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Research article

# Interleukin-6 expression and its modulation by diacerein in a rat model of chronic stress induced cardiac dysfunction

Vipul Agarwal [a], Arjun Singh Kaushik [a], Mujeeba Rehman [a], Rishabh Chaudhary [a], Talha Jawaid [b], Mehnaz Kamal [c], Vikas Mishra [a,*]

[a] Department of Pharmaceutical Sciences, Babasaheb Bhimrao Ambedkar University, Vidya Vihar, Raebareli Road, Lucknow, 226025, UP, India
[b] Department of Pharmacology, College of Medicine, Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh 13317, Saudi Arabia
[c] Department of Pharmaceutical Chemistry, College of Pharmacy, Prince Sattam Bin Abdulaziz University, P.O. Box- 173, Al-Kharj 11942, Saudi Arabia

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ABSTRACT

People with chronic stress have higher levels of pro-inflammatory cytokines, which enhance their susceptibility to cardiovascular diseases. Diacerein has ability to modulate pro-inflammatory cytokines such as IL-1β and IL-6; however, its efficacy in chronic stress associated cardiovascular diseases is not yet assessed. In this study, we standardized a rat model of chronic unpredictable stress (CUS) demonstrating cardiovascular dysfunctions and further assessed the effect of IL-6 modulator, diacerein, on cardiovascular functions in CUS exposed rats. The CUS procedure consisted of exposing male albino Wistar rats to random stressors, everyday for 8 weeks. The binding affinity of diacerein with IL-6 was ascertained using Docking tools viz AutoDock and SwissDock. Moreover, diacerein was administered (50 mg/kg/day x 20 days P.O) post CUS exposure to rats and the serum IL-6 levels and heart functions of CUS rats were determined by ELISA and ECG-HRV analysis, respectively. 8 weeks of CUS exposure resulted in two-fold increase in serum corticosterone and IL-6 levels in rats. The ECG and HRV analysis of CUS rats showed altered sinus rhythm, elevated heart rate, systolic blood pressure and sympathetic tone. Molecular docking studies revealed diacerein high binding affinity towards IL-6 receptor. The post-treatment of diacerein in CUS rats prevented these cardiovascular dysfunctions. Our findings thus suggests that IL-6 may have a prominent role in chronic stress induced cardiovascular dysfunctions and diacerein, could be used as a preventive measure for such conditions.

## 1. Introduction

Chronic stress, resulting from prolonged exposure to physical and psychological stressors, is associated with enhanced risk for cardiovascular, metabolic, gastrointestinal and mental disorders (Rozanski et al., 1999; Mayer, 2000; Tamashiro et al., 2011; Gulbidi et al., 2015; Tafet and Nemeroff, 2016; Cui et al., 2019). The precise neurobiological mechanisms underlying these associations are not yet clearly understood. However, it has been reported that chronic stress triggers long-term dysregulation of stress hormones (catecholamines and cortisol), which alters the pattern of cytokine release from immune cells and facilitates the production of pro-inflammatory cytokines over anti-inflammatory cytokines, thereby inducing a state of chronic inflammation (Liu et al., 2017).

C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and nuclear factor kappa B (NF-κB) are some of the pro-inflammatory proteins or cytokines that are elevated following chronic stress (Miller et al., 2009; Maydych, 2019). Among these cytokines, meta-analysis studies revealed IL-6 to be the consistently elevated cytokine in the blood of patients with post-traumatic stress disorder (PTSD) and depression (Passos et al., 2015). IL-6 and its soluble receptor α (sIL-6Rα) complex play a key role in the transition from acute to chronic inflammation by switching the nature of the leucocyte infiltrate from polymorphonuclear neutrophils to monocyte/macrophages (Hurst et al., 2001; Kaplanski et al., 2003). Moreover, IL-6 also exerts stimulatory effects on T-and B-cells, thereby facilitating chronic inflammatory responses (Gabay, 2006).

Several studies have found significant correlation between long term elevation of IL-6 and cardiovascular diseases resulting in morbidity and mortality (Gabriel et al., 2004; Baune et al., 2011; Zhang et al., 2018; Gager et al., 2020). IL-6 level was found elevated in the heart tissue of patients with dilated cardiomyopathy and end-stage heart failure.

* Corresponding author.
*E-mail address:* vikasmishra12@gmail.com (V. Mishra).

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