CHAPTER 1

INTRODUCTION
1. Introduction

Depression is a mood disorder in which feelings of sadness, anger or frustration interfere with the daily life for weeks or longer. The symptoms of depression includes agitation, restlessness and anger, irritability, becoming isolated, fatigue and lack of energy, hopeless and helpless feeling, worthless, self-hate, loss of interest or pleasure in activities that were once enjoyed, sleep-wake abnormalities, thoughts of death or suicide etc [1].

Depression is associated with the hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA axis) [2-3]. The hormone cortisol is the end product of activation of the HPA axis. It has been reported that uncontrollable stressors likely to be associated with elevations in cortisol level [3]. Hyperactivation of HPA axis is known to induce neurodegenerative process, reduce neurogenesis and associated with cognitive dysfunction [4-5]. Prolonged elevation of cortisol inhibits insulin secretion from pancreatic β-cells, decrease glucose uptake and utilization, stimulates glucagon secretion, hepatic glucose production, decreased body weight and induces type 2 diabetes like state [6-7].

The chronic unpredictable mild stress model (CUMS) is a widely used model for induction of depressive like behaviour in rodents, which consists of the repeated exposure to an array of unpredictable and mild stressors over a sustained period of time [8-9]. Unpredictable mild foot shock stress for 21 days induced significant hyperglycaemia, glucose intolerance, hypercorticosteronemia, gastric ulcerations, male sexual dysfunction, immunosuppression, cognitive deficits and mental depression in rats [10]. Exposure to 21 days of CUMS significantly reduced brain-pancreas relative protein and induced hyperglycemia and hypoinsulinemia [11].

Clinically, depression and diabetes are co-morbid. Diabetes make the symptoms of depression worse [12]. At the same time, depression reduces overall physical and mental health, not only increasing the risk for diabetes but making diabetes symptoms worse. Studies have shown that people with depression and diabetes have more severe diabetes symptoms than people who do not have diabetes [13]. In animal models, depressive phenotype is associated with hyperglycaemia, insulin resistance, hypercorticosteronemia, cognitive deficits, immunosuppression and hypoinsulinemia [10-11].

Hyperglycemia is associated with oxidative stress in hippocampus, resulting in neurological disorders such as memory impairment, depressive like behaviour and anxiety [14-15]. Hypercorticosteronemia induces over production of reactive oxygen species and elevation of cytosolic calcium, and subsequent increase in the calcium dependent death in neuronal cells [16]. Evidence suggest that elevated corticosterone level as observed in stress, induces dysregulation of insulin receptor (IR), thereby decreased metabolic activities and plasticity of hippocampal neurons resulting in cognitive dysfunction [17-19].

Chronic activation of the HPA axis lead to condition called glucocorticoid resistance where immune cells are no longer to hear cortisol signal, thus leading to increases in both cortisol level and inflammation [3]. Reactive nitrogen species such as nitric oxide (NO) has been implicated in stress mediated inflammation and cognitive deficit [20]. In addition, NO impairs autophagy (ATG) in rat primary cortical neurons which is known to modulate neuronal health [21].

The hippocampus region of brain that regulates learning and memory processes is vulnerable to oxidative stress and hypercortisolemia [22-24], during the depressive episodes [25]. Hippocampal muscarinic receptors are known to modulate cognition. Thus, hippocampal cholinergic dysfunctions might underlie depression associated cognitive impairments [25]. Administration of selective muscarinic acetylcholine receptor 1 (mAChR1) antagonists induces spatial memory impairment [26]. mAChR4 function as presynaptic autoreceptor in hippocampal neurons to inhibit acetylcholine (ACh) release [27], which is known to be involved in learning and memory processes [28]. Upregulation of mAChR4 in striatal neurons inhibits locomotor activity in mice [29]. Chronic stress activates acetylcholinesterase (AChE), resulting in reduced amount of ACh in synaptic cleft [30]. Depression dysregulate brain derived neurotrophic factor (BDNF) and mitogen activated protein kinase (MAPK) levels, which is known for its modulation in synaptic plasticity [31-32].

Depression results in increased neurodegeneration and decreased hippocampal neurogenesis [33]. It has been demonstrated that glucocorticoid treatment induces arrest of the neural cell cycle [34] and apoptosis in neuronal progenitors and mature neurons [35]. Suppression of neurogenesis affects mood [5], fear conditioning, synaptic plasticity [36] and memory [37]. Sonic hedgehog (Shh), a mitogenic protein, has been implicated in neurological disorders. It has been demonstrated that, dysregulation of Shh co-receptors like patched (Ptch) and
smoothened (Smo) within the dentate gyrus subfield of the hippocampus is associated with depressive phenotype [38].

Diabetes can be caused by low insulin, resistance to insulin, or both [39-40]. Prolonged hyperglycemia often associated with damage to nerves in the body that occurs due to high blood sugar level [41]. In the central nervous system, diabetes exacerbates depression, phobias, anorexia and cognitive deficit [42-43]. Clinically, patients with diabetes are at increased risk of developing depression and cognitive impairment as compared to the general population [44-45]. Diabetes induces oxidative stress and inflammation in the hippocampal neurons resulting in neurodegeneration [14, 46]. Animal models also revealed the persistence of depression and neurocognitive impairment during chronic diabetes. Streptozotocin (STZ) induced diabetes showed depressive like behaviour [47-48] and cognitive deficit in rodents [49].

STZ is an antibiotic [50], induces hyperglycaemia by its direct cytotoxic action on the pancreatic β-cells [51-52]. In STZ treated mice, changes in spinal terminals of calcitonin gene-related peptide in sensory neurons were observed 4 weeks after diabetes and progressively worsened with time [53]. STZ induced chronic diabetes induced depressive like behaviour in animals. In addition, STZ induced diabetic animals showed a significant hypolocomotion [54] and cognitive dysfunction [55].

Many signaling pathway has been involved in the pathogenesis of diabetic neuropathy. Dysfunctioning of neuronal peroxisome proliferator-activated receptor-γ (PPARγ) was observed in cognitive dysfunction [56]. A recent study reported that, downregulation of PPARγ levels in the hippocampus of diabetic mice [57] is associated with depressive like behaviour in forced swim test [58]. Further, downregulation of IR expression in hypothalamus induces depressive like behaviour in rats [59]. Diabetic neuropathies in brain are exacerbated by severe deficiency of BDNF with depressive behaviour [60].

Diabetes induces oxidative stress and inflammation in hippocampus [14]. Chronic diabetes is known to elevate the level of NO. NO induces inflammation of hippocampal neurons [30]. NO derived from inducible form of nitric oxide synthase (iNOS) contribute to the depressive like behaviors in mice due to neurodegenerative effects in the cerebral cortex [20].
Choline acetyltransferase (ChAT) and AChE are responsible for the synthesis and metabolism of ACh. Evidence suggests that ChAT, a specific marker for functional state of cholinergic neurons [61], activity is reduced during STZ administration resulting in cognitive deficit [62-63]. STZ increases AChE activity in hippocampus resulting in learning and memory deficit [64]. Previous study suggest that STZ-induced diabetes significantly downregulated the expression of mAChR1 in hippocampus termed cholinergic dysfunction [64]. Chronic diabetes resulted in motor activity deficit [65]. Upregulation of mAChR4 in the striatum inhibits dopaminergic-D1 receptor-induced locomotor stimulation in mice [29]. Autophagic dysfunction has also been observed in diabetes mice [66].

Saint John's wort also known as *Hypericum perforatum* is a flowering plant, belonging to the family Hypericaceae [67-68]. The herb of St. John's wort has been used from centuries to treat various ailments including depression [69-70]. Clinical trials in patients revealed that Hypericum extract is superior for depressive disorder and their effectiveness is similar to that of standard antidepressants with fewer side effects [71]. Hypericum extract improves spatial memory [72], proliferation of progenitor cells and dendritic spine, restored the synaptic plasticity [73] and Alzheimer's pathology [74]. Hypericum extract is a suitable alternative for the management of depressive disorder associated with cognitive impairment [75]. St. John's Wort and its active constituent hyperforin protect rat as well as human islets against cytokine mediated β-cell injury in type 1 diabetes [76]. Hypericum administration significantly reduced hyperglycemia in STZ treated diabetic rats. Clinically, Saint John's wort induces photosensitivity and has interaction with many drugs [67].

In randomized controlled trial, fluoxetine (FLX) exerted neurocognitive improvement in patients with moderate depression [77]. FLX attenuated impaired cognition in depressed rodents as well [78]. FLX upregulated BDNF levels in hippocampus and modulated adult neurogenesis and depressive-like behaviour [79]. FLX treatment reduced the level of glycated hemoglobin during co-mobidity depression and diabetes in rodents. FLX ameliorated spatial learning and showed hypoglycaemic and antidepressant effects during CUMS associated diabetes [80]. FLX is also prescribed for variety of pathological conditions including mood and eating disorders [81], obsessive compulsive disorders [82], depression in the elderly [83] and dysthymia [84]. In view of pathogenesis in type 2 diabetes mellitus and brain disease, antidiabetic medications known to positively modulate the metabolism of neuronal cell,
which could be of clinical importance for the treatment of neurological disorders [85]. Rosiglitazone (ROSI) is a thiazolidinedione class of oral antidiabetic drug for therapy of type 2 diabetes mellitus [86-87]. ROSI increases glucose transport in adipose tissue and muscle by enhancing synthesis and translocation of glucose transporters [88-89]. ROSI showed central anti-diabetic action against D-glucose fed and STZ-induced diabetes in rodents [90]. ROSI is known to protect cognitive impairment in individuals with type 2 diabetes [91]. ROSI improves cognition and memory performance in patients with mild Alzheimer disease and animal models of Alzheimer disease [92]. It has been reported that, insulin sensitizing drug ROSI exhibited significant declines in depression severity associated with insulin resistance [93]. Mice administered with ROSI showed increased hippocampal neurogenesis during depression [94].

Currently available antidepressants are known to improve neurocognitive functions depending on clinical, social and emotional factors [95]. Studies have shown that, therapy with antidepressants is correlated with an increased risk of suicidal behaviour in those aged under 25 [96]. Sexual side effects are also common with the use of FLX, such as loss of sexual drive, failure to reach orgasm and erectile dysfunction [97]. Antidepressant medication use increases the risk of hyperglycemia and diabetes mellitus. The incidence of diagnosed diabetes is higher among antidepressant users than nonusers [98-99]. Many currently available antidiabetic drugs are known to induce hypoglycaemia and associated cognitive impairment [100]. It has been reported that patients receiving chronic pioglitazone therapy showed increased incidence of bladder cancer compared to general population [101-102]. Chronic rosiglitazone therapy is associated with an increased incidence of myocardial infarction and heart failure in type 2 diabetic patients [103].

*Urtica dioica* (UD) is an herbaceous plant and commonly known as stinging nettle, belonging to the family Urticaceae [104-105]. Administration of UD leaves repaired pancreatic tissue damage in STZ induced diabetic rats [106]. In earlier studies, UD administration significantly reduced hyperglycemia, insulin resistance and hyperlipidemia in fructose induced diabetic rats [107]. In clinical trial, UD is reported to have glycemic control in type 2 diabetic patients by lowering the levels of fasting and postprandial blood glucose [108]. Earlier studies reported that administration of diabetic patients with UD significantly increased antioxidant capacity and reduced inflammatory stress and glycated hemoglobin [109-110].