The effect of pterostilbene and its active ingredients on experimental pulmonary fibrosis in asthma: a meta-analysis

Yanfang Peng¹, Xianqun Xu², Taisheng Ye¹, Yingwen Zhang¹

¹Department of Traditional Chinese Medicine, Zhongnan Hospital of Wuhan University, Wuhan, China
²Department of Laboratory Medicine, Zhongnan Hospital of Wuhan University, Wuhan, China

Abstract

Introduction: Pulmonary fibrosis (PF) is a chronic progressive interstitial lung disease caused by a variety of factors.

Aim: To systematically evaluate the therapeutic effect of pterostilbene (PTE) on experimental PF in asthma and other oxidative damage pathway-related diseases, and to provide evidence for clinical treatment.

Material and methods: Chinese and English databases such as CNKI, Wanfang, VIP, PubMed, Embase, Cochrane Library, and CBM were searched by computer. The Chinese literature on pterostilbene for the treatment of asthma by evaluating experimental pulmonary fibrosis, diabetes, and myocardial infarction was collected from the establishment of a randomized controlled trial until May 2021. Outcome indicators include related physical and chemical indicators such as MDA and SOD. Data were analysed using Review Manager 5.4 software after screening by 2 researchers.

Results: Seven randomized controlled animal experiments were included, with a total sample size of 62 cases. Meta-analysis results showed the following: 1) compared with pulmonary fibrosis, diabetes and other model groups, the pterostilbene intervention group were able to up-regulate SOD, and the effect was better than that of the model group (MD = 20.87, 95% CI: 19.41–22.33; n = 7, I² = 96%); the pterostilbene intervention group could also up-regulate the expression of GSH, and its effect was better than that of the model group (MD = 9.37, 95% CI: 8.67–10.07; n = 2, I² = 98%). The MDA level of the intervention group was significantly down regulated, and the intervention group was also better than the model group. Pterostilbene can prevent experimental PF by lowering the level of MDA.

Conclusions: Pterostilbene can effectively improve experimental pulmonary fibrosis, diabetes, myocardial infarction, and other oxidative damage pathway-related diseases have certain guiding significance for clinical trials on asthma.

Key words: pterostilbene, pulmonary fibrosis, asthma.

Introduction

Pulmonary fibrosis (PF) is a chronic progressive interstitial lung disease caused by a variety of factors, clinically characterized by active dyspnoea, restrictive ventilatory dysfunction, hypoxaemia, and ultimately death from respiratory and circulatory failure, with serious harm to human health [1, 2]. Oxidative stress is one of the molecular mechanisms of PF [3]. Type 2 diabetes mellitus (T2MD) is a common disease characterized by polyphagia, polyphagia, polyuria, and weight loss, which has a complex pathogenesis and is associated with insulin resistance [4, 5]. Studies have shown that high blood sugar can induce accumulation of reactive oxygen species (ROS) and lead to oxidative stress [6].

Rosewood astragalus is the active ingredient of Dragon’s blood and the bioactive ingredient of rosewood, grape, and blueberry. It is a natural plant extract that can prevent oxidative stress, and has anti-tumour, anti-inflammatory, and anti-fibrosis effects. Rosewood astragalus is a methylated derivative of resveratrol with higher bioavailability. Therefore, Pterocarpus roseus L. is a kind of natural plant active ingredient with low toxicity, high efficiency, rich resources, and low price.
studies have shown that *Pterocarpus roseus* L. has an antioxidant effect [7, 8]. However, there are some problems such as the small scale of research and uncertain specific efficacy.

**Aim**

In this paper, the therapeutic effects of *Pterocarpus* on oxidative pathway-related diseases such as pulmonary fibrosis, diabetes mellitus, and myocardial infarction were evaluated systematically.

**Material and methods**

**Document retrieval**

A computer search was performed of all the randomly controlled animal experiments in Chinese and English databases such as China HowNet (CNKI), Wanfang, VIP, PubMed, Embase, Cochrane, and China Biomedical Database (CBM) on the efficacy of *Curcuma zedoaria* and its active ingredients on experimental HF.

The database was searched up to 31 May 2021. The Chinese search words were “Rosewood Astragalus”, “Effective Ingredients of Rosewood”, “Extract of Rosewood”, “Decoction of Rosewood”, etc. The English search words were “pterostilbene”, “pterostilbene ingredient”, “pterostilbene extract”, “pterostilbene water decoction”, etc.

**Inclusion criteria**

1. Type of randomized controlled animal experiment.
2. Subjects animal PF models established by different modelling methods (both rats and mice may be used).
3. The intervention group was treated with normal saline or routine feeding, and the intervention group was treated with *Pterocarpus membranaceus*. The dosage and course of treatment were not limited.
4. Outcome indicators malondialdehyde (MDA), superoxide dismutase (SOD), and other physicochemical factors.

**Exclusion criteria**

(1) Repeated publication; (2) Failure to obtain the full text; (3) Severe complications of the study subjects prior to or during the study; and (4) Inclusion of other CHM ingredients or compound preparations in the intervention.

**Literature screening and data extraction**

Two researchers used Note Express software to screen the literature independently by reading abstracts and full texts according to the inclusion criteria and exclusion criteria. Extracted information included: authors, publication time, sample size, randomized protocol, interventions, outcome indicators, and Jadad score, with a one-by-one cross-check. In case of disagreement, a third researcher helped to resolve the problem.

**Quality evaluation**

Quality evaluation criteria were evaluated using the SYRCLE Animal Experimental Risk Assessment Tool. The evaluation was conducted by 2 researchers independently and checked with each other. In the case of disagreement, discussion and consultation was performed with a third researcher. The assessment items include the following: (1) whether the generation or application of the allocation sequence was sufficient; (2) whether the baseline of each group was the same; (3) whether the allocation was sufficient; (4) whether the animals were randomly placed during the experiment; (5) whether the researchers were blinded; (6) whether the animals in the outcome evaluation were randomly selected; (7) whether the outcome evaluators were blinded; (8) whether incomplete data were reported; (9) whether the study report was irrelevant to the selective outcome report; and (10) whether there was no other bias. Each item was divided into 3 levels of (yes, no) and presented in the relevant table.

**Statistical analysis**

Rev Man 5.4 software was used for data consolidation and statistical analysis. The odds ratio (OR) and 95% confidence interval (CI) were used as the statistical analysis of effect indicators for the binary variables, and the weighted mean difference (WMD) and 95% confidence interval (CI) were used as the statistical analysis of effect for the continuous variables. The difference of *p* < 0.05 was considered as statistically significant. The heterogeneity was analysed by *χ*² test and *I*². The heterogeneity of 95% CI, *p* > 75% was too large to be combined, *p* < 25% was small, and *p* < 0.05 was statistically significant. Publication bias was also assessed using Rev Man 5.4 software for funnel mapping. If the literature was distributed symmetrically in the funnel diagram, the probability of publication bias was small. If the funnel distribution was obviously asymmetric, there was a large publication bias.

**Results**

**Results according to the searching strategy**

Three hundred and eighty-nine related literatures were searched, 296 duplicated literatures were excluded. The remaining 7 articles were included in the systematic evaluation according to the inclusion criteria and exclusion criteria. The process and results of literature screening are shown in Figure 1.

**Basic characteristics of inclusion studies**

Finally, 7 articles were included, including 5 Chinese articles and 2 English articles. The total sample size was 124 cases, including 62 cases in the intervention group and 62 cases in the model group; publication year 2015–2021; rats or mice; basic characteristics of the included
A total of 348 articles were obtained from the database: CNKI (n = 65), VIP (n = 86), Wanfang (n = 78), PubMed (n = 45), Embase (n = 42), Cochrane library (n = 32), CBM (n = 41).

Excluded (86)
1) Review, case report, review
A sexually researched, unavailable essay
Poems: 83
2) Prior to or during the study
Serious complications, no intervention
Notes: 3 essays

Included in 7 meta-analyses

Figure 1. Literature screening process and results

Table 1. Essential characteristics of the inclusion study

| Included literature | Year | Sample size (T/C) | Animals | Moulding method | Grouping | Baseline |
|---------------------|------|------------------|---------|-----------------|----------|---------|
| Ruoli               | 2021 | 6/6              | Mouse   | Bleomycin       | Random   | Comparable |
| Peng                | 2021 | 6/6              | Rat     | Bleomycin       | Random   | Comparable |
| Xinxin              | 2018 | 10/10            | Rat     | Streptozotocin  | Random   | Comparable |
| Shuli Chen          | 2018 | 10/10            | Rat     | Ligation of root vessels of left anterior descending branch of heart | Random | Comparable |
| Xinxin Liu          | 2018 | 10/10            | Rat     | Streptozotocin  | Random   | Comparable |
| Kosuru R            | 2017 | 10/10            | Rat     | Fructose diet   | Random   | Comparable |
| Lin YJ              | 2015 | 10/10            | Rat     | Chloral hydrate | Random   | Comparable |

Note: T was the intervention group, C was the model group.

Table 2. Intervention methods and outcome indicators included in the study

| Included literature | Course of intervention | T Intervention | C Intervention | Main outcome indicators |
|---------------------|------------------------|----------------|----------------|-------------------------|
| Ruoli Wang          | 28 days                | Pterocarpus roseus | Normal saline  | MDA, SOD               |
| Yanfang Peng        | 28 days                | Pterocarpus roseus | DMCO solvent   | MDA, SOD               |
| Xinxin Liu          | 49 days                | Pterocarpus roseus | No             | MDA, SOD               |
| Shuli Chen          | 12 h                   | Pterocarpus roseus | No             | SOD                     |
| Xinxin Liu          | 49 days                | Pterocarpus roseus | Sodium carboxymethyl cellulose | MDA, SOD |
| Kosuru R            | 56 days                | Pterocarpus roseus | β-cyclodextrin | SOD                     |
| Lin YJ              | 12 h                   | Pterocarpus roseus | Normal saline  | SOD                     |

Main outcome indicators

1. Relevant physical and chemical indicators
   – Four articles on MDA indicators. A total of 32 subjects were compared with MDA. Using fixed-effect model analysis, the study showed excessive heterogeneity (p < 0.00001, I² = 93%). The effect of PTE on MDA was better than that of the model group (MD = –2.23, 95% CI: –2.68, –1.79, n = 4, I² = 93%). The results are shown in Figure 2.
   – Publication bias plotting is a common method for identifying publication bias. The funnel maps are drawn with the MD values included in the study as abscissa and SE (MD) as ordinate, as shown in Figure 3. Figure 3 shows that the left and right are asymmetrical and not funnel-shaped, suggesting a greater likelihood of publication bias.
   – PF-related MDA markers. Among the 4 articles on pulmonary fibrosis, 2 articles [9] and 12 subjects were
associated with pulmonary fibrosis. Using fixed-effect model analysis, the study showed excessive heterogeneity ($I^2 = 98\%, p < 0.00001$). The effect of PTE on MDA index was better than that of the model group (MD = –2.27, 95% CI: –2.74, –1.80, $n = 2$, $I^2 = 98\%$). The results are shown in Figure 4.

2. Antioxidant associated protein index

– SOD. In this study, 7 articles [10] were used to compare SOD indices among 62 subjects. Using fixed-effect model analysis, the study showed excessive heterogeneity ($I^2 = 96\%, p < 0.00001$). The effect of the intervention group was better than that of the model group (MD = 20.87, 95% CI: 19.41–22.33; $n = 7$, $I^2 = 96\%$). The results are shown in Figure 5.

– Publication bias. Funnel diagrams are drawn with MD values included as abscissa and SE (MD) as ordinate, as shown in Figure 6. Figure 6 shows that the left and right are asymmetrical and not funnel-shaped, suggesting a greater likelihood of publication bias.

– PF-related SOD markers. These 7 articles and 2 articles [11] PF-related SOD markers were compared among 12 subjects. Using fixed-effect model analysis, the study showed that the heterogeneity was close to the critical value of relatively large ($I^2 = 73\%, p = 0.05$). The effect of the intervention group on SOD expression was greater than that of the model group (MD = 14.61, 95% CI: 12.65–16.57, $n = 2$, $I^2 = 73\%$). The results are shown in Figure 7.

### Discussion

PF is a devastating and progressive interstitial lung disease, and there is no effective drug targeting pulmonary fibrosis. Most scholars at home and abroad believe that oxidative stress is the key to pulmonary fibrosis, and that it interacts with other pathophysiological processes to make lung tissue damage and repair imbalance, myo-fibroblasts increase, extracellular matrix accumulation, and jointly promotes the occurrence and development of pulmonary fibrosis. Therefore, it is one of the main ways to treat PF by regulating oxidative stress and related inflammatory factors [12].

Rosewood astragalus (3,5-dimethoxy-4'-hydroxy stilbene) is an active ingredient derived from plants such as rosewood, blueberry, grape, and palm. Astragalus roseus is reported to have anti-cancer, anti-inflammatory, anti-oxidant, and analgesic effects [13]. Rosewood astragalus is a non-flavonoid polyphenolic compound derived from resveratrol by methoxyl substitution of the third and fifth phenolic hydroxyl groups. Resveratrol is metabolized into Pterocarpus roseus and spruce new glycoside; hence, they have similar pharmacological characteristics. Experiments show that, under the same conditions, rosewood stilbene has higher bioavailability and bioactivity than resveratrol [14].

In terms of safety, no significant toxic or side effects were observed when sandalwood was administered to...
Figure 2. MDA Forest Map

Figure 3. Experimental efficiency funnel diagram

Figure 4. Forest maps of pulmonary fibrosis associated with experimental MDA

Figure 5. SOD
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animals at a dose of 3000 mg/(kg · day) Therefore, Rosewood stilbene may be more suitable for further development and clinical application than resveratrol. Similar to resveratrol, Pterocarpus roseus is considered to be a powerful natural antioxidant, manifested in the following ways: 1) reducing oxidative stress and reactive oxygen species (ROS), such as hydrogen peroxide (H2O2) and superoxide anion (O2–); and 2) increasing expression of SOD in different cell lines. MDA is an important factor of oxidative stress, which has toxic effects on cells and tissues. SOD is a classical antioxidant enzyme. The content of SOD in mouse lung indirectly reflects the oxidative state of the lung. The intervention included in this study was Pterocarpus roseus. The results showed that Pterocarpus roseus L. can promote cell antioxidant function through multiple targets and multiple pathways, and play a role in treating experimental liver fibrosis, diabetes, myocardial infarction, and other oxidative pathway-related diseases. Although this paper used rigorous screening criteria, there are still some limitations, such as the inclusion of literature dominated by Chinese, and generally low quality evaluation, which may lead to selective bias and other uncertainties. Now the unified evaluation system and standard of curative effect will be formed, and the principle of multi-center, large sample and random control will be adopted in the experiments and clinical studies, and the objective indexes will be brought into consideration, so as to form a high-level evidence-based basis and further guide the clinical work.

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Conflict of interest

The authors declare no conflict of interest.

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