6- Summary and Conclusion

In the present study, the protective effect of three test drugs of different classes and mechanisms of action telmisartan, cinnarizine and N-acetylcysteine (NAC) each in two dose levels were investigated in controlling bronchial asthma symptoms experimentally induced in rats as compared to reference standard treatment dexamethasone (DEXA) in a dose of 1 mg/kg/day.

To fulfill this aim, bronchial asthma was induced experimentally in rats using antigen challenge with ovalbumin (OVA). Briefly, rats were sensitized intraperitoneally with 200 µg OVA/10 mg $Al(OH)_3$ for each rat at days 1, 2, 3 and 11. Rats then were intranasally challenged with 300 µl of saline containing 1.5 mg OVA at days 20, 21 and 22. The effect was studied after administration of the test drugs for 2 weeks before challenge and for 3 days of challenge. Blood samples, BALF and lung samples were collected 24 h after the last challenge.

The protective effect of test drugs was evaluated based on estimation of respiratory functions, namely tidal volume (TV) and peak expiratory flow rate (PEFR) tests, serum immunoglobulin E (IgE), absolute eosinophil count (AEC) in pellets of bronchoalveolar lavage fluid (BALF), total nitrate/nitrite (NOx) level in BALF, as well as oxidative stress markers as reduced glutathione (GSH) and malondialdehyde (MDA) levels and superoxide dismutase (SOD) activity in lung homogenates. Additionally, inflammatory cytokines parameters as tumor necrosis factor-alpha (TNF-α) and interlukine-5 (IL-5) levels in lung homogenates were estimated. Finally, histopathological examination of lung sections was conducted.

6.1-The Main Findings of the Present Investigation Can Be Summarized as Follows:

1. OVA induced bronchial asthma was manifested by significant decrease of both TV and PEFR, which were significantly increased with DEXA administration.

2. Telmisartan, cinnarizine and NAC each in two dose levels significantly increased TV and PEFR as compared to asthma control.

3. OVA significantly increased serum IgE level, which was significantly decreased in DEXA group.

4. Telmisartan, cinnarizine and NAC each in the two dose levels significantly decreased serum IgE levels as compared to asthma control.

5. OVA significantly increased both AEC and NOx level in BALF that were decreased by administration of DEXA.

6. Telmisartan, cinnarizine and NAC each in two dose levels significantly decreased NOx in BALF. Moreover, telmisartan and NAC each in the two dose levels significantly decreased AEC in BALF pellets. Also, cinnarizine in high dose level significantly decreased AEC while in low dose level didn't have this effect.

7. OVA significantly increased oxidative stress biomarkers as decreased both GSH level and SOD activity and increased MDA level in lung homogenate, while DEXA administration significantly increased GSH level and SOD activity and decreased MDA level.

8. Telmisartan, cinnarizine and NAC each in two dose levels significantly increased GSH level and attenuated MDA level in lung homogenates. Alternatively, the activity of SOD was significantly increased by

telmisartan in higher and lower doses, while increased significantly only with the higher doses of cinnarizine and NAC, not with their lower doses.

9. OVA significantly increased inflammatory cytokines as lung content of TNF-α and IL-5, which were significantly decreased by administration of DEXA.

10. Interestingly, telmisartan, cinnarizine and NAC each in the two dose levels significantly decreased both TNF-α and IL-5 levels in lung tissues.

11. OVA challenge induced severe distortion of bronchial and alveolar architectures, with severe infiltration of inflammatory cells, especially eosinophils. Administration of DEXA improved and nearly normalized lung architectures.

12. Telmisartan, cinnarizine and NAC each in two dose levels improved the lung architecture and reduced peribronchiolar and perivascular inflammatory cells infiltration, especially in their higher dose level.

6.2-From the Previous Findings, the Following Could Be Concluded:

1. Telmisartan, the angiotensin II receptor blocker, may have potential protecting effects against experimentally-induced bronchial asthma in rats probably due to its bronchodilator, antioxidant and anti-inflammatory effects.

2. Cinnarizine, the Ca^{2+} channel blocker, showed potential action as anti-oxidant, bronchodilator and also anti-inflammatory agent, moreover its action on IgE.

3. N-acetylcysteine action was investigated in that study, and showed also potential protective effects against bronchial asthma induced in rats.

4. Finally, that study can reveal that new drugs with different pharmacological actions and classes can be used effectively for protecting from bronchial asthma, accordingly getting rid of the problems of using corticosteroids due to their adverse effects and tolerance.

In conclusion, telmisartan, cinnarizine and NAC are good anti-asthmatic agents with efficacy comparable to DEXA, and may be promising for further clinical trials for prophylaxis against attacks of bronchial asthma in human.