Investigating the Role of Angiotensin Receptor Blockers (Arbs) In High Fat Diet-Induced Sarcopenic Rats Associated Muscle Wasting

Priyanka Prajapati[1]*, Anand Kumar[2], Areesh Zehra[3], and Sapana Kushwaha[4]

Abstract

Sarcopenia-induced muscle loss has a significant societal impact on older people and progressively increases frailty and disability. The anabolic hormone insulin growth factor-1 (IGF-1) is a key growth hormone for muscle growth by inducing protein synthesis while catabolic muscle RING-finger protein-1 (MuRF-1) has been identified as E3 ubiquitin ligases and mediated proteolysis. The present study aimed to screen Angiotensin Receptor Blockers (ARBs) binding affinity to specified proteins through an *in-silico* approach. Out of eight ARBs, azilsartan and telmisartan exhibited good affinity to IGF-1 and MuRF-1 proteins. Then lead ARB, azilsartan (AZL) was further investigated in High-Fat Diet (HFD)-induced sarcopenia-associated muscle loss in the rat model. Male *Sprague Dawley* rats, 6 and 14 months were used as young and old, respectively, and divided into control and treatment. The control group was treated with vehicles and azilsartan treatment. Old rats were further fed with HFD for 4 months and served HFD-induced old rats. Further, HFD-induced sarcopenic rats were divided into the old control and AZL-treated old group. AZL was given at the dose of 8 mg/kg, *per oral* for 6 weeks. After treatment, rats were analyzed for functional muscle tests and results showed that AZL significantly increased muscle coordination and locomotor activities in sarcopenic rats. Next, animals were sacrificed, and gastrocnemius muscles were collected for oxidative stress and antioxidant levels. Results showed that AZL significantly restored glutathione and reduced lipid peroxidation and protein carbonyl levels. In conclusion, azilsartan treatment showed significant muscle coordination activity and restoration of antioxidants status in HFD-induced sarcopenic rats. These findings suggest that AZL could be a good intervention to prevent and treat old-age muscle wasting.

Keywords: Sarcopenia, azilsartan, antioxidants, High fat diet, skeletal muscle.

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Introduction

Sarcopenia is defined to have lower muscle mass and strength and decreased physical activities in the aged population (TRIVEDI and KHATRI, 2022). According to the Asian Working Group for Sarcopenia (AWGS), 2019 consensus diagnosing sarcopenia needs evaluation of both muscle quality and quantity (Chen et al., 2020). Further, oxidative stress, proinflammatory markers, and apoptotic cell death with obesity worsen the skeletal muscle condition in the older population (Li et al., 2022). Recently, an angiotensin receptor blocker (ARB), losartan has shown efficacy in a clinical trial for improving muscle function and grip strength and was found to be effective in sarcopenic subjects . Moreover, new generation of "sartan" category, azilsartan has been FDA approved as a antihypertensive drug (Hjermitslev et al., 2017). Study reports that angiotensin II causes the skeletal muscle wasting and inhibition of Ang II proven to be useful in maintaining skeletal muscle fibre composition, and endothelial function (Deminice et al., 2020, Kingsley et al., 2021, Zhou et al., 2015, Semprun-Prieto et al., 2011, Silva et al., 2019). Furthermore, perindopril, an angiotensin converting enzyme inhibitor is also showed positive results in clinical trial against the treatment of sarcopenia in combination with

***Corresponding Author:** Priyanka Prajapati
Address:[1*,2,3,4]Department of Pharmaceutical Sciences, School of Pharmaceutical Sciences, Babasaheb Bhimrao Ambedkar University, Vidya Vihar, Raebareli Road, Lucknow-226025, India. [1*]Email: priyanka243prajapati@gmail.com; ravin.k90@bbau.ac.in

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