INTRODUCTION

Ethanol dependence is a complex, progressive, chronic, recurring disorder, characterized by an urge to drink heavily and loss of control over the quantity of ethanol consumed, even with the knowledge of the toxicities associated with it. Several millions of individuals worldwide are affected by ethanol dependence and it has immense repercussions on the individuals financial, social and health status. [1] All the agents known to cause dependence, such as ethanol, opioids, cocaine, amphetamine, cannabinoids, nicotine, have reinforcing properties that are known to enhance neuronal activity in specific brain regions. These agents elevate the extracellular dopamine neurotransmitter levels in nucleus accumbens. [2]

The effect of ethanol in the central nervous system (CNS) is mediated by different neurotransmitters. Multiple receptor activity and neurochemical systems are involved at various cellular sites in CNS in the reward and drug-seeking behavior with ethanol. The alteration of synaptic transmission under the influence of ethanol occurs due to the modulation of neuronal excitability by interacting with voltage and ligand-gated ion channels, thereby affecting the functions of many neurotransmitter systems in the brain, like GABA, glutamate, opioids, nitric oxide, 5-HT etc. [3] In the initial phases of ethanol dependence, positive reinforcement is important. On chronic exposure, it interferes with neuronal circuits that control various motivational processes. Repeated exposure produces changes in sensitivity to ethanol due to neuroadaptations and produces a withdrawal syndrome on deprivation of ethanol consumption. Chronic exposure to ethanol may result in persistent neural deficits. Relapse to ethanol dependence is common even after prolonged periods of deprivation from ethanol. [2]

Opioid antagonists have shown to reduce the ethanol consumption in rodents. [4] Microdialysis experiments in rats have shown that naltrexone, an opioid antagonist, blocks the elevated levels of dopamine induced by ethanol in various regions of the brain. [5] The association of opioid system responsible for the progression of ethanol dependence is evident from the effective treatment of ethanol dependence by naltrexone. [6] The exact role of the endogenous opioid system in ethanol dependence is not yet well understood. However, evidence indicates that ethanol influences the actions of the mesolimbic dopaminergic pathway in the brain, mediating through opioid
receptors. Its interaction with opioid receptors is either direct or indirect. [7] Inhibitory effect of naltrexone on GABAergic neurons in the ventral midbrain may affect the dopamine reward pathway in ethanol dependence. [8]

The role of glutamate receptors in hyperexcitability following withdrawal from alcohol, as well as in alcohol-seeking behavior is well documented in the literature. [9] Acamprosate suppresses excessive glutaminergic activity by blocking NMDA and metabotropic glutamate receptors and has proved to be effective in ethanol dependence. [10]

Understanding the neural mechanism involved in the progression from ethanol use to ethanol dependence is one of the leading goals in ethanol research. Despite extensive research on the neurobiological mechanism of ethanol dependence, a common cause of this disorder has not been established. A wide range of techniques are used in preclinical research to evaluate the behavioral, cellular as well as molecular changes involved in the progression to ethanol dependence. These are used in association with animal models that mimic diverse components of ethanol dependence in humans. [11] Preclinical models play a very important role in exploring the mechanism of development and treatment of ethanol dependence. Being a complex disorder, it is difficult to replicate ethanol dependence in rodents, as animal models cannot completely mimic all the characteristics of ethanol dependence. However, the animal models to mimic initiation and maintenance of ethanol drinking, and seeking during ethanol abstinence and relapse have been successfully produced in a laboratory setup. [12, 13]

Rodents are important in preclinical screening of drugs for the management of ethanol dependence. However, one of the greatest challenge faced by researchers in this area, is to develop a standard rodent model consuming ethanol voluntarily in high amounts without any initiation procedure. Because of the unpleasant taste of ethanol, various procedures like sucrose fading technique have been developed to initiate ethanol drinking in rodents. [14] There also are reports that show standard laboratory rats, such as Wistar rats consuming a large amount of ethanol voluntarily, used as rodent models of voluntary ethanol consumption. [15]
As ethanol dependence affects millions of individuals throughout the world, effective management of the condition is essential. Though there has been some progress in the pharmacotherapy of this disorder, these therapies may not be effective for all individuals. Drugs like naltrexone, acamprosate and disulfiram are used in the management of ethanol dependence. However, maintaining abstinence after withdrawal and preventing relapse is still a major challenge. In addition, these drugs have certain limitations. Naltrexone may not be effective in all patients, may be due to genetic variations in the µ opioid receptor gene. [16] Disulfiram and naltrexone are associated with hepatotoxicity. It was reported that a majority of the deaths in ethanol dependence are due to liver disease. [17] Though ethanol itself is associated with liver disease, exacerbation or worsening of the condition may occur with the use of these drugs, especially when they are used for a prolonged duration. Similarly, another approved medication, acamprosate, is associated with renal toxicity and should not be given to patients with renal impairment. [18] Hence, exploring additional therapeutic approaches and continued research to discover new drugs is a necessity in this area.

The complexity of genetic and environmental factors involved in the development of ethanol dependence demands the search for newer pharmacological interventions that are effective across all patient populations. [19] Based on the available evidence, it is unlikely that a single molecule will be effective in all patients of ethanol dependence. Hence, clinicians may have to individualize the drug therapy depending upon the response in specific patient populations.

Melatonin, chemically N-acetyl-5-methoxytryptamine, is a hormone synthesized from tryptophan in the pineal gland. It exerts its action through three different receptors (MT1, MT2 and MT3). Though its primary role is in maintaining the circadian rhythm, it has effect on various organs and neurotransmitters. It has been reported that acute and chronic consumption of ethanol reduces melatonin levels in the blood. [20] Melatonin has several potential therapeutic benefits in conditions like jet lag and shift work sleep disorders. Melatonin has extremely low acute toxicity, as evidenced in the animal as well as human studies. The LD50 could not be established in animal studies and even at a high dose of 800 mg/kg body weight did not have serious adverse effects. The minor adverse effects associated with it are headache, insomnia, rash, and nightmares.
[21] It has been categorized as a dietary supplement by the US Food and Drug Administration. It has 30-50% oral bioavailability and has a half-life of 30-50 minutes.

Administration of melatonin entrains the circadian clock by its direct effect on the suprachiasmatic nucleus (SCN). These circadian rhythms are important in maintaining the functions of vital systems in the body. Disturbances in these circadian rhythms may affect the physical as well as mental health. Genetic abnormalities in normal circadian gene functions are implicated in various psychiatric diseases. Circadian genes in limbic regions of CNS have been suggested to play an essential role in the progression of ethanol dependence. [22]

Studies have shown increased generation of reactive oxygen species and mitochondrial dysfunction during ethanol hangover. [23] Melatonin has anti-oxidative properties through direct free radical scavenging action as well as indirect action by stimulating various anti-oxidative enzymes. [24] Melatonin also has an inhibitory effect on NMDA receptor, thereby suppressing glutaminergic excitotoxicity and has been shown to have a prominent effect on the opioid system as well. [25] Morphine-induced rewarding effect has been shown to be reversed by melatonin by the activation of melatonergic MT2 receptor subtype in the CNS. [26] The ability of melatonin to reverse morphine dependence and tolerance may involve the suppression of nitric oxide synthase activity. All these evidences prompted us to carry out this research to explore the possibility of melatonin being useful in the treatment of ethanol dependence. As there are insufficient data available on the effects of melatonin on ethanol consumption, this study was planned to determine the possible beneficial effects of melatonin on ethanol consumption using suitable animal models of acute and chronic ethanol drinking. Several reviews [27-29] have stressed on the necessity of evaluating the effects of test compounds in ethanol dependence by more than one procedure, to allow for higher pharmacological differentiation in the efficacy. Hence, several models of ethanol drinking were employed in this study.