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Introduction

Whenever any endogenous or exogenous stimuli is perceived by the body as an unpleasant or threatening, a wide range of body systems and processes are activated and generates a synchronized response against particular stimuli, or stressor. In humans, stress typically describes a condition that can have an impact on a person’s mental and physical well-being. This is called as the stress response, an essential part of the adaptive biological system (Lederbogen et al., 2011). A stressor is any external stimuli that disturb the physiological functioning of the body (McEwen, 2007). Stress, however, is not a single entity and there are several different kinds of stressors that can be distinguished. The stressful stimuli can be acute or can be of chronic nature. It may occur only once, or may rather take place in a repetitive manner, that can be anticipated. Chronic stress is known to have several pathophysiological alterations in body such as neuro-endocrine activation (limbic-hypothalamic-pituitary-adrenal system) (Bonfiglio et al., 2011) and hormonal (corticosterone release) functions (Fuchs and Flugge, 1998). Sustained and persistent stressful conditions can precipitate affective disorders such as depression, cognitive dysfunction and other neurodegenerative disorders, which can lead to extreme release of oxygen free radicals (Maes et al., 2011).

In an organism, different types of stress mediators trigger a wide range of hormonal and neuronal fluctuations that results in behavioral (cognitive deficits, depression behavior, etc.) and physiological alterations (HPA axis trigger and release of corticosteroids) (Henry and Stephens, 1977). These types of stress mediators are known to cause autonomic changes but when stimulation reaches to its peak, it causes several neuropsychiatric and neurological disturbances (Hennessy and Levine, 1979). Response to stress is uneven and therefore there are individual differences in how an individual experience a stress response and its body’s reaction to the response (Weiner, 1992).
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Stress and stressors

Stress is defined as the body's reaction to a change that requires a physical, mental or emotional adjustment or response. It can come from any situation or thought that makes you feel frustrated, angry, nervous, or anxious. Conceptually, stress can be any threat real or perceived to the well being of an organism. It can be of two types as shown in Table 1.

Table 1: Types of stress

<table>
<thead>
<tr>
<th>Systemic/Physiologic stress</th>
<th>Processive/Psychogenic stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>• It is real threat to well being</td>
<td>• It depends upon perception</td>
</tr>
<tr>
<td>• Physical characteristics of the stimulus itself place immediate responsive demands on the organism</td>
<td>• Quality of the stressful stimulus depends upon the interpretation glucopyranoside</td>
</tr>
<tr>
<td>• Conscious awareness of the stimulus is not required by the organism</td>
<td>• The severity of the stressor and its physiologic impact can vary amongst the individuals</td>
</tr>
<tr>
<td>• e.g. Injury with the loss of blood</td>
<td>• e.g. Threat posed by some kind of loss</td>
</tr>
</tbody>
</table>

Stressor is a stimulus either internal or external, which activates the hypothalamic pituitary adrenal axis and sympathetic nervous system resulting in various physiological alterations (Maier and Watkins, 1998). Long term exposure to stressors can cause depression, post-traumatic stress disorder and cognitive disorders (Nirmal et al., 2008). The degree of behavioral control that an individual has over a stressor often determines the consequence of that stressor and plays a key role in the development of various pathological problems (Christianson et al., 2009). The threshold to cope with the stressors is a fundamental requirement for survival (Sahin and Gümüslü, 2007).
Epidemiology of stress

The economic burden of stress-induced neurological diseases is globally expected to increase in the coming years (Yale, 2001). The World Health Organization (WHO) survey estimates that 3.96% of human subject population would suffer from stress-related depression symptoms by the year 2020, (Vos et al., 2013). The WHO study in general health care found that 10.4% of patients suffer from stress and its linked diseases such as depression (North and Pfefferbaum, 2013). Similarly, the National Comorbidity Survey (NCS) found that 17.3% of the general population has experienced an episode of major depression and 24.5% suffered from other stress disorders at some time during their lives (Wakefield and Schmitz, 2013). The Property and Casualty Insurance Edition of United States (PCIE) estimates that $150 billion of revenue is being lost due to stress stress-related mental illness and substance addiction. The Washington Business Group on Health found that 46% of all employees are severely stressed to the point of burnout. In relation to patients suffering from heart disease, it has been calculated that the cost of treatment and lost output are $117 billion and 13.5 million people are affected globally (Wimo et al., 2013). Depression and other stress related disorders including memory loss enforce substantial loads on the individual in terms of impairment of daily activities, work productivity and cost to health care providers. Since stress is the most common underlying condition leading to depression and cognitive deficits, there is a medical need for prevention, early intervention, treatment of stress and related comorbid psychiatrics (Leach et al., 2013).

Neurobiology of chronic stress

The hippocampus and cerebral cortex are the most sensitive and malleable regions of the brain associated with chronic stress response. Within the hippocampus, the input from the entorhinal cortex to the dentate gyrus is ratified by the connections between dentate gyrus and CA3 pyramidal neurons. The circuitry of the dentate gyrus-CA3 system is believed to play a role in the memory of sequences of events, although long-term storage of memory occurs in other brain regions (Howard et al., 2011). But,
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because dentate gyrus–CA3 system is so delicately balanced in its function and vulnerability to damage, there is also adaptive structural plasticity, in that new neurons continue to be produced in the dentate gyrus throughout adult life; and CA3 pyramidal cells undergo a reversible remodeling of their dendrites in conditions, such as hibernation and chronic stress, including a combination of food restriction and increased physical activity (McEwen, 2010). Whatever the physiological significance of these changes, be it protection or increased vulnerability to damage, the hippocampus undergoes a number of adaptive changes in response to acute and chronic stress (Conrad, 2008, McEwen, 2007). The prefrontal cortex (PFC) is involved in working memory, self-regulatory, goal-directed behaviors, displays remarkable structural and functional plasticity during chronic stress. Neural circuitry, molecular profiles and neurochemistry can be changed by experiences, which influence behavior as well as neuroendocrine and autonomic functions (McEwen and Morrison, 2013).

HPA-axis in chronic stress: The core stress response system consists of the hypothalamus which controls the secretion of ACTH from the anterior pituitary and stimulates the secretion by the adrenal cortex of glucocorticoid hormones, mainly cortisol in humans (Lovejoy and de Lannoy, 2013). During stress, the amplitude and synchronization of the CRH and arginine – vasopressin pulsations (AVP) in the hypophyseal portal system markedly increases which results in increase of ACTH and cortisol secretory episodes (Benfield et al., 2013; Perez-Tejada et al., 2013). Circulating ACTH is the key regulator of glucocorticoid secretion by the adrenal cortex and has a major role in stress response. Other hormones or cytokines, either originating from the adrenal medulla or from the systemic circulation, as well as neuronal information from the autonomic innervations of the adrenal cortex may also participate in the regulation of cortisol secretion (Abedelmalek et al., 2013, Guest et al., 2014).

Glucocorticoids are the final effectors of the HPA axis and participate in the control of whole body homeostasis and the organism’s response to stress. They play a key regulatory role on the basal activity of the HPA axis and on the termination of the stress response by acting at extra hypothalamic
centers, the hypothalamus and pituitary gland (Frodl and O'Keane, 2013). The inhibitory glucocorticoid feedback on the ACTH secretory response acts to limit the duration of the total tissue exposure to glucocorticoids, thus, minimizing the catabolic, anti-reproductive and immunosuppressive effects of these hormones (Wang et al., 2008). Secretion of corticosterone also triggers oxidative stress and ultimately leads to memory deficits (Sato et al., 2010a).

In addition, chronic unpredictable model of stress is also involved in activation of hypothalamic–pituitary–adrenal (HPA) axis which has also been reported in Alzheimer's patients (Landfield et al., 2007). Additionally, glucocorticoids secreted during stressful events are known to influence memory consolidation and retrieval (Roozendaal, 2002). Chronic stress induced by removal of olfactory bulbs (OBX) also results in significant rise in the serum corticosterone levels indicating hyperactivity of the HPA-axis (Song et al., 1994). Since increase in the corticosterone levels may lead to the behavioral alterations including depression like symptoms (Busquet et al., 2010), therefore it is possible to suggest that OBX-induced behavioral alterations are due to the increased levels of the serum corticosterone. Further, head traumatic injury causes damage to the neuronal tissue through primary and secondary injuries via activation of HPA axis and excess secretion of corticosterone (Maiya et al., 2008). Therefore, HPA axis plays an important role not only in maintaining the body's response to stress but also in boosting the response in the event of additional stress stimuli.

**Chronic stress induced oxidative damage:** Elevated level of oxygen free radicals such as superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO) and peroxynitrite caused a significant cell injury (Niki, 2013). Since proteins are the major components of biological systems and they play an important role in a variety of cellular functions; therefore, increase in oxidative damage to proteins could be an important physiological setback to an organism (Thomas, 2013). Ablation of olfactory bulbs has been reported to be associated with production of oxygen reactive species and depletion of antioxidant defense enzymes (Tasset et al., 2010). A significant increase in lipid peroxidation and marked decrease in the activity of reduced glutathione
and antioxidant enzymes in the brain of OBX rats were also documented (Tasset et al., 2010).

During oxidative stress, mitochondrial membrane transition permeability increases and causes significant loss of mitochondrial NAD$_2^+$ that further contribute to cell injury. Oxidative stress can lead to apoptosis in neurons, endothelial cells (ECs) and smooth muscle cells that involve separate as well as over lapping pathways. Chronic unpredictable stress increases the malondialdehyde, nitrites concentration, depletion of reduced glutathione and catalase in animal's brain (Rinwa and Kumar, 2012). Similarly, other forms of chronic stress have been shown to increase the levels of lipoperoxides in rat livers and plasma and decrease the levels of reduced glutathione in erythrocytes and liver (Meng et al., 2013). Psychological stress is one of factor for oxidative toxicity and has pro-oxidant properties that augment oxidative processes (Sutherland et al., 2013). Oxidative stress is also known to play a critical role in the pathogenesis of traumatic brain injury (Bayir et al., 2003). Generations of free radicals including super-oxide and hydroxyl ions after head injury are important contributors in the pathogenesis of secondary damage (Kontos and Wei, 1986). Studies have shown a significant increase in oxidative stress markers in cerebrospinal fluid of patients suffering from head trauma (Bayir et al., 2002). However, their interactions are still elusive to define the exact pathway of stress and reactive oxygen species for the development of chronic stress and related neurological disorders.

**Chronic stress induced neuroinflammation:** Chronic stress is associated with increased concentrations of inflammatory biomarkers in human blood (Rohleder, 2012). The effects of HPA axis hormone (cortisol) have been characterized as anti-inflammatory, and inhibit the components of the immune system under all circumstances (Dhabhar et al., 2012). The main feature of CNS inflammation includes glial activation, edema formation and accumulation of free radicals (Lucas et al., 2006). Chronic unpredictable stress is known to cause microglial activation, resulting into
neuroinflammation in hippocampus and other brain parts and showing imbalance in memory functions (Farooq et al., 2012). Animals exposed to this type of stress shows impairment of spatial learning and memory in different behavioural paradigms (Bian et al., 2012). Glucocorticoids are known to have anti-inflammatory, immunosuppressive and immunomodulatory properties under standard conditions (Nair et al., 2007). In an earlier study, experimental model of chronic unpredictable stress fails to suppress the increased expression of IL-1β and TNF-α following infusion of LPS into the prefrontal cortex (De Pablos et al., 2006; Munhoz et al., 2006). Similarly, high stress concentrations of corticosterone aggravate increase in IL-1β and TNF-α mRNA and protein levels (MacPherson et al., 2005).

Recent study has shown that stress induces the release of pro-inflammatory mediators such as nitric oxide (NO), prostaglandins and neuro-inflammatory cytokines (Jaremka et al., 2013). Earlier report has also shown that excessive neuroinflammation can be deleterious to the injured brain (Stoica and Faden, 2010) and can promote neurodegeneration leading to functional decline. Brain trauma causes activation of caspase-3 pathway by down-regulating Bcl-2/Bax ratio, which ultimately leads to neuronal apoptosis (Mao et al., 2014). A few studies have shown that physical or psychological stress can modulate cytokine expression and causes inflammation within the brain or the periphery (Schmidt et al., 2014, Lucas et al., 2006). In case of chronic stress, there is an imbalance between pro and anti-inflammatory cytokine level (Lyman et al., 2013). Another model of stress, olfactory bulbectomy is linked to the generation of inflammatory cytokines like TNF-α (Blomster et al., 2011). Earlier study have found an elevated levels of TNF-α following OBX in cerebral cortex and hippocampal brain regions, suggesting inflammatory reaction accompanied by neuronal damage (Song et al., 2009). Unfortunately, the mechanisms underlying these novel actions remain unknown but their understanding is crucial in the evaluation of potential therapeutic benefits of drug molecules.

**Chronic stress induced apoptotic cascade:** Apoptosis is a highly regulated process and commonly called as the programmed cell death. Mainly two types of apoptotic pathways namely intrinsic and extrinsic (or death receptor)
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have been well reported (Croxen and Finlay, 2009). The most widely studied form of intrinsic apoptosis is initiated by the stress mediated release of cytochrome-C from the mitochondria and results into initiation of apoptotic signalling cascade (Verfaillie et al., 2013). Stress activated autophagy have been shown by recent neurodegenerative study on experimental animals (Murrow and Debnath, 2013). Different types of stressors lead to DNA damage, free radical generation, and removal of nutrients, oxygen or growth factors, generation of pro-inflammatory cytokines as well as stimulate the normal physiological processes such as aging and neurodegeneration (Fiocchetti et al., 2013). Apoptosis induced oxidative stress can lead to a variety of diseased conditions such as cognitive loss, Alzheimer’s disease, pain sensation, and brain trauma (Maiese et al., 2010). In response to stress, some specific proteins regulate the release of cytochrome-C, which activate caspases, the main executors of apoptosis. Enhanced apoptosis has been detected in chronic unpredictable stress model in experimental rodents (Brunton, 2013). It has been shown that chronic unpredictable stress caused a decrease in Bcl-2 level in the hippocampus (Murthy et al., 2013). Bax is another pro-apoptotic molecule that induces apoptosis with an early release of cytochrome-C preceding caspase activation and subsequent proteolysis (Fulda, 2013; Schmidt et al., 2014). These findings are in concurrence with report from Hall and Macrides (Hall and Macrides, 1983), who found neuronal cell death in different brain regions following olfactory bulbectomy. These results are further evidenced through earlier study which showed presence of a large number of inflammatory and apoptotic cells in neurons of the temporal cortex and hippocampus following olfactory bulbectomy (Nesterova et al., 2008). Recent study have also suggested an increase in inflammatory mediators after traumatic brain injury may contribute to progressive neurodegeneration and release of many apoptotic factors (Schaible et al. 2013), that finally results into cognitive deficits.

Neurotrophins alterations in chronic stress: Neurotrophins, particularly brain derived neurotrophic factor (BDNF), have acknowledged a widespread attention due to their role in the etiology and treatment of several neurological disorders. Apart from their well-known role in the nervous system, BDNF
expressed in peripheral tissues including lungs, spleen and can thus potentially contribute to both normal physiology and pathophysiology of several diseases (Prakash and Martin, 2014). BDNF is a member of the nerve growth factor family that is important for neuronal survival and plasticity. Neurogenesis is recognized in adult mammals including humans and is promoted by different neurotrophic factors, constituting an inherent repair mechanism following injury. BDNF is known to enhance the function and growth of selective neuronal populations in the hippocampus, and thus is a crucial factor for maintaining the molecular processes underlying cognitive function (Vaynman et al., 2007). There are several reports which show that neurotrophin system is dysregulated in stress induced-depression and other related syndromes such as (a) reduced circulating levels of BDNF in clinical patients with mood disorders, and (b) increased BDNF expression and signaling in the brain on treatment with antidepressants (Castren and Rantamaki, 2008; Duman and Monteggia, 2006). One of the clinical report found that in medication-free depressed patients who committed suicide, BDNF levels were reduced in both the brain regions such as hippocampus and frontal cortex (Karege et al., 2005). Earlier report have found reduction in hippocampal BDNF levels in depressed patients, but no corresponding changes in TrkB levels was observed (Dunham et al., 2009). Wu and its group have also suggested that brain traumatic injury reduces BDNF levels in experimental animals (Wu et al., 2006).

Hippocampal neurogenesis is influenced by a number of environmental factors and both physical and psychosocial stress decreases the subgranular zone (SGZ) progenitor cell proliferation and restrains the formation of hippocampal neurons (Surget et al., 2011). Stress hormones play a vital role in the suppression of hippocampal neurogenesis. In particular, glucocorticoids have been known to inhibit the proliferation and production of newer hippocampal neurons (Cameron and Gould, 1994). Further, there is increasing evidence demonstrating that chronic unpredictable stress decreases the expression of BDNF in limbic structures (Hansson et al., 2006). BDNF expression is powerfully regulated by corticosteroids through activation of gluco and mineralocorticoid receptors (Hansson et al., 2006). Furthermore,
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Olfactory bulbectomy as a chronic model of stress has also been reported to alter neurogenesis in several regions of brain, which is one of the putative pathogenic mechanisms to explain depression (Koo et al., 2010). There is evidence that olfactory bulbectomy can lead to reductions of the volume not only of the hippocampal neurogenesis, but also of the amygdala that might be due to atrophy and loss of neurons (Douma et al., 2011).

Consequences of chronic stress

Exposure to prolonged stress has rather negative effects and increases the risk to develop psychopathology such as depression, cognitive deficits etc. in vulnerable individuals. Earlier study also indicates that prolonged exposure to stress affects the function of excitatory synapses (Alfarez et al., 2003). In all hippocampal areas, induction of long term potentiation (LTP) is greatly impaired after a prolonged period of mild stress or chronic corticosteroid exposure (Alfarez et al., 2003). Reports at the cellular level indicate that prolonged exposure to stress, via corticosteroid actions, inhibits glutamatergic synaptic transmission in the prefrontal cortex. These effects are mediated by enhanced ubiquitin/proteasome-mediated degradation and loss of synaptic NMDA receptors and AMPA receptors (Yuen et al., 2012). In addition to enhanced corticosteroid hormone levels, also CRH has been implicated in detrimental effects of prolonged stress on hippocampal function (Ivy et al., 2010). Importantly, disruption of excitatory synaptic transmission after exposure to chronic stress has been implicated in impaired learning and memory (Yuen et al., 2012). Taken together, these studies demonstrate that a history of chronic stress exposure disrupts excitatory synaptic transmission and synaptic plasticity leading to several neurological and other disorders.

Chronic stress induced metabolic changes: Activation of the stress system leads to both behavioral and hormonal changes that improve the ability of the organism to adjust homeostasis and increase its chances for survival (Chrousos, 2000) There is an important role of hypothalamic CRH in inhibiting gonadotropin-releasing hormone secretion during stress, while via somatostatin. It also inhibits growth hormone, thyrotropin- releasing hormone and thyrotropin secretion, suppressing thus reproduction, growth and thyroid
function. Chronic activation of the stress system would be expected to increase visceral adiposity, decrease lean body (muscle and bone) mass and suppress osteoblastic activity (Tsigos and Chrousos, 2002). Glucocorticoids directly inhibit pituitary gonadotropin, growth hormone and thyrotropin secretion and make the target tissues of sex steroids and growth factors resistant to these substances (Chrousos and Gold, 1992). Stress-induced hypercortisolism and visceral obesity and their cardiovascular as well as other sequel increase the mortality risk of affected subjects by 2-3-fold and curtail their life expectancy by several years (Tsigos and Chrousos, 2002).

Chronic stress induced immunological changes: Stress has been associated with the impaired immune function and increased susceptibility to infectious diseases (Connor and Leonard, 1998). It is now believed that the nervous, endocrine and immune systems are so intimately connected that they should be regarded as single network rather than three separate systems (Connor and Leonard, 1998). It is widely accepted that psychological stress and psychiatric illness can compromise immune function and soluble mediators released by immune cells can affect central nervous system thus producing alterations in behavior (Leonard, 1995). In clinical population, exposure to stressful life events such as academic examinations and divorce was reported to cause impairments in various aspects of cellular immune function (Bartrop et al., 1977). There are also reports of immune activation, in addition to immunosuppression in both depressed and subjects exposed to stressful life events (Connor and Leonard, 1998).

Chronic stress induced depression: The role of stress in the development, expression, and progression of depression is well established. In clinical population, 80% of major depressive episodes (MDEs) are preceded by major stressful life events (Hammen, 2005). It has been estimated that stressors are directly related to work or job profile (Hammen, 2005). In addition, chronic stressors have been linked to poorer diagnosis and more frequent degenerative symptoms following therapy (Hawley et al., 2007). Severe
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Stressors have been generally linked with an increased risk of depression. Chronic stressors and events characterized by perceived (a) lack of control, (b) inability to escape or resolve the aversive situation (e.g., entrapment), or (c) loss of status (e.g., humiliation) appear to be particularly depressive (Kendler et al., 2003). Report showing the uncontrollability component of stressors is consistent with data indicating that perceived control over stressors is a key modulator of physiological stress responses (Dickerson and Kemeny, 2004). Second, chronic stressors play a stronger role in triggering first episodes of depression than recurrences, and the association between stressors and depression becomes weaker with increasing number of episodes (Kendler et al., 2003).

The preclinical literature suggests that hyperactivity of central CRH neuronal activity may be involved in the pathophysiology of depressive disorders (Heuser et al., 1996). In particular, the hypercortisolemia and impaired negative feedback of cortisol on the HPA system observed in depression have been attributed to a primary central CRH hyperdrive (Heuser et al., 1998). About 50% of patients suffering from depression have a hyperactive HPA system resulting in hypercortisolism (Checkley, 1996). Interestingly, preliminary evidence suggests that feedback resistance and mild hypercortisolism are already present in healthy subjects at genetic risk for chronic stress-induced depression syndrome (Holsboer et al., 1995). Therefore, stressful life events and depression share a complex relationship and interacting factors (Fig. 1). The role of neuroinflammatory cytokines, oxidative damage and their association with depression like state is also need to be explored further to examine the pathophysiology of depression associated with chronic stress. Investigating this type of causality is also important for developing a theoretical model of depression and understanding cascade of biological events that lead to depression like symptoms.
Chronic stress exposure

Nitric oxide (NO) generation

Oxidative-Nitrosative Stress

Cytokines (TNF-α, IL-6)

Neuronal Damage

DEPRESSION

Fig 1 Schematic presentation of pathways involved in chronic stress-induced depression

Chronic stress induced cognitive dysfunction: Memory impairment is a common and usual comorbidity associated with exposure to prolonged stress. Chronic stress is known to influence cognitive task in various psychiatric patients. Chronic stress has been found to induce cognitive deficits that lead to loss of synaptic connectivity and perhaps neuronal networks in limbic brain structures including hippocampus and cortex. This further leads to loss of cholinergic neurons and results into dementia. Hippocampus is reported to play a key role in spatial learning and memory (Bai et al., 2009). Since hippocampus has abundant inputs from the basal forebrain cholinergic system and thus acetylcholine (ACh) plays a crucial role in learning and memory (Prado et al., 2006). Acetylcholine is degraded by the enzyme acetylcholinesterase, terminating its physiological action. Alzheimer’s disease affects cholinergic system resulting in decreased activity of acetylcholinesterase (Dai et al., 2002). Stress has been well documented to induce increased activity of acetylcholinesterase enzyme (Nijholt et al., 2004). In general, longer duration stressors (i.e., chronic) tend to result in memory
impairments (Schoenfeld and Gould, 2013). The source of the stressor is also important for understanding its pathology. When the act of training is intrinsically stressful such as fear conditioning, the learning process tends to be facilitated by stress. However, when the training is not as stressful or the stressful experience occurs at a time distant from training, the consequences become less predictable (Korosi et al., 2013). Finally, demographic factors, such as sex and age, can alter the way stress modulates learning and memory (Lighthall et al., 2013). Regardless of these many variables, most published studies implicate similar brain regions at the intersection between stress and learning. These regions include hippocampus and cerebral cortex.

One of the most important brain areas that regulates stress response and is at the same time affected by stress responses is the hippocampus. Landfield and its group (Landfield et al., 1981) showed that cumulative stress exposure influenced hippocampal viability and compromised cognition. Subsequently, Sapolsky and its group (Sapolsky et al., 1986) reported that chronic stress causes a loss of pyramidal neurons in the hippocampus, accompanied by cognitive deficits in rats. Another study described that training rats for 6 months in a two-way shuttle escape task, using low intensity foot shock stress (4 h/days) resulted in endogenous hypercortisolism and CA1 pyramidal neuronal loss in senescence rats (Kerr et al., 1991), while others reported reactive gliosis, reduced dendritic branching and reductions in volume and in CA1/CA3 cell numbers (Sapolsky et al., 1986). The "glucocorticoid cascade hypothesis" has been proposed to be a pathogenic mechanism underlying chronic stress effects on the brain, and considered relevant for human disorders associated with peripheral HPA axis changes that were similar to the structural changes in the hippocampus, like Alzheimer’s disease (AD), traumatic stress disorder (TSD) and depression (Sapolsky et al., 1986). There is a large and overwhelming literature indicating that glucocorticoids modulate processes related to learning and memory. The types of learning that are affected include declarative memory and other tasks such as, visual-spatial tests and trace conditioning (Datson et al., 2013). Thus, the learning deficits are likely to be mediated by the presence of excessive amounts of endogenous glucocorticoids (Schwabe and Wolf, 2012).
High concentrations of glucocorticoids as well as stressful manipulations elicit poor retrieval of declarative information in healthy participants. In rodents, exposure to chronic stressors tends to impair cognition and many of these stress effects are mediated by corticosterone secretion (Rinwa and Kumar, 2012). For example, injecting corticosterone peripherally enhances the acquisition of a classically conditioned eye blink response, in which an animal learns to associate an auditory stimulus with an aversive stimulation to the eyelid (Beylin et al., 2001). If the training conditions themselves are intrinsically stressful then learning can be affected, such that animals trained in a cold water maze task learn better than those trained in warm water (Conboy and Sandi, 2009). Thus, chronic stress plays a central role in regulating learning and memory process after stressful life experience and tends to have a bigger impact on normal physiology of the body (Fig. 2).

**Fig 2** Multiple pathways involved in chronic stress-induced cognitive deficits
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**Chronic stress induced other neurological diseases:** In recent years, role of chronic stress in neurological disease has intensified, and with it comes an appreciation for the true importance of stress management in a wide array of conditions (Shively and Willard, 2012). Added attention to stress as a comorbid disease factor has uncovered links between stress and stroke (Stuller et al., 2012), epilepsy (Danzer, 2012), visceral pain (Larauche et al., 2012), metabolic disorders including diabetes (Reagan, 2012), anxiety (Eiland and McEwen, 2012), and Parkinson’s disease (Hemmerle et al., 2012). The mechanisms of these effects are yet to be elucidated more fully. However, it is clear that many of the ways in which both stress and its CNS effects are through shared mechanisms, with particular regard to the neuroendocrine and immune systems from the level of the tissues, cells and even intracellular components. A better understanding of the processes by which stress and its neurological deficits affect health will lead to a greater capacity for pharmacological as well as therapeutic intervention.

**Experimental models of stress**

Different animal models have been developed for chronic stress induced neurological disorders like olfactory bulbectomy model, chronic unpredictable stress model etc. These animal models are used to screen various new chemical entities and to develop better understanding of underlying molecular pathway and cascade involved in chronic stress pathology (Table 2).

**Table 2: Types of stressors used in animal studies**

<table>
<thead>
<tr>
<th>A) Animal models for acute stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Physical stressors: Restraint shock, swimming, immobilization, sleep deprivation, loud noises, novelty and social conflict</td>
</tr>
<tr>
<td>✓ Psychological stressors:</td>
</tr>
<tr>
<td>• Social isolation, exposure to unfamiliar objects</td>
</tr>
<tr>
<td>• Psychological stressors have a major physical component</td>
</tr>
</tbody>
</table>
B) Animal models for chronic stress

✓ Chronic unpredictable stress: These includes repeated, alternate exposure to physical and psychological stressors so as to prevent habituation
✓ Olfactory bulbectomy model: Bilateral destruction of olfactory bulbs is known to cause complex alterations in behavioral, biochemical and cellular cascades, many of which are comparable to those seen in patients with major depression
✓ Traumatic brain injury model: It is known to activate several cellular cascades such as neuroinflammation, oxidative stress and excitotoxic damage

C) Other specific animal models

✓ Learned helplessness
✓ Feared conditioning

Chronic unpredictable stress (CUS) model

The chronic unpredictable, variable or intermittent stress (CUS, also referred to as chronic mild stress model), is a widely used rodent model to study stress pathology, which consists of repeated exposure to an array of varying and unpredictable, mild stressors over a sustained period of time (ranging from 10 days to 8 weeks). CUS model was originally developed by Paul Willner and colleagues in the late 1980s (Kessler et al., 1985). In humans, long-term exposure to uncontrollable and unpredictable life stressors is often said to be a major precipitant in the development of neurological disorders (Kendler et al., 1999). However, many neurological problems develop in the absence of any notable life stress, and many individuals experience chronic exposure to significant life stressors and yet never develop neurological disorders such as cognitive deficits (Kendler et al., 1999). With that caveat in mind, exposure to life stressors is one of the most reliable precipitating factors in the development of a neurological episode. Based on this knowledge, work performed by Katz and colleagues in the early
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1980s demonstrated that exposure of rodents to severe stressors resulted in a reduction in locomotor activity and of their consumption of rewarding, palatable substances such as sucrose (Katz, 1982). With these findings in mind, Willner and its group developed the chronic mild stress model by using repeated exposure of unpredictable “micro stressors”, making the model more ethical and ethologically valid than that employed by Katz and colleagues. Moreover, study has shown the brain stimulation reward and dopaminergic release in response to rewarding stimuli (Willner, 2007). Chronic unpredictable stress is known to stimulate hypothalamic–pituitary–adrenocortical (HPA) axis and increases corticosterone secretion, which causes impairment of hippocampus-dependent cognitive performance (Kurukulasuriya et al., 2004). Corticosterone secretion is further known to increase oxidative stress and ultimately leads to memory deficits (Sato et al., 2010). Among numerous animal models of stress, chronic unpredictable stress is the most exploited and useful experimental model to study stress pathology in animals (Willner, 2007).

During the last two decades since the inception of this model, there has been an explosion of behavioral research, which has extended the behavioral endpoints of this model to other facets of neurological problems beyond hedonic processing and reward salience. Thus, despite a few anomalous findings from some laboratories, and regardless of some continuing controversies about the reliability of this model from laboratory to laboratory, the chronic mild stress model has been widely accepted as a valid model of “behavioral” neurodegenerative deficits in rodents.

Olfactory bulbectomy (OBX) model

Olfactory bulbectomy (OBX) is widely acceptable model of depression (Kelly et al., 1997). It is also a useful model for the evaluation of antidepressant activity (van Riezen and Leonard, 1990). Watson was the first investigator who commented on the behavioral changes such as irritability and pugnacious occurring in rats following bilateral bulbectomy (Watson, 1907). The persistent effects of OBX manifest themselves 4 weeks after surgery. Behavioral, physiological, endocrinological and immunological changes
caused by OBX in rats closely resembles with human depression (Kelly et al., 1997). It has been demonstrated that OBX syndrome does not result from permanent anosmia, but is a consequence of widespread, long-lasting changes in synaptic connectivity and neural activity in several brain regions, including the olfactory–limbic circuitry (Kelly et al., 1997). The lesion-induced reorganization processes in the limbic and cortical areas appear to be responsible for the secondary, behavioral abnormalities appearing after 4 weeks in the OBX rats (van Riezen and Leonard, 1990). These behavioral, OBX-induced alterations are reversed by a chronic administration of antidepressant drugs, including selective serotonin reuptake inhibitors (SSRIs) (Mar et al., 2000). This suggests that an impairment of the central serotonergic system may play an important role in mediating behavioral, biochemical and neurochemical changes observed following OBX (Song and Leonard, 2005).

Bilateral destruction of the olfactory bulbs caused a complex alteration in behavioral, biochemical and cellular cascades (Song and Leonard, 2005). Bulb ablation results in anhedonia like state in sucrose preference test (Wieronska et al., 2001), increased hyperactivity in a novel environment (Breuer et al., 2008) and increased immobility time (Song and Leonard, 2005). Furthermore, OBX has also been reported to alter neurogenesis in several regions of brain, which is one of the putative pathogenic mechanisms to explain depression (Koo et al., 2010). Studies have proved that damage to the hippocampal neurons can be reversed by chronic antidepressant treatments (Duman et al., 1997). Interestingly, these OBX induced changes are independent of anosmia (Van Riezen et al., 1977). Since olfactory bulb projects into different regions of the brain (cortex, amygdala and hippocampus), thus ablation of these bulbs results in neurodegeneration in the projection areas (Song and Leonard, 2005), which possibly explains OBX-induced behavioral changes. Since OBX-induced depression-like behavior responds to chronic and not acute antidepressant treatment, thus OBX is considered as one of most reliable models to evaluate antidepressant drugs (Song and Leonard, 2005).
Mild traumatic brain injury (mTBI) model

Traumatic brain injury (TBI) is defined as an insult to the brain from an external mechanical force leading to temporary or permanent neuro-logical impairments (cognitive, physical and psychosocial) associated with an altered level of consciousness. TBI is one of the most common head injuries and comprises 70–90% of all brain trauma cases (Bazarian et al., 1999). Among the survivors of TBI, changes in emotional and social behaviour are the common and deteriorating consequences of TBI including long term- cognitive or memory impairment, aggressiveness, depression and mood disorders (Kontos and Wei, 1986). Human head injury can never be truly replicated in experimental models, but it serves the purpose of exploring therapeutic strategies relevant to TBI. Animal models of TBI play an important role in the process of evaluating and understanding the complex physiologic, behavioral, and histopathological changes associated with TBI. A number of clinical research and animal studies from past several years have now established the principal mechanism of brain damage after head injury; it is either direct impact or acceleration/deceleration types of injury. Direct impact results from striking the head with an object. In opposite to it, acceleration/deceleration brain injury results from unrestricted head movement after injury. So, in an attempt to replicate the human brain injury, various animal models of TBI have been proposed, these models include; cortical contusion injury (CCI), fluid percussion model (FP), weight-drop model, vacuum deformation, impact brain injury, non impact head acceleration models and indirect dynamic brain injury.

In most of the animal experiments, weight drop method of TBI is used to deliver a standard diffuse traumatic impact to the animals (Marmarou et al., 1994). This method has been shown to create graded brain injury in experimental animals, where severity of injury is directly related to the mass and height from which the weight is released (Marmarou et al., 1994). The weight drop TBI model stimulates proinflammatory mediators, caspases and encourages release of pro-apoptotic Bcl-2 family members (Cernak, 2005). Free radical generation induced by brain injury is known to play a critical role in the pathogenesis of post-traumatic injury (Kontos and Wei, 1986). Studies
have shown that excessive neuroinflammation can be deleterious to the injured brain (Stoica and Faden, 2010) and can promote severe neurodegeneration leading to functional decline. Brain trauma causes an activation of caspase-3 pathway by down-regulating Bcl-2/Bax ratio, which ultimately leads to neuronal apoptosis (Mao et al., 2014). Brain injury leads to increased corticosterone secretion and elevates level of oxidative-nitrosative stress mediators (Kumar et al., 2013). Among several harmful consequences associated with brain injury, cognitive dysfunction is most common (Beers, 1992). Cognitive processes are known to be at risk following head trauma due to the selective vulnerability of hippocampus (Ozdemir et al., 2005) which plays a crucial role in the processing of spatial learning and memory. Head trauma survivors face difficulty to navigate in a novel environment and perform significantly worse on the spatial learning task (Skelton et al., 2000).

Therefore, a major requirement in choosing a model of TBI is to develop a system that will provide a high-level of useful and accurate impact data. A variety of morphological, cellular, molecular, and behavior-al changes have been characterized across experimental models and different laboratories. In conclusion, there are numerous rodent models of TBI available, widely varying in their ability to model pathological mechanisms associated with human TBI. They provide the experimental backbone for investigating TBI induced pathogenesis and for the initial testing of neuroprotective compounds.

Management of chronic stress

Stress management needs a comprehensive approach due to its very broad dimensions in pathology. Therefore, one can easily classify its treatment in two categories non-pharmacological therapy and pharmacological interventions. Non-pharmacological therapy mainly includes exercising, yoga, meditation, laughter therapy, physiotherapy in trauma cases, deep breathing, relaxation and motivation techniques. Sometimes, the combination of both pharmacological and non-pharmacological techniques can be used. Pharmacological treatment includes number of drugs such as benzodiazepines, nootropics, tricyclic antidepressants and other antioxidants (Table 3).
Table 3: Pharmacological and non-pharmacological management (proposed) of chronic stress

<table>
<thead>
<tr>
<th>Management</th>
<th>Chronic unpredictable stress</th>
<th>Olfactory bullectomy induced depression</th>
<th>Traumatic brain injury</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-pharmacological</strong></td>
<td><strong>Exercising</strong>: Exercising is a most effective way to becoming stress-free. Walking, light aerobics, jogging and riding a cycle or bike is the simplest way to stress-out. <strong>Deep breathing</strong>: This technique has been an integral part of the spiritual practices (Brown and Gerbarg, 2009).</td>
<td><strong>Yoga</strong>: Yoga can also be used as a relaxation technique to relieve depression. <strong>Meditation</strong>: Meditation can help you get rid of negative feelings and depression. <strong>Laughter</strong>: Laughter in life can increase the energy and take away any negative vibes.</td>
<td><strong>Relaxation</strong>: Relaxation can help to relieve traumatic stress and put mind at ease. <strong>Physiotherapy</strong>: These therapies are useful for trauma cases. <strong>Motivation Techniques</strong>: These techniques can effectively reduce trauma injury induced memory loss cases (Jensen et al., 2012).</td>
</tr>
<tr>
<td><strong>Pharmacological</strong></td>
<td><strong>Benzodiazepine</strong> <em>(BZD’s)</em>: Diazepam and chlordiazepoxide are effective treatment against chronic stress. (Chen et al., 2011) <strong>Nootropics</strong>: The memory enhancing drugs like piracetam are helpful to overcome chronic stress induced cognitive loss.</td>
<td><strong>Tricyclic antidepressants</strong>: Trazodone, mirtapazine and amitriptyline are prescribed for treatment of depression. <strong>5-HT1A receptor agonists</strong>: They are effective to overcome depression state (Ettenberg and Bernardi, 2006).</td>
<td><strong>Peptidergic drugs</strong>: Cerebrolysin with endogenous neuropeptides and erythropoietin is effective against brain trauma cases. <strong>Psychostimulants</strong>: Such as methylphenidate are most commonly used to treat brain trauma disorders.</td>
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</table>
Antioxidants in stress management

Antioxidants play an important role in maintaining a balance between free radicals produced in the pathology of stress. These antioxidants are recognized to change the redox state and regulate oxidative processes involved in the pathways of cell proliferation and death. Oxidative stress, resulting from mitochondrial dysfunction, excitotoxicity, or neuroinflammation, is implicated in numerous neurodegenerative conditions. Antioxidants have strong scientific support to be developed as novel therapies for neurodegenerative diseases. Many of these natural antioxidants are not only active scavengers of free radicals but also act as modulators of pro-survival or pro-apoptotic signaling pathways (Motterlini et al., 2000). As a result, these compounds may have a greater potential for therapeutic success than drugs with only one mechanism of action. The multiple modes of action of antioxidants to mitigate oxidative stress and promote neuronal survival signals likely underlie their effectiveness in so many in vitro and in vivo models of neuronal injury and neurodegenerative disease (Mancuso et al., 2012). Although individual neurodegenerative diseases manifest in distinct neuronal cell types, oxidative stress and suppression of neuronal survival signals are common to many of these pathological conditions and appear to be highly relevant targets for treatment.

In other cases, oxidative damage due to mitochondrial dysfunction is a primary cause of cell death and neuronal loss. Catalytic antioxidants can intervene at each of these steps, preventing cell death in response to mitochondrial dysfunction or excitotoxicity and preventing the immune-response–driven vicious cycle of increased oxidative and nitrosative damage, which can contribute to subsequent cell death and disease progression (Rinwa and Kumar, 2012). Epidemiological studies prove that that many of antioxidant compounds possess anti-inflammatory (Motterlini et al., 2000), anti-atherosclerotic (Thilakarathna and Rupasinghe, 2012), anti-tumor (Joseph et al., 2012), anti-bacterial and neuroprotectant (Mancuso et al., 2012) activities. Natural food-derived components have received great attention in the last two decades, and several biological activities showing promising anti-inflammatory, antioxidant, and anti-apoptotic-modulatory potential have been
identified (Rinwa and Kumar, 2012; 2013). Therefore, multiple ways exist in which these antioxidants can exert the protective effects observed in the in vitro and in vivo models of neurodegeneration, and much promise is seen that these compounds may present useful therapies in human disease.

**Therapeutic interventions employed in study**

**Curcumin:** Curcumin is the principal curcuminoid of the popular Indian spice turmeric which is obtained from rhizome of *Curcuma longa* Linn. (Family-Zingiberaceae). The other two curcuminoids are desmethoxycurcumin and bis-desmethoxycurcumin. The curcuminoids are natural phenols and are responsible for the yellow color of turmeric. In the crude extract of rhizomes of *C. longa* about 70–76% curcumin is present along with about 16% demethoxycurcumin and 8% bisdemethoxycurcumin (Huang et al., 1995).

![Structure of curcumin](image-url)
Turmeric has been used historically as a component of Indian Ayurvedic medicine since 1900 BC to treat a wide variety of ailments (Aggarwal et al., 2007). Research in the latter half of the 20th century has identified curcumin as responsible for most of the biological activity of turmeric (Aggarwal et al., 2007). Curcumin acts as a free radical scavenger and antioxidant, inhibiting lipid peroxidation (Molina-Jijón et al., 2011) and oxidative DNA damage. Besides, curcumin also possess diverse pharmacological properties such as antioxidant (Sugiyama et al., 1996), anti-inflammatory (Srimal et al., 1973), and neuroprotective activities (Thiyagarajan and Sharma, 2004). Curcumin have previously been reported to possess antidepressant-like effects in different experimental models (Kulkarni and Mehta, 1985). It has been shown that antioxidant activities of curcumin are comparable to those of vitamin C and E (Blumenthal et al., 2000). Manganese complexes of curcumin are proved to have great capacity to protect brain lipids against peroxidation (Vajragupta et al., 2003). Our laboratory also suggests that curcumin restored mitochondrial dysfunction and various mitochondrial enzyme complex activities (Kumar et al., 2011). Curcumin has also shown to have restored depleted levels of biogenic amines (Xu et al., 2005). It has been documented that curcumin has a significant attenuation effect on pro-inflammatory cytokines (TNF-a) (Cho et al., 2007). Curcumin is also known to enhance the level of brain derived neurotrophic factor (BDNF) (Wang et al., 2008a). Earlier, curcumin is also reported to significantly reduce stress induced increase in serum corticosterone levels in rats (Xu et al., 2006).

The Siegel Life Project funded an initial study on curcumin for Alzheimer's in 1997-1998 through the UCLA Center on Aging. They found that curcumin was particularly effective in reducing neurodegeneration, oxidative damage, diffuse plaque deposition, aberrant inflammation and impaired inflammatory clearance following beta-amyloid infusion (Frautschy et al., 2001). This led to testing in a transgenic animal model where it was shown to dramatically diminish plaque burden and overall inflammation, but also increase plaque associated inflammatory cells suggesting clearance (Lim et al., 2001). Numerous studies have demonstrated that curcumin promotes neurogenesis by increasing brain-derived neurotrophic factor (BDNF) (Wu et
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Curcumin was found to be pharmacologically safe in human clinical trials with doses up to 10g/day. A phase 1 human trial with 25 subjects using up to 8000 mg of curcumin per day for three months found no toxicity from curcumin (Chainani, 2003).

Although many preclinical studies suggest curcumin’s beneficial effect in the prevention and treatment of several diseases, the effectiveness of curcumin has not yet been demonstrated in randomized, placebo-controlled, double-blind clinical trials (Mancuso and Barone, 2009a). Numerous clinical trials in humans were underway, studying the effect of curcumin on various neurological diseases, including multiple myeloma, pancreatic cancer, myelodysplastic syndromes, colon cancer, psoriasis and Alzheimer's disease (Hatcher et al., 2008; Singh and Sankhla, 2010).

American ginseng: It is an herbaceous perennial plant, commonly used as Chinese or herbal medicine from last 5,000 years (Kennedy and Scholey, 2003). American ginseng (Panax quinquefolium), belonging to the family Araliaceae is a native plant of North America and cultivated in many countries. The major active constituents of ginseng are triterpenoid saponins (ginsenosides), which are four-ringed steroidal structure and responsible for their therapeutic effects on the central nervous system (Nah et al., 2007). Ginsenosides are categorized in three major groups based on triterpene aglycones include panazydol, panaxytriol and oleanolic acid derivatives (Kim and Lee, 2010).

[Chemical structure of ginsenoside]
Other chemical compounds extracted from American ginseng include alkanes, alkynes and sterols, fatty acids, mono-triterpene, phenylpropanoids, kairomones, carbohydrates (sugars and polysaccharides), amines, flavonoids, organic acids and vitamins. Also amino acids, nucleic acids, various enzymes and inorganic compounds (including germanium) are obtained from ginseng (Chang et al., 2003). Ginsenosides are well-known for their antioxidant and free radical scavenging properties (Li et al., 1999). It has been shown that ginsenosides are the most effective agents in the treatment and prevention of cancer. More than 60 different types of ginseng have been identified that are in different parts of the plant including roots, leaves and fruits (Qu et al., 2009). Some active ginseng metabolites have also shown beneficial effects on neurotransmitter levels (Xu et al., 2010). Studies have shown antidepressant effects of oral ginsenosides in both forced swimming test and chronic mild stress model of depression (Dang et al., 2009). Further, ginsenosides are also well known for their neuroprotective effects in various animal models (Lian et al., 2005; Lee et al., 2006). Earlier, study demonstrated that ginseng attenuated plasma corticosterone level (Sheikh et al., 2007). Saponins derived from American ginseng significantly attenuated apoptotic factor (caspase-12) (Wang et al., 2012) and are known to show protection against ischemia (Lim et al., 1997).
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Ginsenoside Rg1 and Rb1 increases the proliferation and differentiation of neural progenitor cells in dentate gyrus of hippocampus of normal adult mice and global ischemia model in gerbils (Cheng et al., 2005). In addition, Rg1 increases the expression of brain derived neurotrophic factor, Bcl-2 and antioxidant enzyme and increased the number of synapses and mossy fiber sprouting in CA3 regions of hippocampus suggesting the role of Rg1 in the modulation of synaptic plasticity and possibly to the increased cognitive function in Alzheimer's disease (Cheng et al., 2005). Similarly, when the mixture of brain-derived neurotrophic factors (BDNF) and ginsenosides Rg1 and Rb1 was treated to human neural stem cell during the differentiation procedure, it promoted cell survival and enhanced neuronal outgrowth and the expression of synaptic marker proteins, which was evidenced by time lapse microscopy, immunostaining, and Western blot analysis (Wang and Kisaalita, 2011). In general, ginseng and even a single compound of ginsenoside produce its effects on multiple sites of action, which make it an ideal candidate to develop multi-target drugs.

Therefore, all these studies reveal that ginseng and ginsenosides affect various aspects of diseases including neuropsychiatric disorders. Even with the vast array of researches conducted during last two decades, it still needs elaboration on the molecular and cellular mechanism of action of ginsenosides. Obviously, investigations using more pharmacological model systems would be essential to unravel the therapeutic efficacy as well as molecular mechanisms of ginseng.

Quercetin: Quercetin (3,5,7,3',4'-penta hydroxyl flavone) is a flavonoid that has a flavone nucleus composed of two benzene rings linked through a heterocyclic pyrone ring. Quercetin is a flavonoid, in other words, a plant pigment with a molecular structure like or derived from flavone. Quercetin is a dietary flavonol that is frequently found in foods, is especially abundant in onions (347 mg/kg), berries (60–120 mg/kg), and apples (36 mg/kg) (Harwood et al., 2007). It can be used as an ingredient in supplements, beverages, or
foods. Quercetin is a flavonoid widely distributed in nature. The name has been used since 1857, and is derived from quercetum (oak forest), after Quercus.

![Chemical structure of quercetin](image)

As an antioxidant, it combats the destructive “free radical” molecules that play a part in many diseases. Quercetin has been acknowledged to have various beneficial effects on human health including cardiovascular protective, anticancer, antiviral, and anti-inflammatory activities (Kumar et al., 2008). Quercetin also prevents the reduction of intracellular antioxidant defense systems, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) and glutathione reductase (GR) (Molina et al., 2003). It has been suggested that quercetin has ameliorating effects on cognitive dysfunctions induced by various compounds, such as ethanol, d-galactose, and colchicine. In addition, quercetin is thought to alleviate cognitive deficits induced by surgical methods, such as ischemia (Kumar et al., 2008). More recently, Kawabata and its group (Kawabata et al., 2010) reported that quercetin attenuates stress-induced behavioral depression through reduction in the HPA axis activation by the suppression of the CRF mRNA expression in the hypothalamus. Earlier, quercetin has also been reported to attenuate high glucose-induced expression of proinflammatory cytokines (Wu et al., 2009).
In a previous study, it has been shown that quercetin attenuate high glucose-induced expression of proinflammatory cytokines including TNF-α, interleukin-1 β in human monocyctic THP-1 cells (Wu et al., 2009). Quercetin and its enriched foods have shown antidepressant-like activity; however, its mechanisms of action remain unclear. In addition, quercetin is reported to increase the insulin sensitivity (Kannappan & Anuradha, 2009). Quercetin is also reported to reduce diabetic complications, like, neuropathy, nephropathy, retinopathy, heart diseases, and depression (Kato et al., 2008). Moreover, several experimental investigations showed the potential of quercetin against cognitive deficit in various animal models (Rinwa and Kumar, 2013). Memory improvement was also observed by Patil and its group (Patil et al., 2003) after quercetin was administered intraperitoneally for seven days to mice suffering from age-related or lipopolysaccharide treatment-induced cognitive impairment. In this case, the passive avoidance and elevated plus maze tests were utilized and the improvement was associated with the inhibition of cyclooxygenase-2 and inducible nitric oxide synthase. Mice fed for eight weeks with quercetin (5 and 10 mg/kg per day) exhibited significantly improved learning ability and memory compared with control mice injected daily with d-galactose (d-Gal) (50 mg/kg per day), as demonstrated by the step-through and Morris water maze tests (Lu et al., 2006).

In conclusion, chronic stress related problems are widespread in our modern society due to life style changes. Chronic stress can initiate a cascade of biological events that can lead to depression, cognitive dysfunctions and other neurological diseases. The pathophysiological mechanism of chronic stress and related complications are unknown and further makes the situation worse. Therefore, there is an urgent need of a novel effective therapy to minimize the global burden of chronic stress and its related problems. The approach towards development of safe and effective drug treatment from traditional herbs can be considered as a novel therapeutic strategy for the treatment of chronic stress and related complications.