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Pharmacological potential of JWH133, a cannabinoid type 2 receptor agonist in neurodegenerative, neurodevelopmental and neuropsychiatric diseases

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ABSTRACT

The pharmacological activation of cannabinoid type 2 receptors (CB2R) gained attention due to its ability to mitigate neuroinflammatory events without eliciting psychotropic actions, a limiting factor for the drugs targeting cannabinoid type 1 receptors (CB1R). Therefore, ligands activating CB2R are receiving enormous importance for therapeutic targeting in numerous neurological diseases including neurodegenerative, neuropsychiatric and neurodevelopmental disorders as well as traumatic injuries and neuropathic pain where neuroinflammation is a common accompaniment. Since the characterization of CB2R, many CB2R selective synthetic ligands have been developed with high selectivity and functional activity. Among numerous ligands, JWH133 has been found one of the compounds with high selectivity for CB2R. JWH133 has been reported to exhibit numerous pharmacological activities including antioxidant, anti-inflammatory, anticancer, cardioprotective, hepatoprotective, gastroprotective, nephroprotective, and immunomodulatory. Recent studies have shown that JWH133 possesses potent neuroprotective properties in several neurological disorders, including neuropathic pain, anxiety, epilepsy, depression, alcoholism, psychosis, stroke, and neurodegeneration. Additionally, JWH133 showed to protect neurons from oxidative damage and inflammation, promote neuronal survival and neurogenesis, and serve as an immunomodulatory agent. The present review comprehensively examined neuropharmacological activities of JWH133 in neurological disorders including neurodegenerative, neurodevelopmental and neuropsychiatric using synoptic tables and elucidated pharmacological mechanisms based on reported observations. Considering the cumulative data, JWH133 appears to be a promising CB2R agonist molecule for further evaluation and it can be a prototype agent in drug discovery and development for a unique class of agents in neurotherapeutics. Further, regulatory toxicology and pharmacokinetic studies are required to determine safety and proceed for clinical evaluation.

1. Introduction

Evidence accumulated over the past few decades has implicated endocannabinoid signaling in a myriad of physiological and pathological processes (Bonnet and Marchalant, 2015), including synaptic plasticity, neurogenesis, and emotional control (Lu and Mackie, 2016). Endocannabinoids and their receptors have been implicated in neuroprotective signaling by protecting neurons, glial cells, and endothelial cells from various insults via suppression of numerous pathogenic events such as oxidative stress, excitotoxicity, neuroinflammation, apoptosis and autophagy (Bonnet and Marchalant, 2015). Several animal studies have highlighted the pharmacological mechanisms and therapeutic

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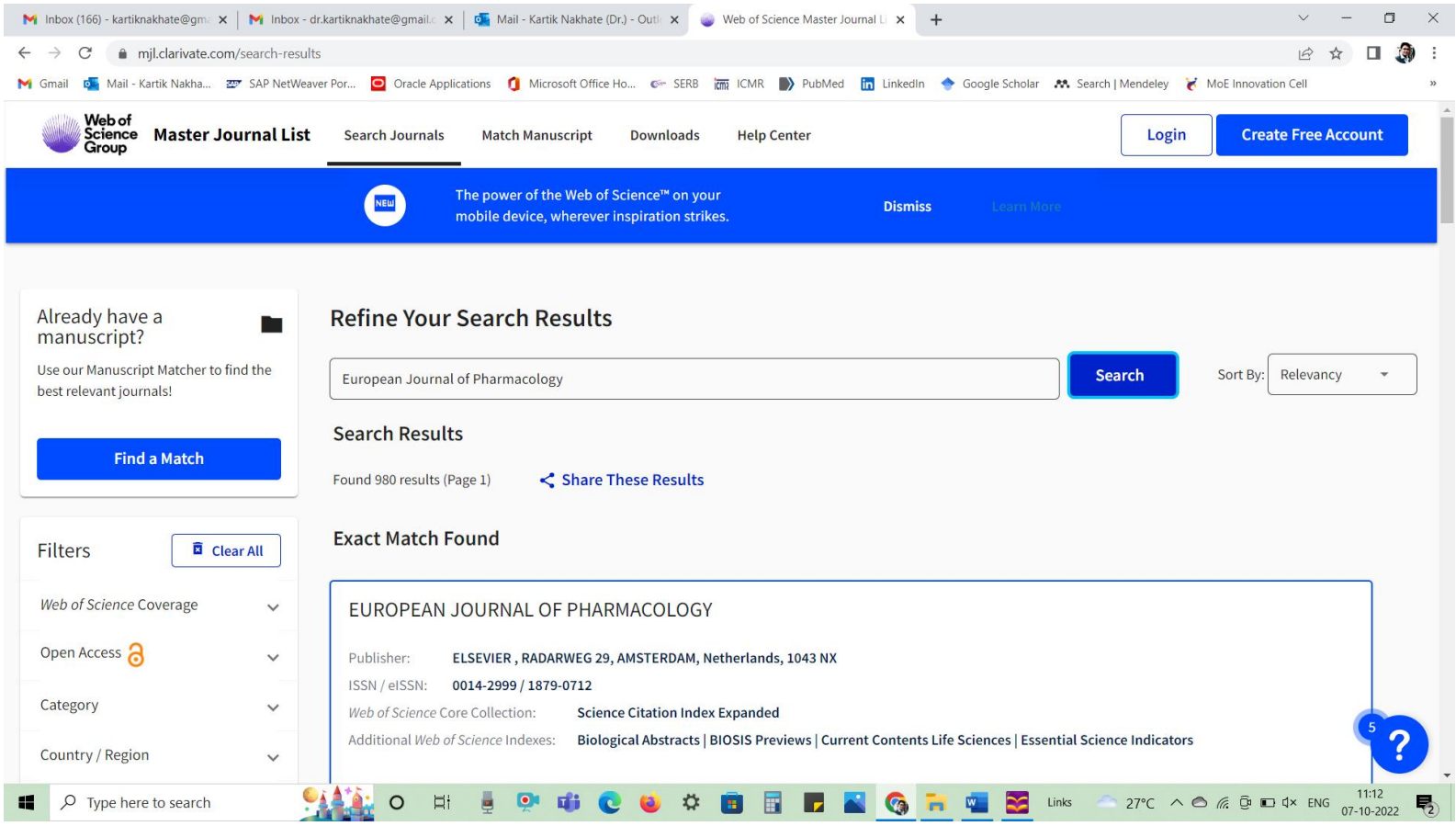
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