Chapter 4
Autophagy Pathways in Major Depressive Disorder

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ABSTRACT

Major depressive disorder (MDD) is a chronic condition with high prevalence, especially in individuals with physical illnesses. This chapter explores autophagy's involvement in MDD, connecting it to oxidative stress, increased pro-inflammatory cytokine levels, and impaired mitochondrial function. Dysregulated autophagy contributes to MDD pathophysiology, offering insights into novel therapeutic strategies. The authors review preclinical and clinical evidence, the effects of conventional antidepressants on autophagy, and the potential of herbal products in modulating these pathways. Understanding autophagy's role in MDD underscores the need for

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further research to develop targeted treatments.

1. INTRODUCTION

Major depressive disorder (MDD) is a widespread and persistent psychiatric illness, impacting nearly 4.7% of people worldwide and representing a significant burden on global mental health (Ferrari et al., 2013). Its prevalence is notably higher in individuals suffering from long-term physical health conditions, among whom the incidence of MDD ranges from 20% to 40%—a rate that is two to three times greater than that observed in the general population (Read et al., 2017). Chronic diseases such as diabetes, cancer, arthritis, cardiovascular conditions, and neurodegenerative disorders frequently co-occur with MDD, reflecting the intricate connection between mental and physical well-being (Read et al., 2017; Almeida et al., 2020). Individuals with MDD commonly display symptoms like reduced enjoyment in previously rewarding activities, persistent low mood, and cognitive difficulties (Otte et al., 2016) . These manifestations extend beyond emotional distress, profoundly disrupting quality of life and overall functioning by impairing mood regulation and cognitive processes (Voros et al., 2020). Neurologically, MDD is associated with dysfunction in the critical brain areas like the hippocampus (HIP) and medial prefrontal cortex (mPFC), critical for emotional and cognitive functions (Belleau et al., 2019; Mokhtari et al., 2019). Unravelling the broader mechanisms driving MDD could open doors to innovative treatment strategies.

Research highlights MDD as a pathological state involving nitrosative and oxidative stress, mitochondrial dysfunction, and impaired autophagy, with studies noting increased pro-inflammatory mediators and enhanced cell-based immune mechanisms (Maes et al., 2011; Gassen & Rein, 2019). Understanding autophagy's role in MDD not only enhances insight into its biological foundations but also suggests new therapeutic possibilities. This chapter reviews preclinical and clinical evidence supporting autophagy's involvement in MDD's pathophysiology, emphasizing its medical implications for advancing treatment approaches

2. AUTOPHAGY PATHWAYS

Autophagy is essential for maintaining cellular homeostasis and is crucial to tissue and organismal function in both physiological and pathological conditions (Rubinsztein et al., 2012; Kroemer et al., 2010). This evolutionarily conserved mechanism facilitates the breakdown of damaged cytosolic components, including pathogens, proteins, organelles, and aggregates, through a meticulously orchestrated

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