapies of beta agonists, inhaled corticosteroids, theophylline and supplemental oxygen for the various symptoms of mild to severe COPD, the only method to truly reverse COPD is lung transplantation. However, in an effort to slow the progression of the disease for those who are not reasonable candidates for transplant, guidelines direct clinicians to emphasize the need for smoking cessation, avoidance of indoor solid fuel pollution, and dusty work environments and regular vaccinations. Unfortunately even with patients modifying their lifestyles and utilizing their recommended medications, they find that with each acute exacerbation of the disease, their symptoms take longer to resolve, they tend to fall ill more frequently, and their quality of life deteriorates.

Use of herbal therapies for treatment of respiratory infections has become a well-researched topic of interest across the globe. Multiple reviews have been performed that have evaluated the efficacy of herbal therapy during acute exacerbations of COPD, yet there are limited data that has been produced pertaining to supplemental treatment of stable COPD. Clinicians are trained to encourage patients to engage in healthful life choices as well as taking
preventative measures to maintain wellness. The population of patients with COPD would benefit from additional preventative therapy to maintain their stable disease state.

**Clinical Relevance**

The evidence provided in this review reflects that there are herbal remedies that have shown to be effective in prolonging stable states of COPD and shortening the length of acute exacerbations.14,15 These two studies14,15 were designed to address these issues. Data sets were obtained in both studies that primarily assessed patients who had been diagnosed with COPD due to smoking and inhalation of excessive air pollution. Patients suffering from COPD due to genetic variations or early childhood disease were not assessed as thoroughly as possible. Additionally, there are other herbs that have been researched and have some promising results for treatment of acute respiratory exacerbations such as Echinacea, Byronia, and Ginseng.1,2; 26-28 These herbs may be additional interventions that may add an additional level of protection to the respiratory systems of patients with COPD.

The results of this review can be used clinically as a suggestion for patients with stable COPD who are motivated to protect their health and slow the progression of the disease.
Both herbal therapies evaluated in this review show promising results for the prolongation of stable COPD. Results from both trials reflect that the combined use of baseline medical therapy and adjunct herbal therapy decreases the number of exacerbations per year as compared to placebo.\textsuperscript{14,15} \textit{P. sidoides} shows an increase in days between exacerbations to be an average of 12 days longer than placebo.\textsuperscript{14} TCM shows a decrease in the average number of acute exacerbations per year of 0.97 exacerbations per 6 months compared to 1.48 exacerbations per 6 months experienced by placebo.\textsuperscript{15}

Additionally, patients are experiencing decreases in duration of acute exacerbations. \textit{P. sidoides} showed an average decrease in length of exacerbations to drop from twelve days to eleven days.\textsuperscript{14} TCM reveals that patients receiving this therapy experience an average of 2 days less of symptoms, a reduction from 6.37 days to 4.39 days per exacerbation.\textsuperscript{15}

Both studies also reflect increases in measurements of FEV\textsubscript{1} and decreases in symptom severity during AECOPD.

\textbf{Limitations of Study}

Each study was evaluated for risk of bias and quality of evidence through the use of the GRADE system.\textsuperscript{19} Both studies reflected a degree of bias and lack of specificity in the evidence reported.

The study evaluating \textit{P. sidoides}\textsuperscript{14} reflects reporting bias due to the lack of
raw data that was crucial to display strength in the quality of evidence of the paper, earning it a grade of low quality of evidence.

Instead of using the average number of days to acute exacerbation and duration of acute exacerbation, the researchers provided the median number of days. Additionally, each patient’s FEV1 was recorded at each visit (days 0, and weeks 4, 8, 12, 16, 20, and 24); however, raw data of these recordings are not included in the published results. Patients included in this study were asked to document their COPD symptoms, health status and use of study medications as well as any other supplementary medications over the course of the six-month study in a daily diary. Reporting bias is likely in this aspect of the research, as each patient may have developed a different evaluation scale of his or her symptoms. Reporting bias appears to be present also due to the lack of data and confidence intervals provided in the paper for all endpoints other than the primary. This may have in turn led to a lack of precision, due to the unreported data that is relevant for this study.14

Although the authors state that the sample populations were statistically equivalent, the patients in the placebo group appeared to have had the likelihood of being sicker due to smoking status and gender imbalance. Additionally, baseline FEV1 measurements after 6 months reflected an average of 3% increase
in the herbal therapy sample, however, it was not commented on by the researchers, and may be a source of underreporting error.¹⁴

The study of TCM reflects bias in the development of the study’s methodologies due to the nature of an open-label study, and a failure to report meaningful data. Due to these flaws this study earned a grade of low quality of evidence.¹⁵

The paper identifies that the research was conducted as an open-label study, and several levels of blinding were implemented by the designers of the study, however, there is still a level of reporting bias that is likely to come from the patients, as they knew which therapy they were receiving throughout the trial. It is possible that the patients divulged their group allocation to the clinical evaluator who assessed their health at each clinical encounter.¹⁵

The TCM study¹⁵ also failed to provide data for all secondary endpoints, which reduced the quality of evidence from high to moderate due to the likelihood of recall bias through the omission of these data. The TCM study was also a study involving three sets of unique herbal therapies. The outcomes of all three of the regimens were compiled and presented in the study, thereby omitting conclusive data for each formulation’s strength or weakness in treatment.¹⁵
Furthermore, both studies are weak in their patient population focus. Each study included patients who were diagnosed with COPD, yet the stages of COPD varied from mild to severe in one study,\textsuperscript{15} and was limited to Sages II and III in the other.\textsuperscript{14} The study of TCM\textsuperscript{15} limited the patient population to those who were 40-80 years of age, a limit that was likely to omit those patients who are suffering from COPD due to sources other than smoke inhalation. Additionally, patients with COPD secondary to smoke inhalation were also identified for specific statistics in the published outcomes. However, patients with other etiologies of COPD were not acutely evaluated, as were the patients with COPD secondary to smoke inhalation. Both studies did not indicate whether the patients involved in the trials had previously been using baseline therapy for their COPD. This omission of information also decreases the strength of the data collected, due to the variability of outcomes for patients who may have been exposed to any type of therapy for the first time while participating in this trial.

Variability across studies was seen through the preliminary methods employed before the study began, and also before the measurement of pulmonary function. The TCM\textsuperscript{15} trial required a washout period of 2 weeks before the initiation of therapy, yet it is unclear if the washout was only for respiratory system medications or all medications. The \textit{P. sidoides}\textsuperscript{14} trial
measured and documented spirometry both before and at least 6 hours after inhalation of ipratropium bromide/fenoterol.

CONCLUSION

COPD is a destructive and oftentimes progressive pulmonary disease that is currently only treated symptomatically while in its stable stage. When patients experience frequent acute exacerbations, their course of disease is accelerated with irreversible reductions in lung function as an unfortunate outcome. Herbal therapies such as *P. sidoides* and TCM are formulations that have promising outcomes in delaying the onset of new exacerbations and reducing the duration of acute exacerbations. Data collected from both studies indicate that there is efficacy in these therapies; however, the data provided are not robust enough to investigate the breadth of efficacy for all patients who suffer from COPD. Additionally, there are multiple confounding factors that complicate the clarity of therapy and treatment efficacy; it is possible that these factors alone or combined may have manifested a level of bias that affects results. Ultimately, it is in the best interest of patients to have another weapon in their arsenal to slow the progressive nature of COPD. Herbal therapies may be a new treatment on the horizon that will protect the lungs today and maintain their health for years to come.
REFERENCES


22. WHO. WHOQOL-BREF. 


TABLE I

<table>
<thead>
<tr>
<th>Frequency of Acute Exacerbations</th>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
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<td>2 RCT</td>
<td>Serious limitations</td>
<td>Serious indirectness</td>
<td>No serious imprecision</td>
<td>No serious inconsistencies</td>
<td>Bias likely</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of Acute Exacerbations</th>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias likely</th>
</tr>
</thead>
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<tr>
<td></td>
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</tr>
</tbody>
</table>

Characteristics of Reviewed Studies, GRADE Profile

FIGURE I

Decrease in duration of AECOPD after 6 months of herbal therapy with TCM or *P. sidoides.*
FIGURE II
Flow Diagram Of Search Results

PRISMA 2009 Flow Diagram

Records identified through database searching
(n = 20)

Additional records identified through other sources
(n = 1)

Records after duplicates removed
(n = 9)

Records screened
(n = 9)

Full-text articles assessed for eligibility
(n = 3)

Full-text articles excluded, with reasons
(n = 1)

Studies included in qualitative synthesis
(n = 2)