CHAPTER-I

1. INTRODUCTION

1.1 Stress

Stress is to be one of the largest killers of human today and the health burden of stress related disorders are rapidly increasing in this world. Our daily lives are full of emotionally arousing experiences, ranging from small annoyances to major life events like the loss of a spouse. Collectively, these potential threats of our bodily homeostasis are referred to as "stress" (Levin *et al.,* 2005). Stressful events ("stressors") can be tangible or mentally evoked and of a physical or psychological nature. The World Health Organization said stress has become a *'World Wide* Epidemic' (The Busy Lifestyle Magazine, 2017) **(**Fig 1.1**)**. This report done by selected stress statistics collected over the period ranging from 2009 to 2016 from US, UK, France, Australia, Japan and European Union and this report shown high percentage of stress noticed in Japan.

A report, about 450 million people suffer from a mental or behavioural disorder (WHO, Geneva, 2001). This amounts to 12.3% of the global burden of disease and predicted to rise up to 15% by 2020 (Reynolds *et al.,* 2003). Nearly half of these people live in the South-East Asia Region and Western Pacific Region, reflecting the relatively large populations said the WHO report.

Worldwide stress was the fourth leading cause of mortality and socioeconomic burden of disease in 2000 and is predicted to be the second leading cause after HIV in the year of 2030 (Mathers and Loncar, 2006).

Prevalence rate for all mental disorders in India was observed to be 65.4/1000 population. Out of which the prevalence rate for affective disorder is estimated to be 31.2/1000 population (Madhu *et al.*, 2001). In October 2016, the National Institute of Mental Health and Neurosciences (NIMHANS) in Bengaluru released a mental health survey that said that the incidence of stress is roughly one in every 20 Indians or 5% of the population. The prevalence of major depression is estimated to be 2% in the general population over 65 years of age (Fountoulakis *et al.*, 2003). About 11.2% school dropouts had severe to extreme grades of depression as against 3% among school going and nil among college going adolescents (Nair *et al.*, 2004).

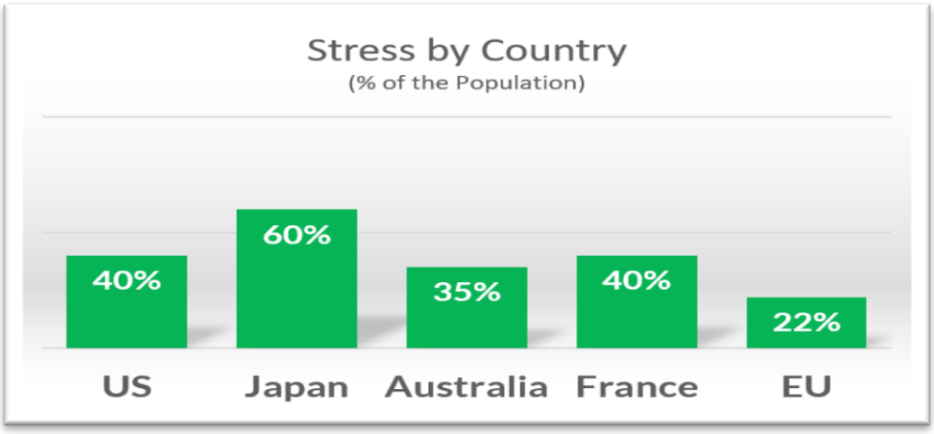

Fig 1.1The percentage of the population experiencing high to moderate stress

Stress is found to be more common in women than men (Vaváková M *et al.*, 2015). Men often show different experience of depression than women and may have different ways of coping with the symptoms.The effects of stress, violence, lack of social support, relational problems, low self-esteem and ruminative cognitive styles are believed to contribute to the vulnerability to depression in women (Stewart *et al*., 2004; Akhtar-Danesh and Landeen, 2007; Posmontier, 2008). Stress can be perceived by low social status, sometimes accompanied by alcohol or drug

dependency, abusive behavior and anger. Stress symptoms are more typical for male patients to hide and compensate functional deficits with overwork or risk-taking behavior (Stewart *et al*., 2004; Akhtar - Danesh and Landeen, 2007) **(**Fig 1.2**).** Its major consequence, lead to suicide**.** The stress disorder is also often associated with suicide and there are between 10 and 20 million suicide attempt every years (Thase and Howland, 1995).

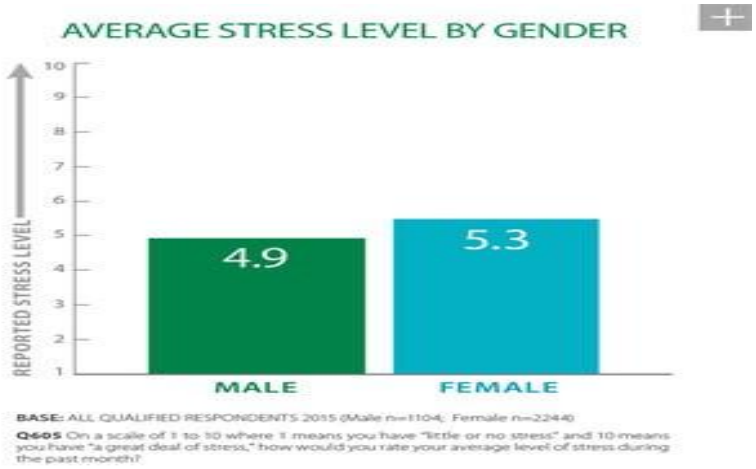

Fig: 1.2 Stress Statistics by Gender

The human society has become complex and in many ways, more demanding. Naturally our physiological responses designed to cope with the ever-increasing adverse situations have not evolved appreciably during the past thousand years (Naik *et al*., 2006). Stress is largely recognized as the precipitant of several psychiatric illnesses, including anxiety and depression (Jong Yuh Cherng *et al*., 2012).

According to Dr. Hans Selye, a pioneer stress researcher in the 1930s, stress includes not only the body's response to physical and psychological demands, but also to the mental and emotional demand. The term "stress" originally originates from mechanics, where it is used as a measure of pressure on a deformable body.

Cannon proposed the fight-or-flight response reaction. This occurs when a person experiences very strong emotions especially those associated with a perceived threat (Cannon, 1932). During the fight-or-flight response, the body is rapidly arousedby activation of both the sympathetic nervous system and the endocrine system.

Selye also proposed that not all states of stress or threatened homeostasis are deleterious, terming healthy stress as 'eustress' and distress as 'pathogenic' stress or bad. In the general population, individuals who lead a stressful lifestyle and show "type A" behavior are recognized as the reasons to be at risk for coronary heart disease (CHD) (Bagheri *et al.,* 2016). Mental stress is more characteristic of the everyday life and demands an active coping mechanism causes elevated sympathetic responses. In humans, a range of various stressful events have been associated with lowering the immune system functioning, including examinations, battle task, vigilance, sleep deprivation and divorce (Shamsdin *et al.,* 2009). Stress is a global menace fortified by the advancement of industrialization and implicated by a variety of factors and environmental, social or pathological phenomenon of life. Considerable evidences published in the last decade have focused on a constellation of neurochemical, biochemical and molecular effects caused by stress in the CNS, endocrine system and immune system (Aloe *et al.,* 2002). It is considered as psychological, physiological, and behavioral response by individuals when they perceive a lack of equilibrium between the demands placed upon them and their ability to meet those demands (Bakker *et al.,* 2006). Common health problems caused or exacerbated by stress include depression and anxiety, pain of any kind, sleep problems, autoimmune diseases, digestive problems, skin conditions, such as

eczema, heart diseases, weight problems, reproductive issues, thinking and memory problems. Anxiety and depression are the most prevalent psychiatric diagnosis in patients who frequently visiting psychiatric clinics (Gautam *et al*., 2012).

Homeostasis regulates the physiological actions in the bodyand depends on the stress and antioxidant levels in the cells. Nowadays stress is involved in the major portion of life has stressful events in both working and non-working individuals and it is a hallmark for pathogenesis of a variety of diseases and disorders (Bruce *et al.*, 2007), such as diabetes mellitus, hypertension, depression, anxiety, immunosuppressant, vascular disorders, male infertility, cognitive dysfunction, peptic ulcer ulcerative colitis, atherosclerosis, cancer, ageing, arthritis, Alzheimer's disease, liver disease etc (Aher *et al.*, 2011).

1.2 Stages of Stress

Hans Selye has proposed the various stages of stress by theory of General Adaptation Syndrome (GAS) (Selye H, 1973). GAS is the three-stage process that describes the physiological changes of the body goes through when under stress (Fig 1.3)

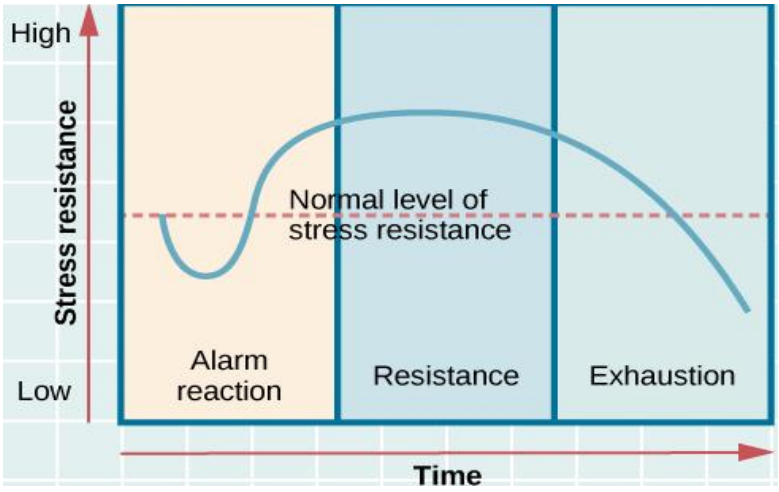

Fig: 1.3 Stages of Stress

1.2.1 Alarm reaction stage

The alarm reaction stage refers to the initial symptoms of the body experiences when under stress. This natural reaction prepares everyone to either flee or protect them self in dangerous situations results, adrenal gland releases cortisol (a stress hormone) and receive a boost of adrenaline, which increases energy by releasing glucose. This fight-or-flight response of alertness occurs in the alarm reaction stage. The general indications of this stage are

- Fast breathing with sweating
- Accelerated heart beat
- Higher blood pressure
- Indigestion.

1.2.2. Resistance stage

After the initial shock of a stressful event and having a fight-or-flight response, the body begins to repair itself. Lower amount of cortisol released to induce heart rate and blood pressure begin to normalize. If the system can overcome stress and the situation is no longer an issue, our body continues to repair itself until hormone levels, heart rate and blood pressure reach a pre-stress state. Some stressful situations continue for extended periods of time and goes through changes that unaware of in an attempt to cope with stress. The body continues to secrete the stress hormone and the blood pressure remains elevated. If the resistance stage continues for too long of a period without pauses to offset the effects of stress, this can lead to the exhaustion stage.

Signs of the resistance stage include:

- Irritability
- Frustration
- Concentration

1.2.3 Exhaustion stage

This is the stage of prolonged or chronic stress. Struggling with stress for long periods can drain the physical, emotional and mental resources of the body no longer has strength to fight stress and lead to the situation become hopeless. Signs of exhaustion include:

- Fatigue
- Burnout
- Depression
- Anxiety
- Decreased stress tolerance
- The physical effects of this stage also weaken the immune system and lead to risk for stress-related illnesses.

1.3. Types of Stress

Stress management can be complicated and confusing because there are different types of stress. Psychologists categorize stress into three different types. They are (Sarah Mae Sincero, 2018)

1. Acute stress,
2. Episodic acute stress
3. Chronic stress.

1.3.1 Acute Stress (AS)

Acute stress is the most common form of stress. It adapt by demands and pressures of the recent past and anticipated demands and pressures of the near future. Acute stress is thrilling and exciting in small doses, but too much is exhausting. This stress can lead to psychological distress, tension, headaches, upset stomach and other symptoms are easily recognized.

1.3.2 Episodic Acute Stress (EAS)

It seems common for people with acute stress reactions to be over aroused, short-tempered, irritable, anxious and tense. Frequently, they describe themselves as having "a lot of nervous energy." The symptoms of episodic acute stress are the symptoms of extended over arousal: persistent tension headaches, migraines, hypertension, chest pain and heart disease.

1.3.3 Chronic Stress (CS)

This stress has unrelenting demands and pressures for seemingly interminable periods of time. With no hope, the individual gives up searching for solutions. Chronic stress kills through suicide, violence, heart attack, stroke and perhaps even cancer. This stage made the people wear down to a final, fatal breakdown. Because physical and mental resources are depleted through long-term attrition, the symptoms of chronic stress are difficult to treat and may require extended medical as well as behavioural treatment and stress management.

1.4 Stress factors

When stress persists and becomes excessive, it culminates to strain that leads to affect a person's physique, psychology and behaviour. Thus the body prepares itself for 'fight or flight' response. The excessive stress develops various symptoms

that harm to individuals performance and health and threaten their inability to cope with the environment. A stressoris concerning with a chemical or biological agent, environmental condition, external stimulus or an event that causes stress to an organism (SatoTadatoshi *et al.,* 2006).

Stress factors broadly fall into four types or categories (Larry Trivieri., 2013)

1. Physical stress
2. Psychological stress
3. Psychosocial stress
4. Psycho spiritual stress

1.4.1 Physical stress:

It is a common type of stress, which refers to actual physical activities and events that wreak havoc on the human body. Traumatically stress caused by injury, infection and surgery. The intense physical labour/over-exertion, environmental pollution includes pesticides, herbicides, toxins, heavy metals, inadequate light, radiation, noise and electromagnetic fields, illness (viral, bacterial, or fungal agents), fatigue, inadequate oxygen supply, hormonal and/or biochemical imbalances, dietary stress (nutritional deficiencies, food allergies and sensitivities, unhealthy eating habits), dehydration, substance abuse, dental challenges and musculo skeletal misalignments/imbalances are effective to this stress.

1.4.2 Psychological stress

The study by Singh and Singh (1992) has found that stress induced by following emotional and cognitive factors. Emotional stress caused by resentments, fears, frustration, sadness, anger, grief and bereavement. Cognitive stress also found by information overload, accelerated sense of time, worry, guilt, shame, jealousy,

resistance, attachments, self-criticism, self-loathing, unworkable perfectionism, anxiety, panic attacks, not feeling like yourself, not feeling like things are real and a sense of being out of control or not being in control and perceptual stress like beliefs, roles, stories, attitudes and worldwide view.

1.4.3 Psychosocial stress

Psychosocial stress is implicated in the development of psychotic symptoms (Johns *et al*., 2004). Upsetting life events of lifetime experience was associated with increased levels of psychotic symptoms (Miller *et al*., 2001) in individuals. Relationship and marriage difficulties (partner, siblings, children, family, employer, co-workers and employer) lack of socialsupport, lack of resources for adequate survival, loss of employment/investments/savings, loss of loved ones, bankruptcy, home foreclosure and isolation.

1.4.4 Psycho-spiritual stress

A key ingredient of stress is expectation. Often we anticipate things to remain the same and then change or the appearance of change causes distress. Likewise, we become distressed if people do not behave as we expect or if events do not work out as we had thought they would. "Let go and let God," is the kind of bumper sticker slogan to most people that intuitively makes them sense, but the power behind its simplicity is in understanding how restraining and driving forces causes distress (The Spiritual Mind and Stress 2007) includes a crisis of values, meaning and purpose, joyless striving instead of productive, satisfying, meaningful and fulfilling work and a misalignment within one's core spiritual beliefs.

Overall, improperly or ineffectively managed stress factors usually take a toll on the body. When stress-related feelings, moods, emotions are made body into the psychosomatic or psychogenic illness that including headaches, heart palpitations, physical/cognitive/emotional pain and suffering, constricted throat and shallow, constricted breathing, clammy palms, fatigue, nausea, anxiety, allergies, asthma, autoimmune syndromes related to an ineffective functioning of the immune system, hypertension (high blood pressure) and gastrointestinal disturbances such as diarrhea, upset stomach, duodenal ulcers and oesophageal reflux syndrome.

1.5 Stress Symptoms

Prolonged stress can result in suppressed immune function, increased susceptibility to infectious and immune-related diseases and cancer. Emotional stress can also result in hormonal imbalances (adrenal, pituitary, thyroidand etcetera) that further interfere with healthy immune functioning. Severe stressors such as war, rape or death of a loved one, do not typically induce depression, but instead lead to syndromes such as post-traumatic stress disorder (PSTD), panic disorder and generalized anxiety disorder (GAD) (Nestler *et al*., 2002). Behr and Newman (1978) have outlined the stress symptoms mainly in three categories: Psychological symptoms which include Cognitive Symptoms and Emotional Symptoms, Physical symptoms and Behavioural symptoms.

1.5.1 Cognitive Symptoms (Singh and Singh 1992)

- Memory problems
- Inability to concentrate
- Poor judgment
- Seeing only the negative

- Anxious or racing thoughts
- Constant worrying

1.5.2 Emotional Symptoms (Singh and Singh 1992)

Stress manifests in various forms of emotional disorders.

- Depression or general unhappiness
- Anxiety and agitation
- Moodiness, irritability or anger
- Feeling overwhelmed
- Loneliness and isolation
- Other mental or emotional health problems.

1.5.3 Physical Symptoms

Most of the early reports suggested that stress directed with physiological symptoms because stress could create changes in metabolism, increase the heart and breathing rates, increase blood pressure and induce heart attacks (Brown 1977).

- Nausea, dizziness
- Asthma
- Loss of sex drive
- Frequent colds or flu
- Ulcer
- Headaches and chest pains
- Bronchial asthma

1.5.4 Behavioral Symptoms (Jagdish 1987)

Commonly stress also bears behavioral symptoms, which are easily observable. There is a general agreement that a high degree drives people who adopt

certain easily visible behavioral symptoms like

- Eating more or less
- Sleeping too much or too little
- Obesity and gluttony
- Withdrawing from others or absenteeism
- Procrastinating or neglecting responsibilities
- Using alcohol, cigarettes or drugs to relax
- Nervous habits (e.g. nail biting, pacing)

1.6 Causes of stress

The situations and pressures that cause stress are known as stressors. Usually stressors as being negative, such as an exhausting work schedule or a rocky relationship. However, anything that puts high demands may be stressful. This includes positive events such as getting married, buying a house, going to college or receiving a promotion. Of course, not all stress is caused by external factors. Stress can also be internal or self-generated, when the burdens excessively about something that may or may not happen or have irrational, pessimistic thoughts about life (Antelman and Caggiula, 1990).

1.6.1 Common external causes of stress(Pestonjee 1987; Evans and Johnson 2000)

- Major life changes
- Work or school
- Relationship difficulties as emotional problems
- Being too busy
- Excessive noise
- Safety hazards

- Lack of privacy and poor air quality
- Poorly designed office space
- children and family

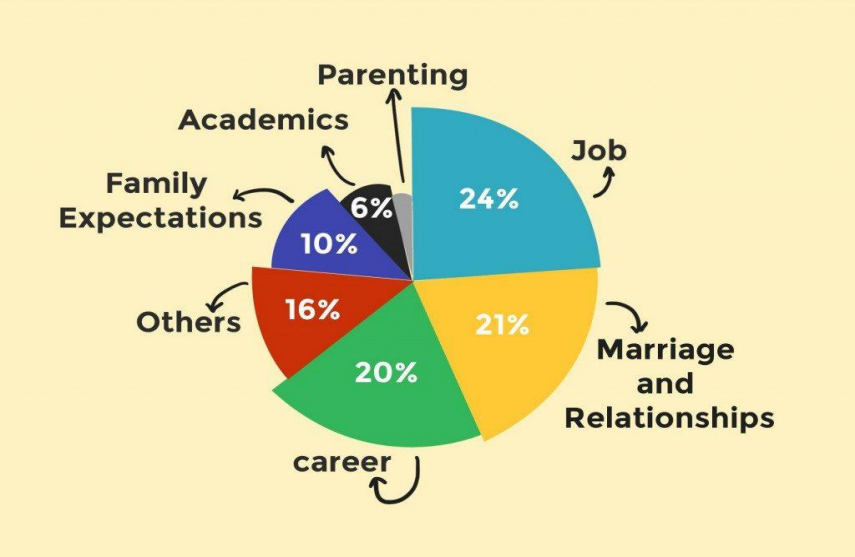

Fig: 1.4 External causes of stress

1.6.2 Common internal causes of stress (Aditya and Sen 1993)

- Pessimism
- Inability to accept uncertainty
- Rigid thinking, lack of flexibility
- Negative self-talk
- Unrealistic expectations / perfectionism
- All-or-nothing attitude
- Grief, guilt, low self-esteem

1.7 Top 10 stressful life events

In 1967, the famous psychiatrists Thomas Holmes and Richard Rahe examined the medical records of over 5,000 medical patients as a way to determine whether stressful events might cause illness. Patients were asked to tally a list of 43

life events based on a relative score. A positive correlationof 0.118 was foundbetween their life events and their illnesses. Their results were published as the Social Readjustment Rating Scale (SRRS) (Holmes and Rahe 1967) known more commonly as the Holmes and Rahe Stress Scale. Subsequent validation has supported the links between stress and illness (Rahe and Arthur 1978). According to the widely validated Holmes and Rahe Stress Scale, these are the top ten stressful life events for individuals that can contribute to illness.

Important Stressors on the Social Readjustment Rating Scale (Holmes and Rahe, 1967) are

1. Death of a spouse.
2. Death of a close family member
3. Divorce
4. Imprisonment
5. Injury or illness
6. Marriage
7. Job loss or dismissal of work
8. Marriage reconciliation
9. Retirement
10. Fathering a child

However, most genes in quest are not stress induced disorderspecific, but overlap with other psychiatric conditions and drug abuse. Yet, no specific gene or a series of genes that induce stress have been reliably identified to date. Rather, certain variations in genes called polymorphisms may increase risk for depression (Rot *et al.*, 2009). The “stress” genes which have been selected under pressure in

ancient environments may have not adapted to the rapid environmental changes of today (Siervo *et al.*, 2009).

A type 1 receptor of corticotrophin-releasing hormone (CRH-R1) also appears to interact with early life adverse experiences in the genesis of adult depression (Bradley *et al*., 2008). A common functional length polymorphism in the serotonin transporter gene (5-HTTLPR) has been suggested to predispose to depression as well as to personality traits of anxiety and pessimism (Lesch *et al*., 1996; Belmaker and Agam, 2008). Yet, it turned out that this 'short allele' 5-HTTLPR polymorphism predicted depression only in association with stressful life events (Caspi *et al*., 2003). A single nucleotide polymorphism (SNP) in the gene encoding brain-derived neurotrophic factor (BDNF), Val66Met, has been shown to interact with the 5-HTTLPR short allele to confer sensitivity to environmental factors (Kaufman *et al*., 2006; Uher, 2008).

1.8 Stress disorder

Experiencing many stressful events early in one's life can also increase the chance of developing major psychiatric disorders (Turner & Lloyd, 1995). Stress can be associated with psychological disorders such as delusions (Kingston and Schuurmans-Stekhoven 2016), general anxiety disorder, depression and post-traumatic stress disorder. It has been suggested that stress is implicated in the etiology of both depressive and anxiety disorders or as a consequence.

1.8.1 Anxiety

Exposure to severely stressful events such as physical/sexual assault, death of a family member, or natural disasters can predispose a person to developing mental illness. Anxiety is an emotional state (mood) often characterized by

apprehension, uneasiness and dreadness. Anxiety occurs when an organism feels or anticipates a threat to its homeostasis. Physical symptoms of anxiety include palpitations, breathlessness and a choking sensation, tightness in the chest, trembling and flushing. Anxiety can also be felt in response to everyday by everyone at situations that may be mentally or emotionally stressful and can therefore be a part of the normal stress response to threatening circumstances (Miller-Keane and O'Toole, 2005).

1.8.2 Depression

Depression is the most prevalent mental disorder and it is recognized to be symptomatically, psychologically and biologically heterogeneous (Thase and Howland 1995). Any form of stressful life event is considered as the initial sign of depression, thereby depression is often thought as a stress related disorder (Pittenger and Duman, 2008). Major depression is characterized by feelings of intense sadness and despair, mental slowing and loss of concentration, pessimistic worry, lack of pleasure, self-deprecation and variable agitation or hostility. Physical changes also occur, particularly in severe, vital or melancholic depression (Tondo *et al*., 2003). The monoamine theory, suggests that depression results from functionally deficient monoaminergic (nor adrenaline (NA) / 5- hydroxytryptamine (5-HT)) transmission in the central nervous system whereas an excess may result in mania (Baker and Dewhurst, 1985). The American Heart Association, fully aware of the established importance of depression in cardiovascular diseases and they have recommended routine depression screening for all heart disease patients (AHA, 2014) due to its high risk factor.

1.8.3 Hyperthyroidism

The relationship between stressful life events and the onset of Graves' disease (GD) was initially documented by Parry in 1825. Psychological distress has been reported in up to 65% of younger patients with hyperthyroidism and physical stress in many older patients (Hoffenberg, 1974). Stress may result in a defect in the immunologic surveillance leading to production of TSH receptor antibodies (Davies *et al.*, 2005). In genetically susceptible individuals stress favors the development of GD by shifting the Th_1-Th_2 immune balance away from Th_1 towards Th_2 (Tsatsoulis, 2006). This shifting may affect the onset or course of GD.

1.8.4 Diabetes Mellitus

Severe stress may be a risk factor for diabetes. Children aged five to nine years with stress were significantly more likely to be diabetic (Thernlund *et al.*, 1995). However, recent-onset Type 1 diabetics, 15-34 years old reported no major stress factors within the year before diagnosis (Littorin *et al.*, 2001). Thus stress in early life may be a risk factor for diabetes, but not in young adults.

1.8.5 Gonadal dysfunction

In females, stress can lead to anovulation, amenorrhea and other menstrual irregularities. Among newly incarcerated women with stress, 9% had amenorrhea and 33% had menstrual irregularity (Allsworth *et al.*, 2007). In males, there can be decreased sperm count, motility and altered morphology (Mc Grady, 1984). Ejaculatory disorders, impotence and oligospermia may be associated with psychological factors in male infertility (Palti, 1969).

1.8.6 Obesity

Mental stress leads to chronic activation of the neuroendocrine systems. Cortisol favors central fat deposition, a decrease in the adipostatic signal leptin and an increase in the orexogenic signal ghrelin, inducing increased appetite and food intake. This phenomenon contributes to the current epidemic of obesity. Obesity is a major risk factor for several chronic conditions including hypertension, cardiovascular disease (CVD), type 2 diabetes and certain types of cancer and as such poses a major challenge to public health care (Lavie *et al.,* 2009). Evidences emerging in the past decade suggest that individuals who are more obese may be more responsive to stress (Black, 2006).

1.8.7 Arthritis

Non-genetic factors, such as aspects of lifestyle may explain approximately 40% of the cases of rheumatoid arthritis (Kopec *et al.,* 2004). Besides diet, lifestyle in relation to stress can play an important role in inflammatory arthritis. It has recently been shown that psychosocial factors, such as fearful experiences and parental disturbance during childhood can predispose to chronic musculoskeletal pain in later-life. These factors are probably just as relevant earlier in history as they are today (Harrison *et al.,* 2006).

1.8.8 Cardiovascular diseases

Hypertension and CVD exhibits a major focal point in the study of psychophysiological disorders because of the cardiovascular system's centrality in the stress response (Everly and Lating, 2002). Each year, heart disease causes approximately one in three deaths in the United States and it is the leading cause of death in the developed world (Centers for Disease Control and Prevention [CDC],

2011; Shapiro, 2005).The risk factors contributing to cardiovascular disorders include social determinants such as aging, income, education and employment status, as well as behavioral risk factors that include unhealthy diet, tobacco use, physical inactivity, and excessive alcohol consumption (World Health Organization, 2013). Over the past few decades, there has been much greater recognition and awareness driven by stress and other psychological factors act as stressors for cardiovascular problems. Stressors include job strain (Trudel *et al*., 2010), natural disasters (Saito *et al.*, 1997), marital conflict (Nealey-Moore *et al.*, 2007) and exposure to high traffic noise levels at one's home (De Kluizenaar *et al*., 2007).

Friedman and his colleague, Ray Rosenman, came to understand that people who are easily prone to heart disease tend to think, feel, intensively driven workaholics, always seem to be in a rush, and act differently than those who are not have been exhibit pattern of Type-A behavior and those who are more relaxed and laid-back were characterized as Type-B (Friedman and Rosenman, 1959).The highest levels of anger were over 6 times more likely than those who indicated less anger to have had a heart attack. Angry and hostile moods can create social strain, mainly in the form of antagonistic social encounters might contribute to cardiovascular disease (Vella *et al.*, 2012). In addition to these Watson *et al.*, (1988) suggested that a number of other negative emotional states referred asnegative affectivityinvolving anger, contempt, disgust, guilt, fear and nervousness that have been linked with the development of both hypertension and heart disease.

1.8.9 Ulcer

Psychological stress may be an important contributing factor in the causation of peptic ulcer (Crawford *et al.*, 2000). Due to stress there is a breakdown in

epithelial defense which appears to be due to decreased mucosal blood flow leading to ischemia, local acidosis, free radical formation and impaired rapid restitution (Spechler *et al.,* 2002). Many stressful situations like burns, brain stem surgery, CNS tumours, trauma, stroke, sepsis, hypotension and even stressful life events may lead to gastric or duodenal ulcers (Narendranathan *et al.,* 2003).

1.8.10 Neurodegenerative disorder

Stress is known to induce alterations in various physiological responses, leading to a pathological state. There is increasing evidence that severe stress affects cognitive functions and leads to the pathogenesis of various neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and aging (Gerard *et al.,* 2000; Perrig *et al.,* 1997). There is also available evidence regarding the role of free radicals in the pathogenesis of Alzheimer's disease, diabetes, cancer and aging (Halliwell *et al.,* 1985; Oberley, 1988).

1.8.11 Immune system

Stress hormones released during hypothalamic pituitary-adrenal (HPA) axis activation can adversely impact immune function. Mainly it inhibits the production of lymphocytes, white blood cells that circulate in the body's fluids that are important in the immune response (Everly and Lating, 2002). Hundreds of studies have been repeatedly demonstrated that many kinds of stressors (public speaking, medical school examinations, unemployment, marital discord, divorce, death of spouse, burnout and job strain, caring for a relative with disease and exposure to the harsh climate) are associated with poor or weakened immune functioning (Glaser and Kiecolt-Glaser, 2005; Kiecolt-Glaser *et al.*, 2002; Segerstrom and Miller, 2004). Evaluation of these findings remember that there is a tangible

physiological connection between the brain and the immune system and concerns the sympathetic nervous system that innervates immune organs such as the thymus, bone marrow, spleen, and even lymph nodes (Maier *et al*., 1994).

1.9 Mechanism of Stress Response

Hormones are chemical messengers that instruct an every cell, organ, gland and system of the body what and how much to do. They are made by endocrine glands and secreted in precise amounts into the bloodstream as directed by the central nervous system. Hypothalamus, a brain area is the chief controller of hormone production that regulates all physiological systems to maintain internal balance (homeostasis). It responds by initiating hormonal adjustments that allow the system to adapt to the changes and maintain or regain homeostasis. A hormonal message transfers from hypothalamus to pituitary, the master endocrine gland, instructing it to send a demand to the appropriate endocrine gland to increase or decrease production of specific hormones.

The adrenals are the main glands for stress responsebecause they make all of the major hormones involved in stress response and adaptation.

1.9.1 Hormones

During stress the hypothalamus gets the adrenals to produce specific hormones via two pathways:

a) Sympatho adrenomedullary (SAM) pathway–direct sympathetic nervous system stimulation of the adrenal medulla to make adrenalin and noradrenalin for the quick, short-term "fight or flight" response.

b) Hypothalamic-pituitary-adrenal (HPA) axis–adrenocorticotropic hormone stimulation of the adrenal cortex by the pituitary to make cortisol, aldosterone and other corticosteroids for more prolonged stress adaptations.

Stress induces adreno - medullary response resulted in greater release of ACTH, which stimulates adrenal medulla and cortex which leads to increase in the weight of adrenal glands (Bhatwadekar *et al.,* 1999, Krupavaram *et al.,* 2007, and Emilia *et al.,* 2000). Activation of the pituitary-adrenal axis is a prominent neuroendocrine response to stress, promoting survival. Stimulation of this axis results in hypothalamic secretion of corticotrophin-releasing factor (CRF) which situated just below the hypothalamus. CRF then stimulates the pituitary to adrenocorticotropin (ACTH) and then travels to the adrenal cortex, or the outer layer of the adrenal glands, and signals a secretion of glucocorticoids, namely corticosterone in animals and cortisol in humans (Breedlove *et al.,* 2007). The ACTH then activates the adrenal glands to secrete a number of hormones into the bloodstream; among the important one is cortisol, known as a stress hormone that can affect virtually every organ within the body and helps to provide that boost of energy at first encounter of a stressor and preparing individual to run away or fight (Weiser, 2014). CRF also initiates 8 - lipotropin and -endorphin hormones. Plasma levels of these hormones can increase two- to fivefold during stress in humans (Hargreaves, 1990). The fight or flight response of corticotrophin-releasing factor (CRF) is targeting a membrane-bound G protein-coupled receptor and remains a key regulator of the HPA axis. In response to chronic stress where the threshold of the organisms exceeds, CRF initiates a cascade of events that culminate in the release of glucocorticoids and thus stress-related disorders (Edwin Jothie Richard *et al.*, 2016).

When a stress response is initiated, the hypothalamus secretes corticotrophin-releasing factor (CRF) to the anterior pituitary, situated just below the hypothalamus, which in turn secretes adrenocorticotropin hormone (ACTH) (Nemeroff *et al*., 1984). This ACTH then travels to the adrenal cortex or the outer layer of the adrenal glands and signals a secretion of glucocorticoids, namely corticosterone in animals and cortisol in humans (Breedlove *et al*., 2007) (Fig1.5).

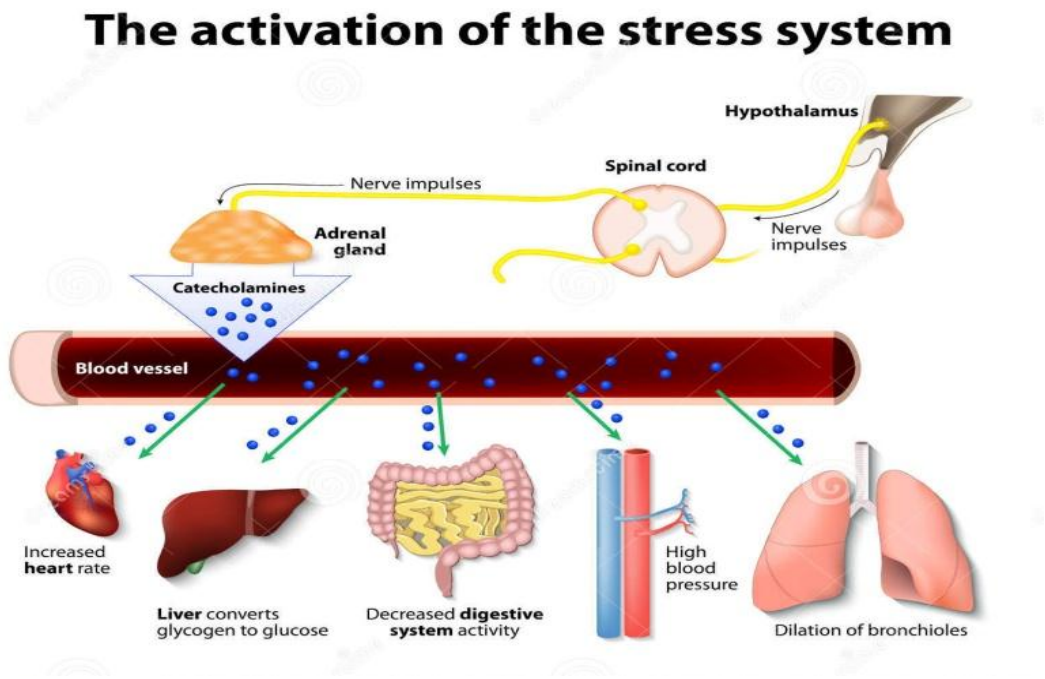

Fig: 1.5 Activation of the stress response system

Adverse situations trigger responses of the adrenals, which result in an increased secretion of a number of hormones including glucocorticoids, catecholamines, β-endorphin, leptin, insulin and growth hormone, the effect of which is to increase mobilization of energy sources and adapt the individual to its new circumstance (Mostl *et al.*, 2002). Thyroid function is usually down-regulated during stressful conditions. T_3 and T_4 levels decrease with stress. Stress inhibits the thyroid-stimulating hormone (TSH) secretion through the action of glucocorticoids

on the central nervous system (Helmreich *et al.*, 2005). Human brain imaging studies confirm involvement of these brain regions in anxiety. Hippocampus (Bohacek *et al.*, 2015) and amygdale (Herman, *et al*., 2003) are both brain regions that are highly responsive to stress in humans and rodents.

1.9.2 Neurotransmitter

Neurotransmitters are often referred to as the body's chemical messengers. They are the molecules used by the nervous system to transmit messages between neurons or from neurons to muscles. NA, DA and 5HT are the important biogenic amines distributed in brain and their functional role is ascertained well in stressful conditions (Constantine *et al.*, 2002; Gonzalo *et al.*, 2003).

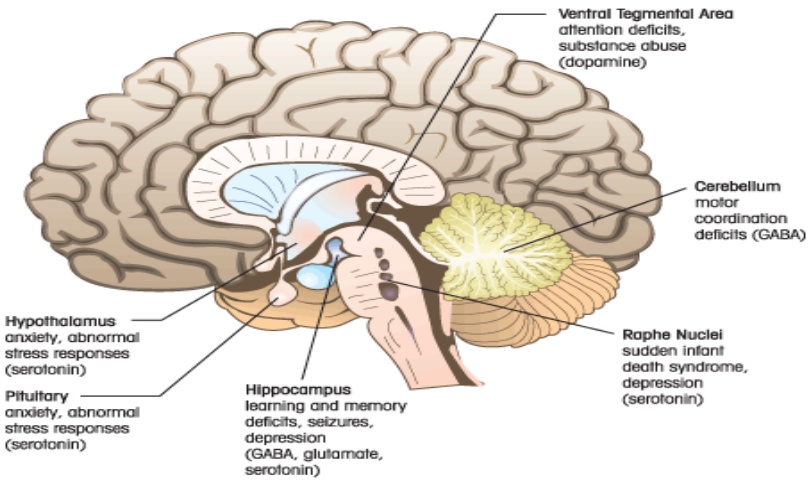

Fig: 1.6 Release of neurotransmitter during stress

Serotonin has been coined the "feel good" neurotransmitter. Dopamine is associated with the reward, or reinforcement, that we get which causes us to continue participating in an activity. It has been implicated in such conditions as Parkinson's disease and Schizophrenia. Dopamine is a neurotransmitter that is associated with addiction and its production is stimulated by drugs such as cocaine,

opiates, and alcohol (which may explain why depressed persons choose to self-medicate with drugs and alcohol. Drugs specifically targeted at dopamine, for example, Survector (amineptine), present the potential for abuse. (Kasper, *et al.*, 2015; Papakostas and Ionescu, 2015) Exposure to severe stressful conditions results in significant decrease in these monoamine levels which is associated with central and peripheral ailments like depression, anxiety and hyperglycemia and declined immunity (Lankupalle *et al*., 2005; Filip *et al*., 2006) (Fig: 1.6).

1.9.3 Biochemical Changes

In the short term, elevated stress hormone levels are beneficial because they prepare the body for emergency situations. However, chronic elevations of stress hormones can have detrimental effects (McEwen, 2007). In addition to the cardiac problems associated with chronically elevated heart rate and blood pressure, adrenal steroids cause changes in structure and function of important brain regions that lead to impairment in emotion, cognition, memory processing, and behaviour (McEwen, 2007, 2012; McEwen and Gianaros, 2010). High levels of cortisol have been shown to produce a number of harmful effects. Increased plasma cortisol can significantly weaken our immune system (Glaser and Kiecolt-Glaser, 2005) and influences the mobilisation of stored fat and carbohydrate reserves which in turn increases blood glucose level. Hyper secretion of cortisol helps in maintenance of internal homeostasis through the process of gluconeogenesis and lipogenesis (Krupavaram *et al.*, 2007). The marked increase in serum cholesterol, triglycerides and BUN (blood urea nitrogen) levels in stress induced animals is due to stimulation of hypothalamo-pitutary axis (HPA) and sympathetic system, resulting in liberation of catecholamines and glucocortico steroids, which inhibits the immune system at

multiple sites like liver, kidney (Schimmer *et al.,* 2006). Stimulation of adrenal medulla and cortex leads to increase in the weight of adrenal glands (Bhatwadekar *et al.,* 1999; Krupavaram *et al.,* 2007; Emilia *et al.,* 2000). Elevated serum cortisol resultedin increased liver mRNA levels thereby causes liver hypertrophy (Singh *et al.,* 1991; Dadkar *et al.,* 1998). The hypotrophy of spleen in stressed animals is due to release of more RBC from spleen (Deepak *et al.,* 2003). NA, DA and 5 HT are the important biogenic amines distributed in functional role are ascertained well in stressful conditions (Constantine *et al.,* 2002; Gonzalo *et al.,* 2003). A decrease in serum concentration of serotonin with the severity of stress suggests that serum serotonin may be taken as a marker of stress perception that may lead to depression (Zeba Haque *et al.,* 2010). Stress hormones may result in persistent increased leptin in circulation. A moderate increase of leptin elicits obesity possibly because of leptin resistance (Zhang *et al.,* 2006). Exposure to severe stressful conditions results in significant decrease in these monoamine levels which is associated with central and peripheral ailments like depression, anxiety, hyperglycemia and declined in immunity (Lankupalle *et al.,* 2005; Filip *et al.,* 2005). The hyper activation of paraventricular nucleus of the hypothalamus causes decrease in mucosal blood flow and hyper contractility through descending projections causes gastric ulcers (McEven, 2000; Jian-Fu Zhang *et al.,* 1997).

The central nervous system is vulnerable to free radical damage because of the brain's high oxygen consumption, its abundant lipid content and the relative paucity of antioxidant enzymes as compared to other tissues (Skaper *et al.*, 1999). Oxygen free radicals and other products of oxidative metabolism have been shown to be neurotoxic (Sayre, *et al.*, 1997). During stressful situations, the energy

requirement of the organism is increased, resulting in enhanced generation of free radicals (Bhaumik *et al.*, 1995).

1.10 Free radicals

In 1900, Gomberg recognized organic free radicals (Riley, 1993). These are chemical species, an atom or molecule that has one or more unpaired electrons in valance shell and is capable of existing independently. As free radical contains an odd number of electron, which make it unstable, short lived and highly reactive therefore it can react quickly with other compound, to gain stability and the attacked molecule loses its electron, it becomes a free radical itself, beginning a chain reaction cascade resulting in disruption of a living cell (VishalTandon *et al.*, 2005). In general, free radicals are very short lived, with half-lives in milli, micro or nanoseconds. Free radicals have been implicated in the etiology of several human diseases as well as ageing (Harman 1956; Halliwell *et al.*, 1997).

Fig: 1.7 Disease states by Free radicals

In 1954, Gershman and Gilbert speculated that the lethal effects of ionizing radiation might be ascribed to formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Gilbert DL, 1981). Free radicals also known as

reactive oxygen species (ROS) and reactive nitrogen species (RNS) are occur due to exogenous sources of ionizing radiation, cigarette smoke, sunlight, toxic chemicals, atmospheric pollutants, over nutrition, changing food habits etc. and/or endogenous sources are pro inflammatory cytokines of TNF - α, IL - 8, IL-1B, mitochondrial electron transport chain, β–oxidation of fat etc., (Devasagayam *et al*., 2004). The most common reactive oxygen species includes superoxide anion (O_2), hydrogen peroxide (H_2O_2), peroxyl radicals (ROO) and reactive hydroxyl radicals (OH).The nitrogen derived free radicals are nitric oxide (NO), peroxynitrite anion (ONOO), nitrogen dioxide (NO_2) and dinitrogen trioxide (N_2O_3) (Kokate *et al*., 2004 and Panchawat *et al*., 2010).

By naturally free radicals either as ROS and RNS carrying beneficial effects only in a regulated manner eg, in maintaining homeostasis at the cellular level, work as signalling molecules, ATP generation in mitochondria, apoptosis, phagocytosis, xenobiotics detoxification are of in our body system (Yoshikawa *et al*.,2000). ROS and free radicals act as alarming substances in the body may cause disruption of membrane fluidity, lipid peroxidation and protein denaturation etc (Anderson *et al*., 1996; Velavan *et al*., 2007). When the level of free radical is more than its demand it may cause chronic and degenerative diseases such as cancer, auto immune disorders, cardio vascular diseases, arthritis, neuro disorders and the most notorious pathological effects are Alzheimer's disease and ageing (Lian, 2008). Many ion channels, which maintain the electrostatic balance of the cell required for many physiological processes such as cell growth and cell death, are now also shown to be regulated by ROS (Lusini *et al,* 2001).

1.11 Oxidative Stress

The relation between free radicals and disease can be explained by the concept of 'oxidative stress' that elaborated by Sies (1986). The most important free radicals in biological system are radical derivatives of oxygen. Oxygen is required to transfer various substances for the release of the energy and detoxifies xenobiotics (Mayes *et al*., 2000). Oxidative process organizes the main causative routes for generating free radicals in foods, drugs and even in living systems (Halliwell *et al*., 1994), because oxygen is the most essential factor indispensable to our life (Geetha *et al*., 2016). In naturally occurring defense molecules in healthy human body gets exposed to adverse physicochemical, environmental or pathological agents such as atmospheric pollutants, cigarette smoking, ultravioletrays, radiation, toxic chemicals, over nutrition and advanced glycation endproducts (AGEs) in diabetes, this delicately maintained balance is shiftedin favour of pro-oxidants resulting in 'oxidative stress'. It has been implicated in the etiology of several (>100) of human diseases and in the process of ageing (Devasagayam *et al*., 2004). These free radicals exert oxidative stress on the body cells, rendering each cell susceptible to 10, 000 oxidative hits per second (Lata and Ahuja 2003). A variety of pathological conditions are induced by oxidative stress such as rheumatoid arthritis, diabetes mellitus and cancer (El Faramawy and Rizk, 2011). Free radical and oxidative stress induced complications from DM include coronary artery disease, neuropathy, nephropathy, retinopathy (Phillips *et al*., 2004) and stroke (Asfandiyarova *et al*., 2007). Stress results in oxidative stress and also decreases antioxidant defense status in the brain, which may form the basis for impaired memory.

1.12 Antioxidants

The current lifestyle related changes (sedentary lifestyle, faulty dietary practices, stress and in some cases smoking/drug abuse/alcohol consumption) may cause over-production of free radicals and reactive oxygen species are crucial for life, many times these can be damaging too. The free radicals produced during oxidative processes that release highly-reactive compounds generated in the body as by-products of normal processes or these may enter the body from the environment (Santosh Jain Passi *et al* ., 2014). 'Antioxidants' are substances that neutralize free radicals or their actions (Sies, 1996). The human body has several mechanisms to counteract oxidative stress by producing antioxidants which are either naturally produced in body, or externally supplied through foods and /or supplements (Valko *et al.*, 2006). A number of natural antioxidants not only reduce oxidative stress, but also provide protection against various degenerative diseases and thus antioxidants play a significant role in health care. Plant foods are the primary sources of naturally occurring antioxidants fruits, vegetables, roots and tubers being the rich sources of polyphenols (Santosh Jain Passi *et al.*, 2014).The antioxidants may be exogenous or endogenous in nature.The endogenous antioxidants can be classified as enzymatic and non- enzymatic (Young*et al.*, 2001; Kohen, *et al.*,2002 ; Willcox *et al.*, 2004).

(i) Enzymatic antioxidants

- Superoxide dismutase (SOD)
- Catalase (CAT)
- Glutathione peroxidase (GPx)
- Glutathione reductase (GRx)

(ii) Non-enzymatic antioxidants

a) Metabolic antioxidants

Lipoic acid, Glutathione, L-arginine, Uric acid, Bilirubin etc.,

b) Nutrient antioxidants

Vitamin E, Vitamin C, Carotenoids, and trace elements (Se, Cu, Zn, Mn).

These nutrient antioxidants belonging to exogenous antioxidants are compounds, which cannot be produced in the body and must be provided through foods. The combination of antioxidants present in blueberry, strawberry and spinach protect the nervous system by inhibiting the enzyme that may be involved in certain neurological disorders including autism, depression and schizophrenia. Antioxidants are possibly beneficial in the treatment of certain neurodegenerative diseases like Alzheimer's disease (AD)/Parkinson's disease (PD) (Santosh Jain Passi *et al.*, 2014). They are also known as radical scavengers, metal chelators, reducing agents and singlet quenchers (Proestos *et al.*, 2006) that inhibit free radical activities by donating the missing electrons without joining the chain of reactions (Sahu *et al., 2009).*

1.13 Stress Medications

Many different types of medications are used in the treatment of anxiety disorders, including traditional anti-anxiety drugs such as benzodiazepines (typically prescribed for short-term use) and newer options like SSRI antidepressants (often recommended as a long-term anxiety solution). These drugs can provide temporary relief, but they also come with side effects and safety concerns some significant. They are also not a cure. In fact, there are many questions about their long-term effectiveness. According to the American Academy of Family Physicians,

benzodiazepines lose their therapeutic anti-anxiety effect after 4 to 6 months of regular use and a recent analysis reported in JAMA Psychiatry found that the effectiveness of SSRIs in treating anxiety has been over estimated and in some cases is no better than placebo.

1.13.1Benzodiazepines

Benzodiazepines (also known as tranquilizers) are the most widely prescribed type of medication but not recommended for longterm treatment due to the following common side effects of these drug (Melinda Smith *et al*., 2017)

- Drowsiness
- Dizziness
- Poor balance or coordination
- Slurred speech
- Trouble concentrating
- Memory problems
- Confusion
- Stomach upset
- Headache
- Blurred vision

1.13.2 SSRI antidepressants (Selective Serotonin (5 HT) Reuptake Inhibitors)

The antidepressants most widely prescribed for stress and anxiety are SSRIs such as Prozac, Zoloft, Paxil, Fluoxetine, Lexapro and Celexa. SSRIs have been used to treat generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, social anxiety disorder, and post-traumatic stress disorder and produces the following common side effects Fatigue (Bondy 2002; Andrade *et al.*, 2003).

- Nausea
- Agitation
- Insomnia
- Sexual dysfunction
- Nervousness
- Increased sweating

1.13.3 Buspirone (BuSpar)

Buspirone is a newer anti-anxiety drug that relieves anxiety by increasing serotonin in the brain and decreasing dopamine. It is a better option for older individuals and people with a history of substance abuse and it has produced common side effects like, SSRI and benzodiazepines (Melinda Smith *et al.*, 2017).

1.13.4 Beta blockers

Beta blockers including drugs such as propranolol (Inderal) and atenolol (Tenormin) are a type of medication used to treat high blood pressure and heart problems. Beta blockers work by blocking the effects of norepinephrine, a stress hormone involved in the fight-or-flight response. This helps control the physical symptoms of anxiety such as rapid heart rate, a trembling voice, sweating, dizziness, and shaky hands (Melinda Smith *et al.*, 2017).

1.13.5 Tricyclics

Tricyclics are older drugs with side effects like dizziness, drowsiness, lack of energy and dry mouth. They can also include nausea and vomiting, constipation, blurred vision and weight gain (Melinda Smith *et al.*, 2017).

1.13.6 Monoamine oxidase inhibitors (MAOIs)

Using an MAOI with some restricted foods (Cheese and red wine) or medications (birth control pills, pain relievers, cold and allergy drugs) can dangerously increase the blood pressure and cause other potentially life threatening side effects.

Besides advances in pharmaceuticals, other approaches of stress management are also important in treatment for stress. While anxiolytic medication is useful in the treatment of anxiety many negative side effects can be experienced.

1.13.7 Exercise

Exercise is a powerful anxiety treatment. Studies show that regular workouts can ease the symptoms just as effectively as medication. Exercise on a regular basis helps to turn down the production of stress hormones and associated neurochemicals. Thus, exercise can help to avoid the damage to our health. In fact, studies have found that exercise is a potent antidepressant, anxiolytic (combats anxiety) and sleeping aid for many people (Pariante *et al.*, 2008).

1.13.8 Music

The main neurotransmitter involved in the reward system is dopamine. Pleasant music releases dopamine (Sutoo *et al.*, 2004) in the nucleus accumbens and another neurotransmitter is serotonin, which is responsible for good mood, while unpleasant music reduced the level of serotonin (Evers *et al.*, 2000). On the other hand, listening to slow music decreased the nor-epinephrine level (a neurotransmitter that regulates arousal) (Yamamoto *et al.*, 2003).

1.13.9 Yoga

Yoga is well known ancient lifestyle approach for healthy mind and healthy body. A review of research published between 1970 and 2004 on the effects of yoga on insulin resistance and cardiovascular disease has been done based on 70 studies (Innes *et al.*, 2005). Yoga is also supported by medical research as a means of helping sufferers to manage their stress. Yoga has been shown to have a regulatory effect on two key neurobiological systems by the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). With repeated exposure to stressors over time, these systems are bombarded by catecholamines like epinephrine and norepinephrine (stress hormones), which can result in their becoming hypervigilant and dysregulated.

The dysfunction of these systems is thought to dispose one to diseases such as "obesity, diabetes, autoimmune disorders, depression, substance abuse, and cardiovascular disease" (Ross and Thomas, 2010). Dr. Bessel Van der Kolk, professor of psychiatry at Boston Medical School and one of the world's leading authorities on post-traumatic stress disorder (PTSD), has recognized this down-regulation benefit of yoga and applied it to his practice with PTSD patients (Vander Kolk, 2009).

1.13.10 Meditation

Throughout the day, when we experience stress, our body is automatically react in ways that prepare us to fight or run, that known as fight-or-flight response and helpful. In some cases of extreme danger, a prolonged state of such agitation can cause physical damage to every part of the body. Meditation affects the body in

exactly the opposite ways that stress does by triggering the body's relaxation response (Bowen *et al.,* 2006).

Meditation has some positive and negative impacts on stress when compare with other stress reduction methods.

- People with physical limitations may find it easier to practice than strenuous physical exercise for stress relief. No special equipment is required.
- Unlike enlisting the help of a professional, meditation is free.
- It does take discipline and commitment to make meditation a regular habit. Some people find it more difficult to maintain as a habit than methods that enlist the help of someone or something outside themselves for added motivation.
- Some people may find it more difficult to free their minds from the thoughts of the day. This may make it more difficult than methods that involve focusing on these events, like journaling or methods that are distracting, like physical exercise or the use of humor.
- Consistent practice matters more than long practice.
- Regular practice matters more than "perfect" practice.
- Unlike some medications and herbal therapies, meditation has few potential side effects.
- Even long-time meditation practitioners find it challenging (Elizabeth Scott *et al.,* 2018).

1.13.11 Alternative Medicines

Drugs with anti-stress properties may induce a state of non-specific resistance against stressful conditions. People to combat stress (Umokoro *et al*.,

2005) routinely use drugs like benzodiazepines, certain CNS stimulants such as amphetamines and caffeine as well as some anabolic steroids. The existing drugs, benzodiazepine anxiolytics, despite having significant antistress activity against acute stress, have not proved effective against chronic stress induced adverse effects on behavior, cognition, peptic ulcer, immunity and hypertension (Elliot *et al.*, 1982). These drugs have adverse effects on the fetus during pregnancy and on the neonate during lactation (Dennehy *et al.*, 2001). Procedures ranging from yoga and meditation to antistress and anxiolytic drugs like benzodiazepines have been used to counter the adverse effects to stress (Trevor *et al.*, 2001), but appear to have limited use, many patients remain untreated, experience adverse effects of drug (Sadock *et al.*, 2000; Manson, 1975) or do not get benefited (Woods *et al.*, 1982).

In current, the herbal medicines were safer than synthetic medicine due to the presence of phytochemicals in the plant extract targeting the biochemical pathway (Norliana Ghazali *et al.*, 2014). It must be essential to know the chemical constituents of plant extract because of its biological activity carried in medicinal, poisonous and nutritive fields (Croteau *et al.*, 2000). Several reviews have been published recently that explore a comprehensive coverage of scientific evidence supporting the antidepressant properties of numerous medicinal plants. Animal behavioural studies (e.g. forced swim test, tail suspension test), brain neurotransmitter quantification and various pharmacological studies involving altered HPA axis activity (Hasler, 2010) and the serotonergic system have been routinely employed to investigate the antidepressant properties of the plants (Hitesh *et al.*, 2011; Talha Jawaid *et al.*, 2011; Mithun Singh Rajput *et al.*, 2011; Gautam *et al.*, 2001)

1.14 Phytotherapy

Nature provides everything for the wellbeing of human and its expensive gifts of medicinal plants are used traditionally over the thousands of years around the world (Sumathi and Parvathi, 2010).Tribal community are using their traditional knowledge system for various health care by using plant as a source of drug and also preserved the wealth of nature as a part of their belief and customs. They are practicing these methods generation after generation successfully through trial and error method and the process is experienced over hundreds of years. This proves that the medicinal plants have been in the focus as lifesaving drugs right from the beginning of the human civilization. The medicinal plants have been the object of research in both systematic and advanced areas of plant sciences (Patil, 2012; Patil Sunil and Patil, 2012).

In recent years, the requirement of medicinal plant products has been increased in a tremendous way (Shelly Rana *et al*., 2016). The unlimited traditional knowledge of mega biodiversity nations like India and China mainly accounts on medicinal plants and healthcare has been provide the basis for research and development to produce novel drugs for major ailments (Polterait, 1997).

India is well known for its rich traditional systems of medicine i.e. Siddha, Ayurveda, Unani and Amchi (Tibetan) besides a vast reservoir of living traditions in ethno medicine. The earliest mention of the plants usage in medicine is found in the Rig Veda, which was written between 4500 and 1600 BC. During British period due to Western culture, our traditional art of natural healing is disappeared. Now it is reappearing due to realization of its importance in curing diseases without any side effects (Janet *et al.*, 2006).

India is one of the 12 global mega biodiversity centers harbouring about 5, 00,000 out of some 10 to 30 million species of living organisms, 17,500 flowering plants, 461 tribal communities. The country accounts for 8% of global biodiversity existing in only 2.4% of the land area in the world. India has contributed at least 167 plants to global agriculture and is the home to two of the world's 25 hotspots- Western Ghats and the Eastern Himalayans (Natesh, 2004).In India, there are more than 450 dye yielding plants, some of which are also endowed with medicinal properties (Siva, 2007).

Plants play a major potential role in the production of novel drugs and acts as a prominent natural resource for herbal medicine (Sunitha *et al*., 2008). In recent years a renewed interest flourished through the green medicine with safe, non-toxic, less side effects and also available in affordable prices (Prabhakaran *et al*., 2010). According to WHO medicinal plants would be the best source to obtain variety of drugs.

The therapeutic value of the medicinal plants based on some bioactive phytochemical constituents that produce a definite physiological action on the human body (Garro, 1986). The medicinal plants are used in the development of drugs and its evaluation is based on phytochemical and pharmacological approach which leads to the drug discovery referred as natural product screening (Foye *et al.*, 2008).

1.14.1 Phytochemicals

Plants have basic nutritional importance by their content of protein, carbohydrate, fats, oils, minerals, vitamins and water responsible for growth and development in man and animals. Phytochemical simply means plant chemicals.

"Phyto" is the Greek word for plant. Phytochemicals are the naturally occurring bio-chemicals in the plant that gives plant their colour, flavour, smell and texture.

More than 88000 secondary metabolites and every year some 4000 new ones are being reported (Farnsworth, 1996). Plants produce enormous number of compounds as part of defence mechanism during metabolism (Bennett and Wallsgrove, 1994). Phytochemicals are classified as primary or secondary constituents, depending on their role in plant metabolism. The primary metabolism is an important for the growth and development of plants and includes of sugars, amino acids, nucleic acids, fatty acids, chlorophylls etc., (Nandhini *et al*., 2014). Secondary metabolites such as alkaloids, flavanoids, tannins, terpenoids, phenolics, steroids, saponins were responsible for multiple biological effects including antimicrobial, antioxidant, ageing, anti-cancer, anti-proliferative, anti-inflammatory and immune modulator activities (Bhubaneswari *et al*., 2014).

Some plant secondary products may exert their action by resembling endogenous metabolites, ligands, hormones, signal transduction molecules, or neurotransmitters and thus have beneficial medicinal effects on humans due to similarities in their potential target sites (e.g. central nervous system, endocrine system, etc.) (Kaufman *et al.*, 2006). Plant based natural constituents can be derived from any part of the plant like bark, leaves, roots, flowers, seeds, fruits, rhizome etc (Gordon, 2001).

The most important phytochemicals, generally used as markers of plant taxonomy and authenticity are secondary metabolites such as alkaloids, carotenoids, chlorophylls / phenolic acids/ flavonoids / anthocyanins or terpenoids / unsaturated fatty acids / phytosterols, but also, in some specific cases saponins, lignans,indoles,

thiols glycosinolates and vitamins A, C & E (Socaciu *et al.*, 2009). Recent research suggested that diets rich in polyphenolic compounds such as quercetin, rutin, naringin, catechin, caffeic acid, gallic acid and chlorogenic acid are very important plant constituents and flavonoids are associated with longer life expectancy (Hu, 2000) and found effective in many health - related properties, such as anticancer, antiviral, anti-inflammatory activities and an ability to inhibit human platelet aggregation (Benavente - García *et al.*,1997) have correlated natural phenolic antioxidants with reduced coronary heart disease.

Pharmacological effects of the medicinal plants are related to its free-radical scavenging properties which include inhibition of lipid peroxidation, maintaining integrity and permeability of cell walls (Turan and Martorano 1985; Kleijnen and Knipschild 1992; Stoll *et al.*, 1996) as well as protection of neurons against oxidative stress (Seif-el-Nasr and El-Fattah 1995; Oyama *et al*., 1996).The major groups of the phytochemicals obtained from plant showed antioxidant activities and are known to prevent several degenerative diseases. A number of Indian medicinal plants are investigated for their antioxidant activity especially selected medicinal plants growing in Himalayan region (IHR) with their potential antioxidant effective in various diseases were reported (Bhatt *et al.*, 2008) for detailed study. Plant secondary metabolites can be grouped into three chemically distinct classes of terpenes, phenolic and nitrogen compounds.

1.14.2 Polyphenols

Polyphenols are naturally occurring compounds found largely in the fruits, vegetables, cereals and beverages like red wine, tea and coffee (Scalbert *et al*., 2005). Phenolic compounds have an aromatic ring that contains various attached

substituent groups such as hydroxyl and methoxy (-O-CH3) groups and often other non-aromatic ring structures (Taiz and Zeiger, 2006). Phenolic compounds are synthesized by Shikimate pathway. The main classes include phenolic acids, flavonoids, stilbenes and lignans (Spencer *et al.*, 2008). They have a wide range of pharmaceutical activities such as antiinflammatory, analgesic, osteoporosis, antitumor, anti-HIV, anti-infective, antihepatotoxic, antilipolytic, antioxidant, vasodilatory, immunostimulant and antiulcerogenic (Wink 1999; Gurib-Fakim 2006). Phenolic structures often have the potential to strongly interact with proteins, due to their hydrophobic benzenoid rings and hydrogen-bonding potential of the phenolic hydroxyl groups. This gives phenolics the ability to act as antioxidants (Parr and Bolwell 2002**)**. There are increasing evidences that as antioxidants, polyphenols may protect cell constituents against oxidative damage and therefore, limit the risk of various degenerative diseases associated with oxidative stress (Luqman *et al.,* 2006; Pandey *et al*., 2009; Pandey and Rizvi 2010).In plants, they serve as effective defence against herbivores (Wink *et al.,* 1999; Gurib-Fakim, 2006). These bioactive components of green tea catechins decreased lipid peroxidation and increased plasma total antioxidant capacity and also attenuated of stress-sensitive signaling pathways, prooxidant enzymes and inducted of antioxidant enzymes including superoxide dismutase, catalase and glutathione peroxidase (Crespy and Williamson 2004).

Polyphenols have diverse biological properties, including

- Protecting our skin against ultraviolet radiation
- Promoting brain health and protecting against dementia
- Supporting normal blood sugar levels

- Promoting normal blood pressure

Polyphenols can help to prevent long-term complications from diabetes, including cardiovascular disease, neuropathy, and retinopathy because they have been the effect to stabilize blood sugar and fat metabolism leads to reduce insulin resistance and lower inflammation in the body (Zahra Bahadoran *et al*., 2013).

Flavonoid polyphenols help to reduce the clumping of platelets in our blood and improve the function of our cells that line our arteries and veins. Platelet clumping is one potential precursor in heart attacks and angina (Hubbard *et al*., 2004). Polyphenols inhibits vascular endothelial growth factor, which causes complications with atherosclerotic plaques in the arteries, a factor in cardiovascular disease (Oak *et al*., 2005).

Polyphenols appear to have a prebiotic effect by improving the nutrition of beneficial bacteria living in human gut. Research has also found improvements in gut flora with consumption of red wine and chocolate in moderation (Nurk *et al*., 2009). Cognitive performance in elderly populations has also been shown to be associated with tea, but not coffee, consumption (Feng Ng *et al*., 2008) and the consumption of polyphenol-rich foods such as chocolate, red wine and tea.

1.14.3 Flavonoids

Flavonoids are 15-carbon compounds generally distributed throughout the plant kingdom. Flavanoids constitute an enormous class of phenolic natural products and present in most plant tissues, often in vacuoles. Flavonoids comprise a diverse set of compounds and perform a wide range of functions. The flavonoids consist of various groups of plant metabolites which include chalcones, aurones, flavanones,

isoflavonoids, flavones, flavonols, leucoanthocyanidins, catechins and anthocyanins. Flavonoids are reported as strong antioxidant bioactive compounds against free radicals (Pandey and Rizvi, 2009).

- Restored the brain levels of monoamines
- Increased the serotonin and dopamine levels sin the CNS
- Upregulation of monoaminergic neurotransmitters
- Interaction with the 5-HT1A, noradrenergic 2 and dopaminergic D1, D2, and D3 receptors
- Interaction with the opioid receptor
- Interaction with presynaptic 5-HT1A receptors
- Increased BDNF (brain-derived neurotrophic factor) levels in the hippocampus
- Promoted ERK phosphorylation and BDNF expression in the hippocampus
- Restored the stressinduced down-regulation of BDNF
- Activation of the BDNF signaling pathway
- Attenuated hyperglycaemia
- Antioxidant effect and attenuated neuro inflammation
- Potentation the GABAA receptor Cl^- ion channel complex

Supression of oxidative-nitrosative stress **(**Lucian Hritcu *et al.*, 2017).

The antidepressant effect of the Hemerocallis citrina Baroniis mediated by the contributions of flavonoids, especially rutin (Thase, 2003) and hesperidin (Du *et al.*, 2014). Its antidepressant effects are due to the interaction with serotonergic, noradrenergic and dopaminergic systems (Machado *et al.*, 2008).

1.14.4 Plants as Antioxidant and Antistress agents

All plants have significant phenolic compounds, such as flavonoids, phenolic acids, tannins, lignins. These compounds have multiple biological effects including antioxidant activity and thus suggest that medicinal plants, which possess good antioxidant potential, are the best supplements for the diseases associated.

The rhizome of *Hedychium spicatum* is stomachic, carminative, bronchodilator, stimulant and tonic and traditionally used in dyspepsia, nausea, vomiting, liver complaint etc. Also, the species is used in preparation of Chyawanprash, traditional ayurvedic mixture, which is known for strong antioxidant properties. Furanoid diterpene hedychenone isolated from the rhizome of this species have shown to possess anti-inflammatory activities. Essential oil of the species and its extract possess strong reducing properties and free radical scavenging properties (Joshi *et al*., 2006; Rawat *et al*., 2011a). Antioxidant activities of the extract are ascribed due to the presence of phenolic content (Rawat *et al*., 2011). The species is considered to be rich antioxidant phytochemicals (Bhatt *et al.*, 2008).

Myrica esculenta, commonly known as 'Kaphal', contain some antioxidant phenolic compounds, such as gallic acid, catechins, hydroxybenzoic acid and coumaric acid. The fruits of this species possess strong reducing properties and free radical scavenging properties of DPPH assay which showed a significant relationship with phenolic and flavonoids content (Rawat *et al*., 2011).

Ocimum sanctum has anti-stress, antioxidant, hepatoprotective, immunomodulating, antiinflammatory, antibacterial, antiviral, antifungal, antipyretic, antidiuretic, antidiabetic, antimalarial and hypolipidemic properties with a wide margin of safety. In Ayurvedic medicine, Tulsi is being used either alone or

in combination with others in various clinical conditions like anxiety, chronic cough, bronchitis, fever, snake and scorpion bites (Mohan Lalit *et al.*, 2011).The aqueous extract decreased LPO formation (thiobarbituric acid reactive substances TBARS) and increased antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) and glutathione transferases (GT). It also increased antioxidant like reduced glutathione (GSH) levels in plasma and liver, lung, kidney and brain of rat (Mohan Lalit *et al.*, 2011; Hussain, *et al.*, 2001). Tulsi has been found to have therapeutic potential as antidiabetic, hypolipidemic and antioxidant medicine.

Daucus carrota Lin has antioxidant and radical scavenging activities are much higher in carrot peel than phloem and xylem tissue. Phenolic acids and flavonoids made greater contribution to the total antioxidant capacity (Zhang Donglin and Hamauzu Yasunori 2002).

*Camellia sinensis*can be considered an important dietary source of polyphenols, particularly flavonoid (Vison J *et al*., 1995; Parmar Namita *et al*., 2012). In Green tea catechin, EGCG (epigallocatechin-3-gallate) is a powerful antioxidant that is capable of protecting erythrocyte membrane bound ATPases against oxidative stress, a significant increase in plasma antioxidant capacity in humans after consumption of moderate amounts (1–6 cups/day) and enhanced blood antioxidant potential leads to reduced oxidative damage in macromolecules such as DNA and lipids (Cabera Carmen *et al*., 2006).

G*lycyrrhiza glabra* hasmedicinal uses in acute case of conjunctivitis, diuretic, demulcent, anti-inflammatory, in peptic ulcer, vomiting and asthma. Its extract was tested by studying the inhibition of radiation induced lipid peroxidation

in rat liver microsomes. It shows its activity through free radical scavenging property (Panchawat *et al*., 2010).

Curcum alonga is a potent antioxidant; it may scavenge the epoxides and prevent binding to macromolecules. In other words, this spice's cell-protective properties are similar to nutrient antioxidants, vitamins C and E, which inhibit free radical reactions (Braga *et al* ., 2003; Basnet and Skalko-Basnet 2011).

Zingiber officinale extracts possess strong antioxidant radical activities as evidenced by the ABTS assay. Both aqueous and ethanol extracts of ginger have significant natural antioxidant activity. Therefore, consumption of ginger might be helpful in combating the progression of various diseases with oxidative stress components such as atherosclerosis and diabetes mellitus among others (Morakinyo *et al*., 2011)

Antioxidant activity of *Melia azedarach* has evaluated by DPPH radical scavenging assay and free radical scavenging ability of the extracts. The result showed that the extract of Melia azedarach, which contains highest amount of phenolic compounds, exhibited the greatest anti-oxidant activity. The high scavenging property may be due to hydroxyl groups existing in the phenolic compounds chemical structure that can provide the necessary components as a radical scavenger (Nahak Gayatri and Sahu Rajani Kanta 2010).

Various drugs are currently used to manage stress and depression, including diazepam, caffeine and certain anabolic steroids. However, these drugs may be associated with severe toxicity and side effects (Desai, 2011). Thus, stress management through dietary modifications (Shinohara *et al*., 2013) and natural

herbs (Desai *et al*., 2011) may be a valuable alternative to antidepressant drugs. Herbal formulations have been used for many years in global level for human wellbeing and to enhance their physical endurance, mental functions and nonspecific resistance of the body have been termed as adaptogens (Saggu *et al.*, 2007). It denotes an agent that improves adaptation capacity of the organism during stress and "Antistress" agent is a pharmacological word for the same meaning an agent, which nullifies or prevents ill effects of stress and improves adaptation (Sharma *et al.*, 2006).The term adaptogen was first coined by Lazarev (1947) is a plant derivative substancecandevelop a state of raised resistance, enabling an organism to cope with different kinds of stressful situations (Wagner *et al.*, 1994).

According to Breckhman and Dardymov (1969), an adaptogen must have the following properties:

- Show a nonspecific activity, i.e., increase in power of resistance against physical, chemical or biological noxious agents;
- Have a normalizing influence independent of the nature of the pathological state
- Be innocuous and not influence normal body functions more than required.

Plants have been known to relieve various diseases in Ayurveda. Rasayanas have been used to promote health and longevity by increasing defense against diseases and revitalizing the body against perturbed physiological situations. In general rasayana plants are possess adaptogenic activity that causing an adaptive reaction and thus appear to increase the general defense power of the organism, improve physical endurance for doing work even in adverse circumstances.

Several herbal drugs have been introduced during the recent past for the cure of emotional disorders, depression, CNS related disorders, anxiety, melancholy, gastric ulcers, rheumatism, cortical synchrony, relaxation of skeletal muscles and drowsiness (Upadhya *et al*., 1988). They are said to increase resistance to stress, trauma, anxiety and fatigue. The term is used mainly by herbalists who also refer to adaptogens as rejuvenating herbs, tonics, rasayanas or restoratives. One specific characteristic of adaptogen action is that its effect is believed to help the body return to a balanced state. Adaptogenic herbs are distinct from other substances in their ability to balance endocrine hormones and the immune system and those they help the body to maintain optimal homeostasis (Winston and Maimes, 2007).

In the indigenous system of the medicine, there are many herbal drugs and formulations recommended to enable one to withstand stress without altering the physiological functions of the body and its potential utility of safer and cheaper herbal medicines as antistress agents have been reported (Meeras *et al*., 2007). Following plants possessing antidepressant activity and this review described by (Gautam *et al*., (2013).

Withania somnifera, Panax ginseng, Caesalpinia bonduc, Hippophae rhamnoides, Garcinia kola, Trichopus zeylanicus, Rhodiola imbricate, Rhodiola rosea, Bacopa monniera, Volvulus alsinoides ,Hoppea dichotoma, Bergenia crassifolia, Butea frondosa, Panax quinquefolium, Zingiber officinale, Eleutherococcus senticosus, Asparagus racemosus, Hypericum perforatum, Ptychopetalum olacoides, Ocimum sanctum, Schisandra chinensis, Clipta alba, Azadirachta indica, Sutherlandia frutescens, Acanthopanax senticosus ,Curcuma longa, Tinospora cordifolia, Psidium guajava, Momordica charantia, Sida

cordifolia, Morus alba, Centella asiatica, Camellia sinensis, Eugenia caryophyllus, Tribulus terristris, Raponticum carthamoides, Piper longum ,Terminalia chebula, Clitoria ternatea, Ginkgo biloba, Heteropterys aphrodisiaca, Astragalus embranaceus, Curculigo orchioides, Tridax procumbens, Allium sativum, Emblica officinalis, Phyllanthus amarus, Amaranthus spinosus, Nardostachys jatamansi, Aegle marmelos.

Areca catechu commonly known as betel nut tree traditionally, it is chewed by locals along with betel leaf due to their psycho-active properties (Jaiswal *et al.* ,2011; Osborne, *et al*., 2011). Its nut possesses the compounds such as alkaloids, tannins, flavones, triterpenes, steroids and fatty acids (Yang *et al*., 2000; Ghelardini *et al*., 2001) and involved in several pharmacological activity including anti-parasitic, anti-inflammatory, anti-oxidant, analgesic, cholinomimetic, and acetylcholinesterase inhibitory properties and also promotes digestive function (Jaiswal, *et al*.,2011;Gilani, *et al*.,2004). In a recent study revealed that treatment with *A. catechu* extracts improved learning and memory in rats (Kulkarni *et al*., 2009).

Ginkgo biloba Linn native of China is occasionally cultivated in Indian gardens and especially, found in Himachal Pradesh. Its extract restored restraint stress-induced elevation in whole brain levels of norepinephrine, dopamine and serotonin and improving mood in healthy older volunteers (Shah *et al*., 2003; Trick *et al*., 2004).Recent study have proved a combination with extract of *G. biloba* with Venlafaxine enhanced the protection of neurons and decreased damage to the brain (Qin *et al*., 2005).

Bacopa monnieri asmall creeping herb traditionally has been used in Ayurveda as a rasayana (medhya-rasayana and aindra-rasayana) to rejuvenate the brain and mental health and promote intellect, memory, and longevity (Singh 2013). Earlier studies suggested that has potent nootropic, cholinergic properties and thus more attention for its purpose to treat neurodegenerative disorders (Kongkeaw, *et al*., 2014) and also demonstrated the anti-depressant activity by the forced swim, tail suspension, chronic unpredictable stress and learned helplessness models using mice and rats. Due to presence of sapononins - bacopasides VI-VIII, bacopaside I, bacopaside II and bacopasaponsin C in *B. monnieri* (Shen *et al*., 2009; Chatterjee, *et al.,* 2010; Banerjee,*et al.,* 2014) showed nootropic and cholinergic properties and has therefore attracted attention for its potential to treat neurodegenerative disorders (Sairam *et al.,* 2002; Le *et al*.,2013; Peth-Nui *et al*., 2012)

Withania somnifera **(**Ashwagandha) the famous Indian ginseng is widely used as a rasayana (rejuvenator) to promote physical and mental health (Singh, *et al*., 2011) and shows hepatoprotective, analgesic activity also increase immunity. It contains multiple bioactive constituents therefore it naturally possesses the medicinal effects such as anti-cancer, neuroprotective, anti-epileptic, spermatogenic, hepatoprotective, anti-microbial, anti-oxidant, anti-inflammatory and anti-arthritic activities (Kumar, *et al.*,2015; Mishra *et al.*,2005).

The free radical scavenging and antioxidant activity of the extract of *Withania somnifera* was measured in terms of hydrogen donating or radical scavenging ability using the stable free radical DPPH (2, 2, diphenyl 1- picryl hydrazyl). Glycowithanolides (WSG) consisting of sitoindosides VII to X and withaferin. Major oxidative free radical scavenging enzymes are superoxide

dismutase (SOD), Catalase (CAT) and glutathione peroxidase (GPX) (Bhattacharya Salil *et al.*, 1997). Recent experimental studies demonstrated that have rich in anti-depressant, anxiolytic and adaptogenic properties in a range of rodent behavioral tests such as the open field test, forced swim test, tail suspension test and learned helplessness test etc (Bhattacharya, *et al*., 2003; Maiti, *et al*., 2011).

Cucurbito pepo on stress induced rats have resulted significant antioxidant and anti depressant activity. Therefore it may be used as a potential resource for natural psychotherapeutic agent against depression and also possess anithelminthic activity and antimicrobial activity (Umadevi *et al.*, 2011).

Terminalia catappa is also known as Indian almond.TC supplementation against chronic mild stress (CMS) induced to rats for a period of 7 weeks suggested that could suppress depression by regulating monoamine neurotransmitters, cortisol, AchE level as well as by amelioration of oxidative stress. Therefore TC can be used as a complementary medicine against depression like disorder (Chandrasekhar *et al.*, 2017).

The medicinal value of the chosen plant *Aplotaxis auriculata* rhizome has been extensively worked out. However, its therapeutic efficacy in antistress activity has not been evaluated. In the present study aimed to investigate the antistress and antioxidant activity of *Aplotaxis auriculata* rhizome extract.

1.15 *Aplotaxis auriculata* rhizome

Mostly grow in hilly area. The Himalayas from Kashmir to Sikkim, Hills area of India, China, Korea, Japan and Sri Lanka.

1.15.1 Taxonomical classification of *Aplotaxis auriculata* DC

Kindom	:	Plantae
Phylum	:	Tracheophyta
Class	:	Mangnoliopsida
Order	:	Asterales
Family	:	Asteraceace
Genus	:	*Aplotaxis*
Species	:	*auriculata*
Botanical name	:	***Aplotaxis auriculata***

Vernacular Name

Tamil	:	Koshtam
Malayalam	:	Kottam
Sanskrit	:	Kushtha
Urdu	:	Kost
Telugu	:	Kostu
Kannada	:	Koshta
Hindi	:	Kust

1.15.2 Morphology

The plants grow up to 2 m in length. The radical leaves have a long stalk. The flower head is sessile, hard, round and 3-5 cm in diameter with dark purple to black flowers. The seeds are achene, about 3 mm long, curved and compressed. The aromatic root is horn like, rough from outside up to 10 cm thick and may be 20 cm or more long, but in trade broken pieces are often available when cut the root depicts a dark brown cylindrical centre (Puri, 2003).

1.15.3 Therapeutic Uses

Aplotaxis auriculata is a native of the mountains around Kashmir and has been used in Hindu medicine from an early age. Its root is described as aromatic, stimulant it is given in spasmodic diseases such as cough, asthma, cholera and deranged digestion, fever, dyspepsia and useful in nerve weakness, improving blood circulation, paralysis, hypoglycemic effect, jaundice and skin diseases.

As an alternative, it is sued in chronic skin diseases and rheumatism. Locally, a paste of it made in rose water is applied to swollen hands and feet and to swelled abdome in obesity ad a a cooling lotion to sprains and contusions. As a reliever of headache, it has been adveated by Kautilya in his Artha sastra. Koshtam, Vidanga and dravanti are to be powdered and used as a snuff. Vangasena advises a lepa or application of the paste obtained by grinding the roots of Kushta and Eranda with kanjika to be applied for headaches. Externally, it is used as an astringent ointment for ulcers and along with Maadhiphala juice and honey as an ointment for the face. It is one of the ingredients of the prepared oils and dusting powder and is mixed both for its fragrance and antiseptic and soothing properties. An extract of the rhizome can be used to lower blood sugar levels, to treat inflammation of the liver, to fight stress, and as an antioxidant. (http://www.indianetzone.com/77 use_pachak_medicines.htm).

Abdul Aseeb and Mariappan (2013) evaluated the glycoproteins as hexose, hexosamine and sialic acid have been measured in the plasma and liver tissues of Diethylnitrosamine (DEN) induced liver cancer rats. This study shows that *Aplotaxis auriculata* root extract (AARE) administration decrease the glycoprotein synthesis in tumor cells. This may be due to the inhibitory action of AARE on the

initiation of DEN activation/detoxification process. AARE offer promise as potential protective effect on carbohydrates moieties as glycoproteins against DEN treated rats.

Nandhini *et al.* (2012) aimed to evaluate *in-vitro* hepato protective activity of *Aplotaxis auriculata* rhizome (200 and 400µg/mL) through CCl4 induced toxicity in hepatocytes. The phytochemical screening revealed the presence of flavonoids, terpenoids, triterpenoids, polyphenol and tannins. All the variables tested such as LPO, GSH, Protein, Bilirubin, ALP, SGOT and SGPT recorded a significant alteration observed in CCl4 exposed hepatocytes. However treatment with *Aplotaxis auriculata* extract restored the level and to near normal values was observed. The potential hepato protective activity of Aplotaxis auriculata is due to the presence of phytochemical constituents present in plant. Some of these phytochemicals such as flavonoids and polyphenolic compounds might have possessed hepato protective activity.

Fig: 1.8 *Aplotaxis auriculata* plant and rhizomes