Prevention of Lung Inflammation by Isoflavone Genistein

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INTRODUCTION

Genistein (Figure 1) is an isoflavone present in many plant species[1]. High dietary intake of isoflavones is associated with improved lung function and reduced risk of developing chronic lung diseases[2]. The lungs are constantly exposed to many airborne pathogens, including the bacterial endotoxin lipopolysaccharides (LPS)[3]. LPS can reach the lungs by inhalation, and exposure to LPS could result in both local (airway) and systemic inflammation[3,4]. Our previous studies demonstrated that genistein reduced the inflammatory responses of human bronchial epithelial BEAS-2B cells to LPS, thus suggesting that it possesses anti-inflammatory activities in the airway.

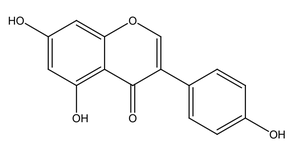
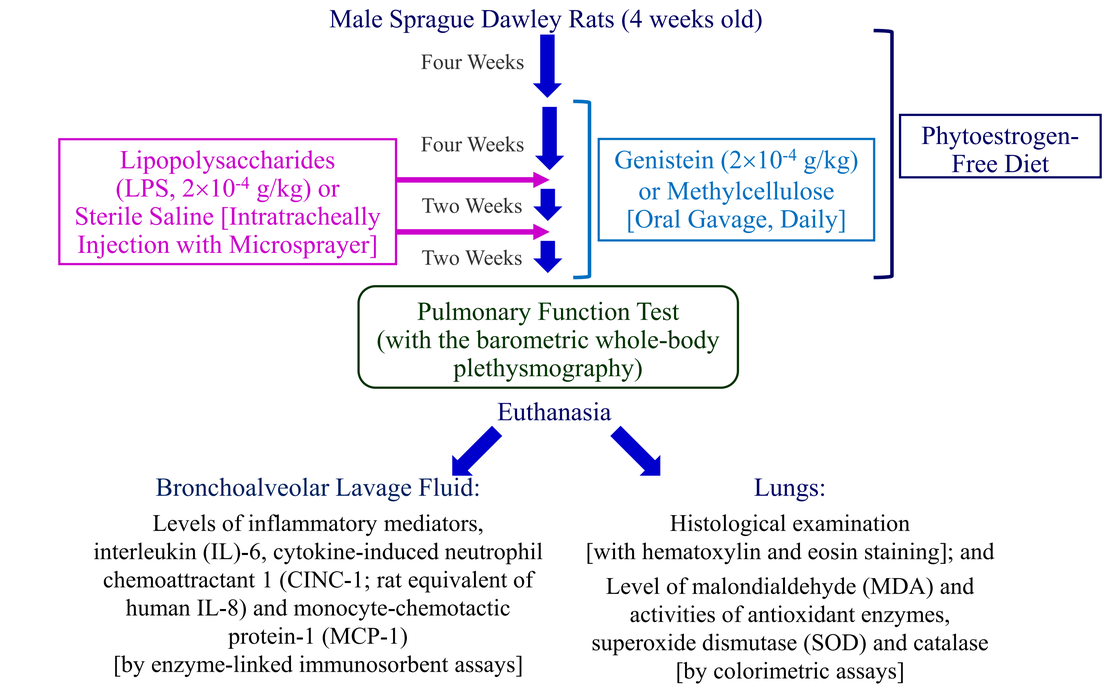


Figure 1 Chemical structure of genistein

OBJECTIVES

The present study examined the effect of genistein on the degree of inflammation caused by repeated exposure to airborne LPS, with the aim to determine whether or not genistein is a potential therapeutic agent to preserve the function of the lung under the pathological conditions associated with inflammatory responses.

METHODS



The animal care and all experimental procedures were approved by the Committee on the Use of Live Animals in Teaching and Research of the University of Hong Kong.

RESULTS

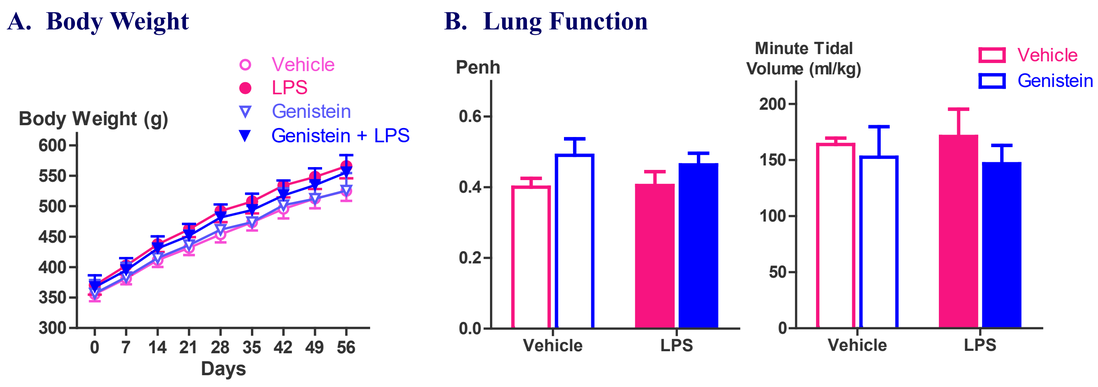


Figure 1 (A) Body weight and (B) lung function, measured with barometric whole-body plethysmography for (*Left panel*) enhanced pause (Penh, the pause between inspiration and expiration which reflects the effort of breathing) and (*Right panel*) minute tidal volumes, of the rats with gavage feeding once daily of methylcellulose (vehicle of genistein, 0.5%) or genistein (10^{-2} g/kg) for 8 weeks and exposed, by microsprayer into the lungs, to airborne lipopolysaccharide (LPS, 2×10^{-4} g/kg) or sterile saline (vehicle of LPS) on day 28 and day 42 after the start of the treatment with genistein/vehicle (day zero). Data are presented as means ± standard error of means (n = 6-8).

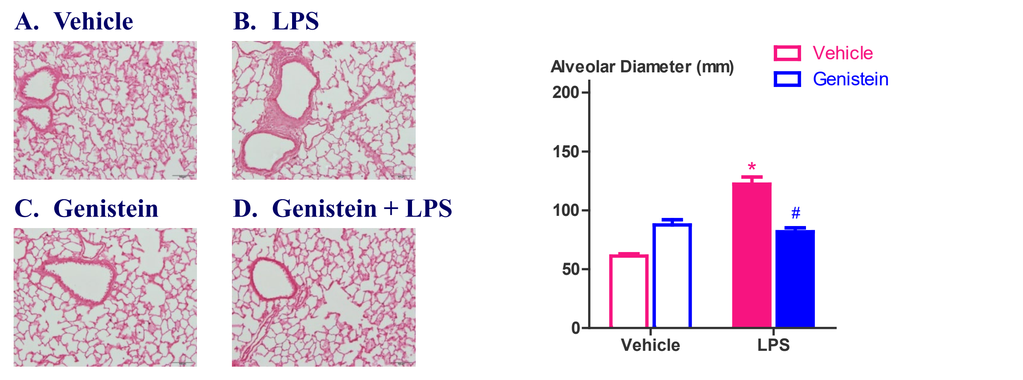


Figure 2 (*Left panel*) Representative photos showing hematoxylin and eosin staining of lung sections of the rats with gavage feeding once daily of (A, B) methylcellulose (vehicle of genistein, 0.5%) or (C, D) genistein (10^{-2} g/kg) for 8 weeks and exposed, by microsprayer into the lungs, to (A, C) sterile saline [vehicle of lipopolysaccharide (LPS)] or (B, D) LPS (2×10^{-4} g/kg) on day 28 and day 42 after the start of the treatment with genistein/vehicle (day zero). (*Right panel*) Average alveolar diameter in lung section photos of different treatment groups presented as mean ± standard error of means (n = 6-8). * $p<0.05$ versus the respective vehicle group without LPS-exposure; # $p<0.05$ versus the respective group without genistein-treatment.

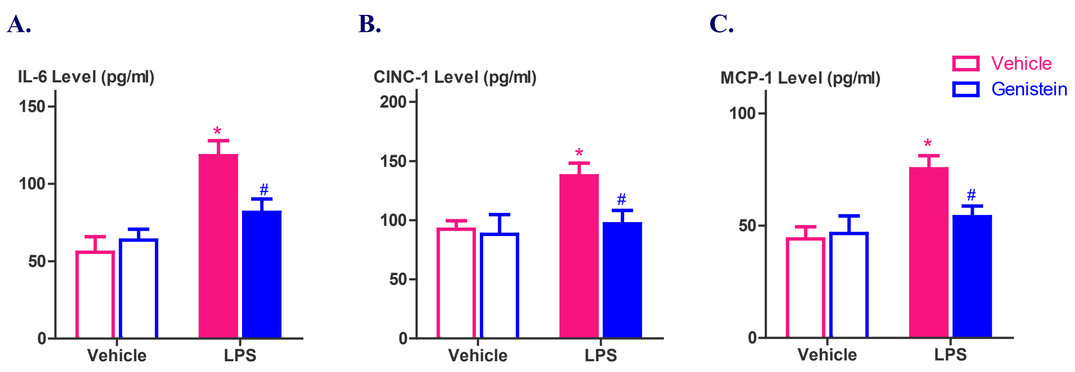


Figure 3 The levels of (A) interleukin (IL)-6, (B) cytokine-induced neutrophil chemoattractant 1 (CINC-1; rat equivalent of human IL-8) and (C) monocyte-chemotactic protein-1 (MCP-1) in bronchoalveolar lavage fluid of the rats with gavage feeding once daily of methylcellulose (vehicle of genistein, 0.5%) or genistein (10^{-2} g/kg) for 8 weeks, and exposed, by microsprayer into the lungs, to sterile saline [vehicle of lipopolysaccharide (LPS)] or LPS (2×10^{-4} g/kg) on day 28 and day 42 after the start of the treatment with genistein/vehicle (day zero). Data are presented as means ± standard error of means (n = 6-8). * $p<0.05$ versus the respective vehicle group without LPS-exposure; # $p<0.05$ versus the respective group without genistein-treatment.

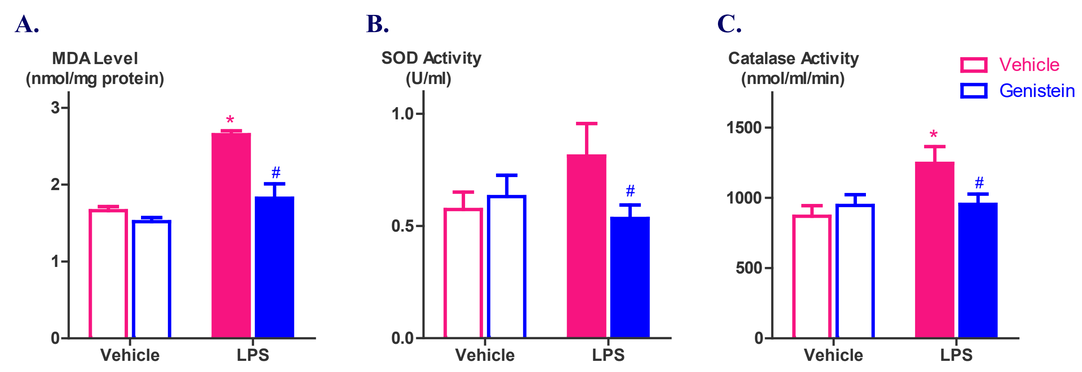


Figure 4 The (A) levels of malondialdehyde (MDA), and the activities of (B) superoxide dismutase (SOD) and (C) catalase in the lung tissues of the rats with gavage feeding once daily of methylcellulose (vehicle of genistein, 0.5%) or genistein (10^{-2} g/kg) for 8 weeks, and exposed, by microsprayer into the lungs, to sterile saline [vehicle of lipopolysaccharide (LPS)] or LPS (2×10^{-4} g/kg) on day 28 and day 42 after the start of the treatment with genistein/vehicle (day zero). Data are presented as means ± standard error of means (n = 6-8). * $p<0.05$ versus the respective vehicle group without LPS-exposure; # $p<0.05$ versus respective group without genistein-treatment.

SUMMARY

- Airborne LPS exposure induces inflammatory responses in the airways, and results in increased oxidative stress leading to damage in the lungs.
- Genistein is effective in protecting the lung against oxidative stress and inflammatory responses caused by airborne LPS exposure.

DISCUSSION

Therapeutic potential of genistein

Long-term intake of genistein prevents the damage of the alveolar structure caused by LPS.

Challenges for clinical usage of genistein

- There are large interindividual variations in the oral bioavailability and pharmacokinetics of genistein.
- Genistein has many biological actions, including estrogenic/anti-estrogenic and vasodilatory effects.

PERSPECTIVES

- Local delivery of genistein to the lung, compared to the oral administration, can reduce the dose required for producing significant anti-inflammatory effect in the airways, thereby reducing the risk of inducing unwanted systemic effects.
- The development of inhalation formulation or pulmonary delivery approaches for genistein would permit the safe and effective use of this isoflavone to prevent/manage the pulmonary inflammation caused by different pathologies.

Acknowledgements

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References:

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