Can Beautyberry treatment improve the success rate of lung transplantation?

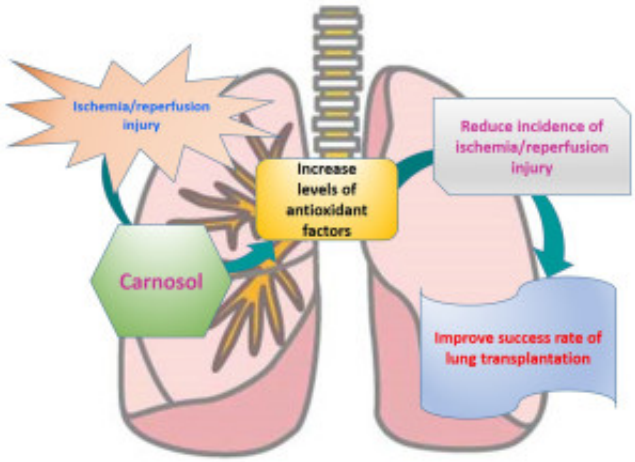
Ischemia/reperfusion injury is a type of organ damage that occurs when blood supply returns to the organ after a period of ischemia and a direct consequence of oxidative stress. It significantly contributes to the risk of mortality in lung transplantation recipients and remains a major complication. Therefore, an efficient preventive strategy for successful treatment of lung ischemia/reperfusion injury could significantly improve the success rate of lung transplantation cases.

We screened compounds associated with anti-oxidative stress in 200 plant extracts by monitoring the activities of an antioxidant cell signaling pathway called Keap1-Nrf2. Nrf2 regulates the expression of antioxidant proteins, which protect against oxidative stress triggered by injury and inflammation. Our results found that *Callicarpa longissima* extract is rich in Nrf2 activators and it was shown to have a strong antioxidant effect. *Callicarpa longissima* is a species of Beautyberry, a shrub that grows in mountainous areas of East Asia. We discovered that the responsible compound to activate Nrf2 is carnosol, which is also found in the herbs rosemary (*Rosmarinus officinalis*) and Mountain desert sage (*Salvia pachyphylla*).

To determine whether it has beneficial effects, we treated lung cells with or without carnosol for 1 hour, then exposed them to hydrogen peroxide (H_2O_2) for an additional 3 hours. Without carnosol, most cells were killed by 50 ?M of H_2O_2, while pre-treatment with carnosol protected cells from H_2O_2-induced cell death. We also found that carnosol increased levels of an Nrf2-dependent antioxidant protein termed heme oxygenase $(HO)^{-1}$ in the cells.

Subsequently, to examine whether carnosol has beneficial effects on lung tissue, we used a mouse

model. Mice received the extract in their daily diet for 1 week, then following euthanasia the lungs were isolated and cultured in medium at 37°C. Lung damage was monitored by the level of lactate dehydrogenase (LDH), an enzyme that leaks from cells undergoing destruction, released into the culture medium. Measurements of LDH showed that post-isolation damage to the lungs in mice treated with carnosol was slower by approximately 1 hour as compared with lungs from control mice treated with DMSO. Also, in the isolated ischemic lungs, carnosol was shown to increase the amount of HO^{-1}.



Finally, to examine the effects of carnosol in a state similar to actual lung disease conditions, we performed left lung ischemia and reperfusion in mice by placing a clamp on lung vessels (pulmonary artery and vein). We then measured the level of blood oxygen (O_2) in order to examine lung function after ischemia/reperfusion injury. Significant maintenance of O_2 level was observed in the carnosol-treated mice, suggesting that the treatment conferred resistance to ischemia and reperfusion injury.

Although research and development of a new drug usually requires a long time period and high cost, drug development by using extracts from natural plants may considerably reduce those. Our results suggest that carnosol is a potent lung protective agent and a novel drug candidate to increase the success rate of lung transplantation.

Publication

Carnosol Is a Potent Lung Protective Agent: Experimental Study on Mice.
Kawamura T, Momozane T, Sanosaka M, Sugimura K, Iida O, Fuchino H, Funaki S, Shintani Y, Inoue M, Minami M, Kawahara N, Takemori H, Okumura M
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