

## Obesity related lung complications and a possible phytochemical therapeutic solution

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### Abstract

Proteases, especially neutrophil elastase (NE), enzyme provide innate immunity in the lung tissues against elastin protein disintegration by microbial attacks. Normally, an antiprotease, called alpha-1-antitrypsin (A1AT), is responsible to keep NE activity in normal range. In most of the leptin-resistant obese subjects, A1AT deficiency develops which leads to a concurrent higher activity of NE. Obesity associated antiprotease-protease imbalance induces various lung complications, i.e. asthma, emphysema, chronic obstructive pulmonary disorders (COPD), cancer, etc. Past studies manifested that plant extracts/compounds reduce human NE activity. This knowledge will help in future to exploit phytochemicals as interventional therapeutic agents to decrease NE over-activity in susceptible obese individuals. Furthermore, the hypothesis discussed in this article will be helpful for researchers working in the fields of lung biology and obesity.

**Keywords:** Obesity; lung complications; phytochemicals.

### Introduction

Enzymes are biomolecules which are proteins in nature, except ribozymes. They act as catalysts to regulate biochemical reactions (metabolism) in the body cells.<sup>1</sup> Enzymes, in living cells, perform multiple physiological functions. For example, in digestive tract lipases, amylase and proteases digest fats, starch and proteins, respectively.<sup>2</sup> Proteases comprise a diverse group of hydrolytic enzymes which plays a significant role in cellular growth and differentiation. These enzymes are widely distributed in nature and are found in plants, animals and microorganisms. The main physiological function of proteases is the activation of zymogens through selective cleavage of their peptides.<sup>3,4</sup> Besides this, mammalian

proteases such as pepsin and trypsin, which are digestive enzymes, are involved in turnover of cellular proteins by converting them into small peptides and amino acids.<sup>5,6</sup> A number of proteases are also reported to have a role in the lysis of fibrin clots, blood clotting and transport of secretory proteins across the membranes.<sup>7</sup>

### Proteases and innate immunity

Serine proteases, being one of the members of endopeptidases, are characterised by the presence of serine group in their active site. Neutrophil elastase (NE) is one of the well-known serine protease that plays an active role in innate immunity to combat microbial infection and is released in the lungs.<sup>8</sup> However, over activity of NE enzyme may damage the lung tissues, if it remains unchecked. Thus NE activity is instantly optimised by antiproteases.<sup>9</sup> One of the most active inhibitors of NE is Alpha-1 antitrypsin (A1AT).<sup>10</sup>

### Protease and antiprotease imbalance

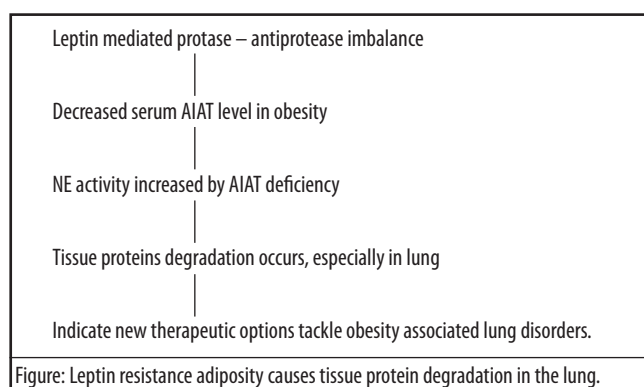
A1AT is produced primarily by the hepatocytes from where it is released into the blood stream. Subsequently, it diffuses into the lung capillaries to counterbalance NE activity, reducing host tissue elastin degradation.<sup>11</sup> In case of A1AT deficiency (A1ATD), NE is not tackled appropriately to protect host tissue proteins in the lungs.<sup>12</sup> This imbalance of protease-antiprotease may lead to chronic obstructive pulmonary disease (COPD), emphysema, asthma, pneumonia, cystic fibrosis and pulmonary carcinomas.<sup>13,14</sup> Previously published studies reported that both genetic and environmental factors contribute to the development of NE-A1AT imbalance in humans.<sup>15</sup>

### Genetic basis of A1AT deficiency

A1ATD is an inherited problem that leads to increased retention of A1AT in hepatocytes and decreased release into the blood stream. It is reported that Z mutation in A1AT-gene leads to alter A1AT-protein conformation.<sup>12</sup> This results in impaired secretion of A1AT protein from hepatocytes into the blood serum.<sup>16</sup> A1AT downregulation in ZZ subjects creates an imbalance between protease and antiprotease in the lungs, as a result NE becomes overactive to damage alveolar tissue leading to pulmonary disorders.<sup>17,18</sup>

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### Environmental and obesogenic factors

An interaction of oxidants in cigarette smoke with A1AT-gene induces lung complications due to the modification of methionine (at position 358) into methionine sulfoxide. This transformation might lead to attenuation of the A1AT inhibitory function, consequently lung tissue proteins are degraded by NE over activity.<sup>19</sup> In addition to this, it is observed that leptin hormone stimulates A1AT expression at both mRNA and protein level in hepatocytes. Whereas, comparative blood serum A1AT level decreases in obese persons because of leptin resistance/dysfunction.<sup>20</sup> As a result, A1ATD and enhanced NE activity occurs in the pulmonary tissues, concomitantly.<sup>21</sup> This leptin resistance-based A1AT-NE equilibrium disturbance might be one of the important factors, which contribute to pulmonary diseases.<sup>22</sup> Therefore, in most of the obese individuals lung-related complications are severely adverse to treatment with available drugs as compared with the normal ones,<sup>23</sup> summarised in the Figure.

### Phytochemicals as interventional therapeutics for lung disorders

Merely, available synthetic medicines are not sufficient to treat chronic complex pulmonary diseases.<sup>24,25</sup> However, previously published studies described that several compounds that were isolated from plants regulate enzyme activity, appropriately.<sup>26,27</sup> It is been reviewed whether proteases and antiproteases deregulation in the lung may be helpful in providing novel therapeutic options for pulmonary disorders.<sup>28,29</sup> Furthermore, in previously published studies flavonoids and polyphenolic compounds were characterised as neutrophil elastase and tyrosine phosphatase inhibitors, respectively, that originated from plants.<sup>30,31</sup> An in vitro study manifested that plant-derived compounds such as viscosol reduces human enzyme activity.<sup>30</sup>

### Conclusions and future prospects

Pronounced effects of obesity on lung physiology make it difficult to treat pulmonary-related pathogenesis in susceptible obese individuals with available therapies

effectively. Obese individuals who are prone to lung complications due to leptin mediated protease-antiprotease imbalance need to be screened prior to developing new generation of drugs for the treatment of lung complications in obesity. Rather than develop synthetic drugs, bioactive compounds derived from medicinal plants could prove more promising in keeping NE activity within optimum range in the lungs of obese patients.

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