Marsilea quadrifolia prevents stress-related behavioural and physiological changes: An updated review

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1. STRESS

"People may very well choose to trade off years of their life, or the possibility of disease or injury, in exchange for the current pleasure, excitement, or stress relief they get from food" Jacob Sullum [1].

Stress is considered to be any condition which results in perturbation of body`s homeostasis. (or) In medicinal terms stress is described as "a physical or physiological stimulus that can produce mental tension or physiological reaction that may lead to illness, it is also considered as to be any conditions which results in perturbation of body`s homeostasis.

According to the World Health Organization WHO, mental well-being is a part of health. The who estimates that about 80% of the population living in developing countries relies almost exclusively on traditional medicine for their primary healthcare needs. India has vast ethnobotanical knowledge in India is form the great tradition of ayurveda, which is a living tradition of practice even today.

Biological stress is a response to physical, chemical, biological and emotional changes, consisting of a pattern of metabolic and behavioral reactions that helps to strengthen the organism [2].

1.1 Stress History

In 1930, endocrinologist, **Hans Selye** a Canadian professor and leading pioneer in stress research, is internationally acknowledged as '**the father of stress'** was attempting to do some research on rats to determine the effects of an ovarian extract. He would try to inject the rats, but would end up dropping them on the floor, chasing them around the room and finally injecting them with the extract. At the end of several months of this, Seyle found that the rats had peptic ulcers, greatly enlarged adrenal glands (the source of two important stress hormones) and shrunken immune tissues. He was surprised to find the same symptoms in control group. He borrowed the engineering term stress to describe the phenomenon. He made two observations as:

1. The body has a set of similar responses to a broad array of stressors.
2. Under certain conditions, the stressors will make you sick.

As Hans Selye believed, "stress is a general adaptation syndrome", i.e., a single stereotypic response elicited by any demand upon the body.

Pathologic conditions related to stress have been a subject of science since 1911 when Walter Cannon applied the engineering concept of stress to a physiologic context, suggesting that emotional stimuli were capable of causing physical damage to the body. Stress and stress-related disorders are a significant cause of disease in modern times, contributing to perhaps 75% of all illnesses. Stress has been postulated to be involved in the etiopathogenesis of a diverse variety of diseases ranging from psychiatric disorder such as anxiety and depression, immunosuppression, endocrine disorders including diabetes mellitus, male sexual dysfunction, cognitive dysfunctions, peptic ulcer, hypertension and ulcerative colitis. Western medicine has developed multiple approaches to coping with stress, including pharmaceutical drugs, exercise, and relaxation techniques like meditation. While these methods can provide some benefits, results are mixed and often unsatisfactory. In the East, researchers have also struggled to find solutions to stress related problems. The benzodiazepine anxiolytics, despite having significant antistress activity against acute models of stress, have not proved effective against chronic stress induced adverse effects on immunity, behavior, cognition, peptic ulcer and hypertension [3-4].

Everybody knows what stress is and nobody knows what it is" stated Selye, the founders of the modern concept of stress. More recently McEwen and Wing Weld commented: "the problem with the word stress is that it has too many meanings". On the other hand, after the pioneering works of Cannon and Selye the concept is so well integrated in our mind that it is hard not to use it: "Stress by any other name?", questioned Dallman. Indeed, stress has been used to describe both what creates an imbalance and the response of the body to it. Therefore, in the scientific literature two terms have been introduced. A *stressor* is anything that disrupts physiological balance. The *stress–response* is the physiological and behavioral reaction emitted by the organism to re-establish the balance. The balance to be maintained is what Claude Bernard called the "internal milieu" and in modern terms is referred to as *homeostasis*. The stress–response is, thus, an adaptive reaction of a body to challenge [5].

In humans, the literature shows that stress affects eating in a bidirectional way; a subgroup, possibly around 30%, decreases food intake and loses weight during or after stress, while most individuals increase their food intake during stress. Given, that people living in Westernized countries live in a palatable food environment, with an abundance of calorically dense food, it makes sense that most people complain of eating more during stress, rather than less. Almost 50% of a US representative sample is concerned with the amount of stress in their life copes by engaging in unhealthy behaviors such as smoking as well as eating for relief. Another survey study shows increased food intake during times of stress, especially in women. The stress-induced drive for dense calories is alarming in the face of the growing obesity[6].

1.1.1 Stressores

Stressors can be broadly classified into two groups:

External Stressors:

External stressors include adverse physical conditions (such as pain, uncomfortably hot or cold temperatures) or stressful psychological environments (such as poor working conditions or abusive relationships).

Internal Stressors:

Internal stressors can also be physical (infections, inflammation) or psychological. An example of an internal psychological stressor is intense worry about a harmful event that may or may not occur. Internal psychological stressors are rare or absent in most animals except humans.

Internal stressors can be classified as under:
Stressors may be of-
Short term (acute)
Long term(chronic)

Acute Stress:

Acute stress is the reaction to an immediate threat, commonly known as the fight or flight response. The threat can be any situation that is experienced, even subconsciously or falsely, as a danger. Acute stress is usually for short time and may be due t work pressure, meeting deadline pressure or minor accident, over exertion, increased physical activity i.e. searching something but you misplaced it, or similar things. Symptoms of this type of tension are headaches, back pain, Stomach problem, rapid heartbeat, muscle ache or body pains [7].

Chronic Stress:

Frequently, however, modern life possesses on-going stressful situations that are not short-lived and the urge to act (to fight or to flee) is suppressed, then it will be chronic. This type of stress is the most serious of all the 3 stress types. Chronic stress is prolonged stress that exists for week, months, or years. This stress due to poverty, broken or stressed families and marriages, chronic illness and successive failure in life. People suffering from this type of stress get used to it and may even not realize that they are under chronic illness and successive failure in life.

The degree of behavioural control that an individual has over a stressor and plays a key role in the development of pathological behaviour after a traumatic event. The potency of cope with the stressors is fundamental requirement for survival. Brain is the target for different stressors because of its high sensitivity to stress-induced degenerative conditions. The brain tissue is made up of large amount of polyunsaturated fatty acid, thus making it vulnerable to free radical attack [8].

Stress does not affect each individual the same way. A stimulus that may be stressful to one individual may not be stressful to another. Environment, life events, and genetics play a role in an individual's tolerance for stress [9]. When an individual perceives a stimulus as stressful a physiological and behavioral response will be displayed.

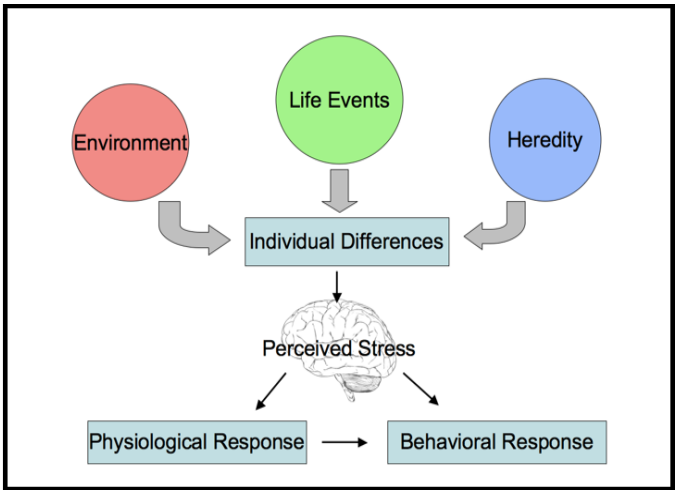

Fig.1.1 Individual differences in stress

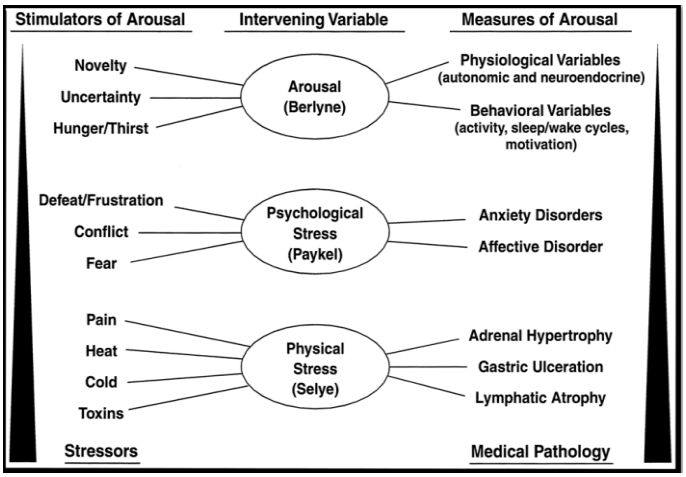

Fig. 1.2 The relationship between the constructs of arousal, psychological stress, physical stress and pathology

1.1.3 Causes of stress

The situations and pressures that cause stress are known as *stressors*. Stressors as being negative, such as an exhausting work schedule or a rocky relationship. However, anything that puts high demands on forces to adjust can be stressful. This includes positive events such as getting married, buying a house, going to college, or receiving a promotion.

1.1.3.1 Common external causes of stress [10]

- Major life changes
- Work
- Relationship difficulties
- Financial problems
- Being too busy
- Children and family

1.1.3.2 Common internal causes of stress

Not all stress is caused by external factors. Stress can also be self-generated:

- Inability to accept uncertainty
- Pessimism
- Negative self-talk
- Unrealistic expectations
- Perfectionism
- Lack of assertiveness

1.1.4 Common effect of stress

1.1.4.1 On body [11]

- Headache
- Muscle tension or pain
- Chest pain
- Fatigue
- Change in sex drive
- Stomach upset
- Sleep problems

1.1.4.2 On mood
- Restlessness
- Anxiety
- Lack of motivation or focus
- Irritability or anger
- Sadness or depression

1.1.4.3 On behaviour
- Tobacco use
- Drug or alcohal abuse
- Social withdrawl

1.1.5 Stress Warning Signs and Symptoms
1.1.5.1 Cognitive Symptoms
- Memory problems
- Inability to concentrate
- Poor judgment
- Seeing only the negative
- Anxious or racing thoughts
- Constant worrying

1.1.5.2 Emotional Symptoms [12]
- Moodiness
- Irritability or short temper
- Agitation, inability to relax
- Feeling overwhelmed
- Sense of loneliness and isolation
- Depression or general unhappiness

1.1.5.3 Physical Symptoms
- Aches and pains, Diarrhea or constipation
- Nausea, dizziness
- Chest pain, rapid heartbeat
- Loss of sex drive
- Frequent colds

1.1.5.4 Behavioural symptoms [13]
- Eating more or less
- Sleeping too much or too little
- Isolating yourself from others
- Procrastinating or neglecting responsibilities
- Using alcohol, cigarettes, or drugs to relax
- Nervous habits (e.g. nail biting, pacing)

1.1.6 Stress-Induced Changes in Immune Function
1.1.6.1 Eustress (acute, physiologically adaptive)
Increased delayed type hypersensitivity, associated with acute spikes in corticosterone and decreased leukocytes in blood (by movement to skin).

1.1.6.2 Distress (chronic, physiologically maladaptive)
Decreased delayed type hypersensitivity, associated with chronically increase basal corticosterone and less decrease in blood leukocytes (i.e., less movement of leukocytes to skin) (Dhabhar *et al.*, 1997).

1.1.7 The Effect of Stress on Body Systems
There are very real effects of stress on body and mind that should help to see the importance of reducing the stress in life [14].

1.1.7.1 Nervous System
This system includes the brain, spinal cord, and all the other nerves running through the rest of the body. The nervous system ensures that the communication between all systems are good. It is also responsible for recognizing and coordinating the body's response to internal and external changes.

The nervous system seems to be the system that is effected the most when stress and anxiety is prevalent and prolonged, however, the effects of stress are widespread through all the other systems as well. Long term effects of stress on body system include anxiety, panic attacks, depression, insomnia [15].

1.1.7.2 Circulatory/Cardiovascular System

This system includes the heart and the blood vessels and it's job is to keep the body alive by circulating blood through the body.
Stress causes irregular heartbeat, chest pain, and constriction of blood vessels.
Long term effects of stress on body system include: high blood pressure, heart disease, heart attack, stroke.

1.1.7.3. Digestive System

This system includes mouth, teeth, tongue, intestines, colon, stomach, esophagus, gallbladder, liver, pancreas, and rectum.
Stress causes digestive upset such as nausea, diarrhea, constipation, appetite abnormalities.
Long term effects of stress on body system include: stomach ulcers, IBD (irritable bowel disease), colitis, acid reflux[16].

1.1.7.4 Respiratory System

This system includes the sinuses, nose, throat, voice-box, windpipe, lungs and diaphragm. The primary function of this system is to exchange gases like oxygen and carbon dioxide in the blood and other parts of the body.
Stress causes shortness of breath, dizziness, hyperventilation
Long term effects of stress on body system include: asthma, chronic sinusitis and other infections.

1.1.7.5 Lymphatic System/Immune System

This system includes the thymus gland, lymph nodes, spleen, tonsils, liver, and appendix. This system is the body's defense system.
Stress causes low immunity opening the door to sickness like colds, flu's, viruses and other illnesses. Long term effects of stress on body system include: Epstein Barr Virus, Fibromyalgia, Candida, Lupus[17].

1.1.7.6. Integumentary System (Skin)

This system includes skin, hair and nails. It serves as a barrier against infection and injury. Believe it or not, stress can cause hair loss, brittle nails, and even acne.
Long term effects of stress on body system include: chronic skin disorders, inability to heal wounds properly, skin infections and premature aging.

1.1.7.7 Endocrine System

This system is responsible for growth development, metabolism, and it has a great responsibility to maintain the body's homeostasis, which is the body's internal and external environment, such as pH level, and temperature by releasing certain hormones. The nervous system works closely with this system because it directs the hormones that the endocrine system releases. This system is also responsible for the release of those stress hormones such as cortisol and adrenaline.
Long term effects of stress on body system include: chronic fatigue syndrome, adrenal fatigue, thyroid problems, and even menstruation irregularities [18].

1.1.7.8. Excretory System/Urinary System

This system includes the skin, digestive system, kidneys, urinary system, bladder, and urethra. It's job is to remove waste from the body in order to help maintain the body's homeostasis.
Long term effects of stress on body system: kidney stones, bladder infections, cystitis, and kidney infections.

1.1.7.9 Muscular System

This system includes all the muscles in the body, it also helps circulate the blood and helps to move food through the digestive system. Long term effects on body system include: muscle tension, muscle aches, spasms, strains and sprains [19].

1.1.7.10 Skeletal System

This system include all the bones, joints and cartilage in the body. Long term effects on body system include: decreased bone density, joint mal function.

1.1.7.11 Reproductive System

This system includes all the sexual organs needed for reproduction. Stress causes a decrease in libido and can also effect the quality of sexual performance.
Long term effects of stress include: impotence and infertility.

1.1.8 Neurotransmitter and Stress

Neurotransmitters are powerful chemicals that regulate numerous physical and emotional processes such as mental performance, emotional states and pain response. Virtually all functions in life are controlled by neurotransmitters.
The four major neurotransmitters that regulate mood are Serotonin, Dopamine, GABA and Nor-epinephrine [20].

1.1.8.1 The Inhibitory System

It is the brains braking system, it prevents the signal from continuing. The inhibitory system slows things down. Serotonin and GABA are examples of inhibitory neurotransmitters.

1.1.8.1.1 GABA (Gamma amino butyric acid)

GABA is the major inhibitory neurotransmitter in the central nervous system. It helps the neurons recover after transmission, reduces anxiety and stress. It regulates nor-epinephrine, adrenaline, dopamine, and serotonin, it is a significant mood modulator.

1.1.8.1.2 Serotonin

Serotonin imbalance is one of the most common contributors to mood problems. Significant reduction in serotonin level increases the responsiveness to stress. Hippocampal serotonin concentration increased during psychosocial conflict in animals. If serotonin level decrease then sadness, depressed mood, anxiety, panic attacks, low energy, migraines, sleeping problems, obsession or compulsions, feel tense and irritable, crave sweets, and have a reduced interest in sex occur[21].

1.1.8.2 The Excitatory Neurotransmitter System

1.1.8.2.1 Epinephrine

It is also known as adrenaline is a neurotransmitter and hormone essential to metabolism. It regulates attention, mental focus, arousal, and cognition. It also inhibits insulin excretion and raises the amounts of fatty acids in the blood. Epinephrine is made from nor-epinephrine and is released from the adrenal glands. Low levels have been can result in fatigue, lack of focus, and difficulty losing weight. High levels have been linked to sleep problems, anxiety and ADHD.

1.1.8.2.2 Dopamine

It is responsible for motivation, interest, and drive. Stress induced changes in dopamine levels within terminal areas seem to involve mainly ventral tegmental area projecting cells. An acute and controllable/escapable physical stress was seen to cause an enhanced DA efflux in the ventral striatum [22]. Low Dopamine levels can drive us to use drugs (self medicate), alcohol, smoke cigarettes, gamble, and/or overeat. High dopamine has been observed in patients with poor GI function, autism, mood swings, psychosis, and children with attention disorders.

1.1.8.2.3 Glutamate

It is the major excitatory neurotransmitter in the brain. It is required for learning and memory. Low levels can lead to tiredness and poor brain activity. Increased levels of glutamate can cause death to the neurons (nerve cells) in the brain. Dysfunction in glutamate levels are involved in many neurodegenerative diseases such as Alzheimer's disease, Parkinson's, Huntington's, and Tourette's. High levels also contribute to Depression, OCD, and Autism. Microinjection of N-methyl-D-aspartate (NMDA) into the dorsomedial hypothalmic nucleus causes an increase in glutamate release and results in cardiovascular response very similar to the one evoked by emotional stress [23].

1.1.8.2.4 Histamine

It is most commonly known for it's role in allergic reactions but it is also involved in neurotransmission and can affect your emotions and behavior as well. Histamine helps control the sleep-wake cycle and promotes the release of epinephrine and norepinephrine. High histamine levels have been linked to obsessive compulsive tendencies, depression, and headache. Low histamine levels can contribute to paranoia, low libido, fatigue, and medication sensitivities.

1.1.8.2.5 Norepinephrine

It is also known as noradrenaline is a excitatory neurotransmitter that is produced by the adrenal medulla or made from dopamine. High levels of norepinephrine are linked to anxiety, stress, high blood pressure, and hyperactivity. Low levels are linked to lack of energy, focus, and motivation [24].

1.1.8.2.6 PEA (Phenylalanine)

It is an excitatory neurotransmitter made from. It is important in focus and concentration. High levels are observed in individuals experiencing "mind racing", sleep problems, anxiety, and schizophrenia. Low PEA is associated with difficulty paying attention or thinking clearly, and in depression.

1.1.9 Stress and Brain

The endocrine stress response begins with activation of the hypothalamic-pituitary-adrenal axis (HPA axis). Neurons in the hypothalamus release corticotropin-releasing hormone (CRH), which then travels to the anterior pituitary gland, stimulating the release of adrenocorticotropic hormone (ACTH). This hormone then travels through the blood to the adrenal cortex to release glucocorticoids. Corticosterone is released from the adrenal cortex in rats, while cortisol is released in humans [25]. Glucocorticoids are anti-inflammatory and important for maintaining homeostasis.

Cortisol leads to beneficial short-term responses. Long-term exposure to cortisol, however, can cause damage to the hippocampus and is associated with many different psychiatric disorders. During times of stress the activity of the HPA axis increases resulting in higher glucocorticoid levels, as seen in depression. Several brain regions involved in the stress response, including the amygdala and hippocampus, modify activity of the HPA axis.

The amygdala is important for HPA axis activity. Located just anterior to the hippocampus, the amygdala is activated during fear conditioning as well as in response to emotionally negative pictures, odors and tastes in humans. The amygdala is also activated during the coding and retrieval of emotional stimuli Three different regions make up the anatomy of the amygdala. The central amygdala is known to contain CRH neurons and has extensive connections with the bed nucleus of the stria terminalis (BNST), which then projects to the paraventricular nucleus of the hypothalamus (PVN) and brain stem. This nucleus of the amygdala is also noted for its relation to the expression of fear. Activation in this area increases after traumatic experiences The basolateral amygdala (BLA) has been shown to be important during fear conditioning as well. Lesion of the BLA or inactivation with muscimol in rats eliminated fear conditioning.

The BLA receives inputs from the hippocampal formation as well as the thalamus and sensory cortical areas. The BLA also sends projections to the central amygdala (CeA) and the prefrontal cortex (PFC). In this way, the BLA is able to associate fear with various sensory information [26].

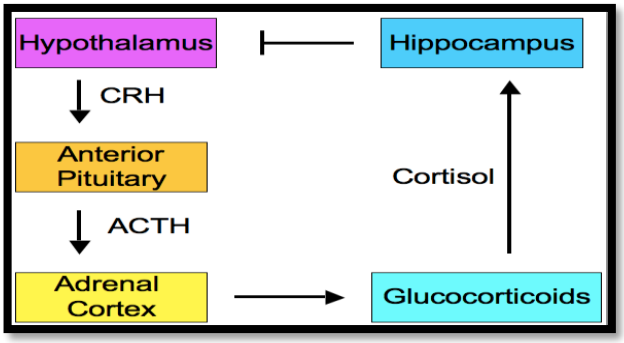

Fig. 1.3 Hypothalamic-Pituitary-Adrenal Axis (HPA)

When an individual perceives a stimulus as stressful a physiological response is displayed in the form of the HPA axis. CRH is released from the PVN, which travels to the anterior pituitary gland. From here ACTH is released into the blood stream and reaches the adrenal cortex. Glucocorticoid release is stimulated from the adrenal cortex and travels to the brain. Glucocorticoid receptors can be found in the hippocampus which when activated stimulate inhibitory control to the hypothalamus as a negative feedback system. CRH = Corticotropin releasing hormone, ACTH = Adrenocorticotropic hormone.

In contrast, the medial amygdala has not been found to be important for fear conditioning. The amygdala has strong connections with the olfactory bulb and piriform cortex. The medial amygdala likely plays a role in social behavior and processes related to social learning and memory. The medial amygdala also plays a role in aggression. The hippocampus and PFC have also been noted for their role in the stress response. The hippocampal formation is known to play a role in the encoding and consolidation of declarative memory. Interestingly, the size of the hippocampus in London cab drivers was found to be larger than age-matched controls. Additionally, this size increase correlated positively with the time spent driving the cab, as cited in. The hippocampus is sensitive to stressful experiences, but changes in the hippocampus following stress are often reversible. An important function of the hippocampus is its regulation of the negative feedback system in the HPA axis. High levels of glucocorticoids in the hippocampus lead to down regulation of receptors, which inhibits the ability of the hippocampus to regulate the HPA axis. The role of the PFC has also been studied because of the human abilities of avoidance and cognition. The PFC is essential for a higher processing of stressful and emotional stimuli [27-28]. A stressful stimulus for one individual may not be stressful for another. This inter-individual difference is dependent upon the PFC, more specifically the medial Prefrontal Cortex (mPFC), found that lesions of the PFC enhanced the response to a train of foot shocks, an acute stressor, suggesting a regulatory function of the PFC over the central amygdale after acute stress. In addition, this response was diminished after exposure to chronic cold stress, suggesting the regulatory function of the PFC decreases after chronic stress [29].

1.1.10 Effect of stress in Brain anatomy

Neuroimaging studies have shown evidence of consistent changes in humans with certain psychopathologies. Amygdala activity is exaggerated in patients with PTSD as well as panic disorder. In PTSD amygdala activity has been directly correlated with the severity of the disorder. Results of neuroimaging studies show that the amygdala is activated in social phobias. The responsiveness of the amygdala increases during public speaking as well as the anticipation of public speaking. Similarly, like PTSD, activity of the amygdala is positively correlated with the severity of anxiety as well as increases in self-reported fear. This effect has also been seen in Generalized Anxiety Disorder. Increased knowledge of how stress affects the amygdale and other brain areas is key to understanding the behaviors associated with these different psychopathologies. Numerous structural changes have been associated with various brain areas in response to stress as shown in fig 1.4[30].

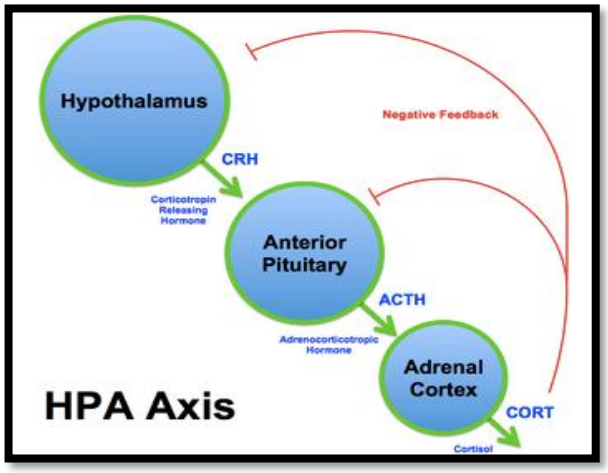

Fig. 1.4 Basic hypothalamic–pituitary adrenal axis summary (corticotropin- releasing hormone = CRH, adrenocorticotropic hormone=ACTH).

The amygdala undergoes growth during adverse experiences. In response to prolonged immobilization stress, dendrites in the BLA were 45% longer than controls. These lengthened dendrites also had increase of spines spines, which are sites of synaptic input. Dendrite lengthening was observed in the BNST, although it did not reach significance. Dendritic arborization was observed in both the BLA and BNST, as evidenced by the number of branch points in dendrites, but not the central amygdale. Chronic cold stress decreased spontaneous firing of CeA neurons, but an increase in firing rate after exposure to a train of foot shocks Cold stress also increased the responsiveness of BLA neurons. Additionally, chronic cold stress diminished the regulatory function of the PFC. That repeated immobilization stress also led to dendritic shortening in the PFC. In contrast to the amygdala, the hippocampus is reduced in response to stress. A reduction was observed in the volume of the hippocampus in tree shrews in response to stress. Stress also reduces the volume of the dentate gyrus of the hippocampus. This area contains adult stem cells and is a site of neurogenesis. Interestingly, acute stress can enhance the excitability of CA1 pyramidal neurons in the hippocampus. It is important to note that these changes are reversible. The hippocampus is noted as one of the most malleable brain regions and changes in this region may not be damage per se, but a form of synaptic plasticity. Similar to the behavioral effects of stress, physiological and neuroanatomical studies show a few discrepancies in the stress response, most notably, the difference in changes to the hippocampus in response to chronic and acute stress. Chronic stress reduces hippocampal volume, while acute stress has excitatory effects. Currently few studies focus on the time delay between the onset of stress and the time of behavior testing, rather than the length of stress. Additionally, the time-course study was done using social defeat, which as mentioned previously is a psychological stressor. In order to complete the full picture, a physical stressor should be examined as well. It is imperative that the time-course of stress itself be studied. Few studies examine the effects of a single session of stress, but have many consecutive long sessions of stress. It is possible that single stress sessions can be enough to create a behavioral response [31-32].

1.1.11 Neurobiological Changes Due to Stress

Many different mechanisms can be studied as underlying the response to stress. This is largely due to the wide range of effects of stress on behavior as well as brain physiology.

Certain neurobiological characteristics are descriptive of patients with different psychopathologies. Depressed patients exhibit hyperactivity of the HPA axis as well as

exaggerated responses of ACTH and cortisol. PET scans of patients with panic disorder elucidate decreased binding in serotonin (5-HT) receptors as well as in social phobia. Altered binding in 5-HT1a receptors is a possible mechanism behind anxiety disorders, such as social phobia and panic disorder. Because of its role as the primary modulator of stress, corticotropin-releasing hormone is a major focus of studies on the biological mechanisms of stress. CRH mRNA has been found in the central medial, and basolateral amygdala. Rats that were separated from their mothers, a form of stress, show increased CRH expression in the central amygdala as well as BNST as adults. In addition, early handling, in which the rats are removed from the cage for several minutes, causes an increase in CRH as well as CRH receptor binding in the amygdala. Since CRH causes the release of ACTH, which in turn triggers the release of corticosterone, the response of these hormones to stress is studied extensively. Early isolation, or separation from mother and littermates, for 8hrs increased ACTH and corticosterone levels as well as glucocorticoid mRNA levels. A single session of restraint stress elevated corticosterone levels, compared to unrestrained controls, 30 minutes after contextual conditioning training[33].

Corticosterone levels remain elevated even 60 minutes after restraint stress. Social defeat stress has also been shown to affect corticosterone and ACTH levels in rats. Defeated rats and rats that were faced with the threat of a defeat showed elevated corticosterone and ACTH when reexposed to the defeat environment 21 days late. After social defeat, defeated rats have higher levels of both hormones when compared to controls. The fos protein can also be used to examine the

effects of stress. The gene c-fos codes for the protein and is recognized as an immediate early gene. When a cell is stimulated it begins synthesizing the fos protein which then acts as a transcriptional activator. Neuronal growth factors through the ras pathway as well as protein kinase C can activate the fos protein. Activation of these pathways results in neuronal growth and differentiation. Fos was found to be highly colocalized with CRF, mRNA in the medial amygdala. In response to stress, fos expression increases in the forebrain, more specifically in the medial amygdala. It is in this brain region that higher fos expression was observed after social defeat stress. Expression of c-fos increased in response to psychosocial encounters regardless of stress or no stress experimental conditions. A psychosocial encounter is one in which an opponent rat blocked by a partition or in a plexiglass box is placed in the home cage of the subject. Rats bred for high levels of anxiety-like behavior on the EPM also exhibit increased fos expression after social defeat. Fos expression in these rats increased in the central amygdala, parts of the medial amygdala, and paraventricular nucleus of the hypothalamus. These data are consistent with evidence of increased dendritic arborization in the amygdala as well as increased levels of glucocorticoids in response to stress [34-35].

1.1.12 Mechanism and formation of reactive oxygen species

Cellular energy metabolism and oxygen consumption are coupled to the generation of ROS. Thus, a reduction in metabolic rate reduces the formation of ROS. This is supported by studies of experimental animals subjected to chronic calorie restriction. There is also limited human evidence from a study performed on a Japanese population in which energy intake was 20% less than the national average. The rates of death due to ROS-associated diseases were decreased in this population, with cerebral vascular disease decreasing by 41%, malignancy by 31%, and heart disease by 41%. The metabolism of toxic compounds could result in the generation of reactive metabolites that have even greater toxicity and deplete cellular antioxidants. In mammals, up regulation of cytochrome P450 (CYP) has been linked to ROS production thus, environmental toxicants are a potential source of ROS. Severe depletion of circulating antioxidants has been observed in smokers. Air pollution, ionizing radiation, UV light, heavy metals, metalloids, pesticides and polycyclic aromatic hydrocarbons among others, induce the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in target tissues, engaging signaling pathways that are activated in response to oxidative stress (OS). In addition, occupational exposure to metals, benzene, cement dust, and multiple other agents is associated with increased lipid peroxidation, increased DNA oxidation, and decreased levels of vitamin E and C. CYP monoxygenases are a major source of ROS during ischemia/reperfusion. Accordingly, drugs that inhibit P450 activity protect cells from ROS-induced damage after ischemia or block the formation of catechol estrogens and their subsequent oxidation, leading to decreased oxidative damage. Finally, evidence suggests that a higher intake of multiple

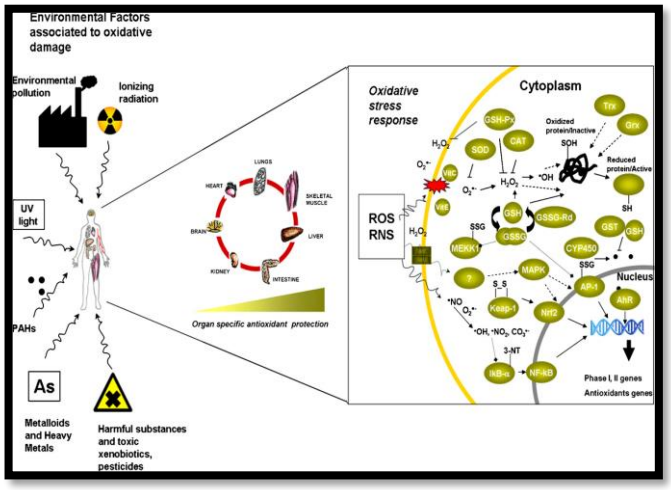

Fig.1.5 Formation of reactive oxygen species

nutrients, including folic acid, potassium, glucosinolates, diallyl sulfides, and flavonoids, greatly reduces the risk of cardiovascular disease associated with air pollution exposure. ROS-induced damage to nucleic acids, proteins, carbohydrates, and lipids alters the function of these macromolecules in cells, tissues, and organs. These perturbations elicit adaptive cellular responses that increase antioxidant defenses and repair mechanisms (e.g., DNA repair). Severe oxidative damage to macromolecules leads to cellular death as shown in fig 1.5[36-37].

1.1.13 Therapeutic strategies Involved in the Management of Stress

Pharmacological approaches

- Benzodiazepines **e**g. flurazepam, diazepam, chlordiazepoxide
- 5-HT1A receptor agonist
- Cyclooxigenase inhibitor
- Antioxidant
- Tricyclic antidepressant Eg. trazodona, mirtapazine, doxepin, amitriptyline [38].

Some common drug used in the stress as Citalopram, Prozac, Citalopram, Amitriptyline, Paxil CR, Paxil, Sertraline, Venlafaxine, Fluoxetine, Mirtazapine, Paroxetine HCl, Escitalopram, PEXEVA, Luvox CR, Sarafem, Fluvoxamine, Prozac Weekly, Remeron SolTab, Paroxetine mesylate.

Table 1.1 Herbal Management of Stress-

Name of Plant	Plant part and extract
Aegle marmelos (Rutaceae)	Standardized dried extract of whole plant
Alstonia scholaris R. Br. (Apocynaceae)	Methanoli extract of dried bark
Allium sativum (Alliceae)	95% ethanolic extract of bulb
Annona muricata (Annonaceae)	Stem bark
Argyreia speciosa Burm .f (Convulvulaceae)	Ethanol, ethyl acetate fractions of root
Asparagus racemosus	Aqueous and milk decoction of root
Bacopamoniera (Scrophulariaceae)	Standardized extract of aerial part
Bergenia crassifolia (Saxifragaceae)	Fermented leaves
Boerhaavia diffusa (Nytiginacea)	Aqueous extract of root powder
Butea monosperma (Fabaceae)	Flower
Caesalpinia bonduc (Caesalpiniaceae)	95% ethanol extract of seed coat
Carum carvi (Umbelliferae)	Aqueous extract of fruit materials
Chloropytum borivillianum (Liliaceae)	Alcoholic, aqueous and successive tuber extracts of roots, leaves
Cnestis ferruginea (Connaraceae)	Aqueous extract of dried root of *Cnestis ferruginea whole plant*
Diospyros peregrina gurke (Ebenaceae)	Ethyl acetate extract of whole plant
Eleutherococcus senticous	The 70% alcoholic extract of powdered roots of *E. senticosus*
Eugenia caryaphullus	Hydro alcoholic extract of buds
Evolvulus alsinoides (convolvulaceae)	Ethanolic extract of whole plant; bioactivity guided purification of n-BuOH soluble fraction from ethanol extract
Fagopyrum esculentum (Polygonaceae)	The powdered drug (whole plant) was extracted with n-hexane, petroleum ether, ethanol and water separately.
Ginkgo biloba (Ginkgoacae)	Standardized leaf extract
Hibiscus cannabinus (Malvaceae)	Methanolic extract of leaves
Hippophae rhamnoides (Elaeagnaceae)	Aqueous lyophilized leaf extract

1.1.13.2 Non -pharmacological approaches

1.1.13.2.1 Exercising

It is the most effective way to becoming stress free. "One should exercise daily this will help to relax and keep mind off things that cause stress [39].

1.1.13.2.2 Relaxation techniques

Relaxation tech. can help relives stress and put the mind at ease. With some daily schedule, stress can be reduced. Healthy rest in order to:

- Go for a walk.
- Spend time in nature.
- Call a good friend.
- Workout stress with a good sweat.
- Write in your journal
- Light scented candles.
- Listen to music.
- See comedy.
- Allow phonetic typing Alpha
- A hot cup of coffee or tea flavor.
- Get a massage

1.1.13.2.3 Laughter

Humor in one's life decrease stress. Laughter is a good medicine for everyone. Laughter in life can increase the positive energy and mitigate any negative vibes.

1.1.13.2.4 Motivation techniques

Motivation provides an impetus to get up and something. Stress can be used as motivator to change the way of thinking in life.

1.2 PLANT DESCRIPTION

Marsilea quadrifolia Linn. a member of Marsileacae is a creeping herbaceous perennial plant. It is also known as Chaupatiya, sunsuniya in Hindi (Asham *et al.,* 2013). As it creeps along the surface new clover like leaves will emerged that are supported by petioles that can grow to a length of 4-6 inches (10-15 cm) (Ashwini *et al.,* 2012). *Marsilea quadrifolia* is an aquatic fern bearing 4 parted leaves resembling "4- leaf clover" (Mathangi *et al*., 2012). The plant prefer light (sandy) and medium (loomy) soil. *Marsilea* is commonly called as Europian Water Clover (Soni *et al.,* 2012).

1.2.1 Taxonomical Classification-

Table no. 1.2

Kingdom	Plantae
Class	Polypodiopside
Order	Salviniales
Family	Marsileaceae
Genus	Marsilea
Species	*Marsilea quadrifolia Marsilea minuta*

Fig.1.2 *Marsilea quadrifolia*

1.2.2 Vernicular names

Hindi - Chaupatiya, sunsuniya
Malyalam - Neeraral
Telugu - Ciklintakura
Tamil - Araikeerai

1.2.3 Description

1.2.3.1 Habitat

It is widely distributed in tropical regions of the world and found throughout India. In marshy places and along the bank and rivers.

1.2.4 Morphology

Leaves- The leaves arise alternately in two rows from the upper surface of the creeping rhizome. Leaves, when young, show circinate venation. The petioles of submerged species are long, weak, cylindrical and flexible, with leaf-lets floating on the surface of water. However, the petiole of species growing on mud orground, are short, cylindrical and upright. At the tip of each petiole, there are four leaflets of equal size, and hence commonly known as four leaf clover. Leaflets obdeltoid, to 3/4" long, glaucous, petioles to 8"long; Sporocarp (ferns) ellipsoid, to 3/16" long, dark brown, on stalks to 3/4" long, attached to base of petioles.

Root-The primary roots are short -lived and are soon replaced by one or two adventitious roots that usually develop at the nodes on the underside of the rhizome.

Rhizome-Rhizome is freely branched and is capable of indefinite growth. The rhizome is well branched and the branches arise at the base of the leaves [40].

1.2.5 Chemical Constituents-

Marsilin (1-triacontanol-cerotate), 3-hydoxy-tri-acontan-11-one, hentriacontan-6-ol, methylamine, beta-sitosterol, marsileagenin A, flavonol -O-mono-and- diglycoside, C-glucoylflavones and C-glucosylxanthones have been isolated from the plant.

Thiaminase enzyme is majorly present in this plant and also present some carbohydrates. It also contain alkaloid, phenols, terpenoids, glycosides, saponin, steroid, tannin and sugar.

1.2.6 Pharmacological actions-

The plant has been reported for its cytotoxic, antibacterial and antioxidant activity.

It has been reported that plant consists of certain pharmacological activities such as antianxiety, anticonvulsant and psychopharmacological studies and also has been proved to be useful against alzheimer's disease.

1.2.7 Traditional uses-

The plant has been used for astringent, hypnotic, diuretic, expectorant, aphrodisiac, anodyne, ophthalmic, constipating, psychopathy, leprosy, haemorrhoids, skin diseases, fever, insomnia and febrifuge. The plant is traditionally used to reduce mental tension and to induce sleep, reducing anxiety and stress in emotional conditions.

Plant pacifies vitiated pitta, cough, bronchitis, diabetes, eye diseases, diarrhea, antidote, antiphloristic, depurative and diuretic [41].
It is also used to treat snake bite and applied to abscesses etc.

1.3 REVIEW OF LITERATURE ON DISEASE

Jameel *et al.*, (2014) evaluated the effects of various physical stress models on serum cortisol level in Wistar male rats. The results showed that rise in serum cortisol level was significantly higher after restraint test than exposing them to forced swim test. This indicated that restraining the rats produced more stress than making them forcefully swim.

Oh *et al.*, (2014) investigated anti-stress activity of *Astragalus membranaceus* in immobilization stress model. The results concluded that *Astragalus membranaceus* had significant antistress property.

Budni *et al.*, (2013) showed folic acid prevents depressive-like behavior and hippocampal antioxidant imbalance induced by restraint stress in mice. The results showed that folic acid displays a specific antidepressant profile in the restraint stress paradigm that may be at least partly due to its antioxidant role.

Govind and Anis, (2013) evaluated antistress potential of *Glycyrrhizin* in forced swim stress model. The results showed that *Glycyrrhizin* had potential for antistress activity.

Huilgol and Jamadar, (2013) evaluated the gastroprotective role of bioflavonoid *Silymarin* in acute cold-restraint induced gastric ulceration in Wistar rats. The results suggested that *Silymarin* protect gastric mucosa from ulceration and increase adherent mucin [42].

Rather and Saravanan, (2013) evaluated the antistress activities of *Nymphaea stellata* flowers ethanolic extract (NSFEE) on immobilization induced stress. The results indicated that the ability of NSFEE to combat immobilization induced-stress alterations and observed effects of NSFEE was due to antioxidant, antilipidimic activities and hence possessed antistress activities.

Ahmed *et al.*, (2012) investigated restraint stress-induced central monoaminergic & oxidative changes in rats & their prevention by novel *Ocimum sanctum* compounds using restraint model. The present findings showed that the anti-stress potential of *Ocimumoside* A and B in relation to their simultaneous modulatory effects on the central monoaminergic and antioxidant systems implicating their therapeutic importance in stress-related disorders.

Bhajipale, (2012) studied the antistress activity of methonolic extract of seed of *Abutilon muticum* by swim indurance test in adult Wistar rats. The results suggested that methonolic extract of *Abutilon muticum* extract had significant antistress activity.

Bathala *et al.*, (2012) studied the efficacy of *Ocimum sanctum* for relieving stress. The results showed that *Ocimum sanctum* possessed significant antistress activity.

Koppula and Choi, (2012) explored the anti-stress and anti-amnesic effects of *Coriandrum sativum* linn (umbelliferae) extract in rats. The results showed that *Coriandrum sativum* might be useful remedy in the management of stress and stress related disorders.

Kumar *et al.*, (2012) investigated the ameliorative role of cilnidipine and nimodipine in immobilization stress-induced behavioral alterations and memory defects in the mice. The results concluded that cilnidipine and nimodipine mediated attenuation of corticosterone release by blockage of calcium channel on the HPA-axis is responsible for beneficial effects in restoration of behavioral alterations and memory deficits in immobilization-induced acute stress in mice.

Pawar and Hugar, (2012) assessed the level of scientific evidence presented by the adaptogens from natural origin by different screening method and to provide a rationale at the molecular level. The results showed that the beneficial stress protective effect of Adaptogen was related to the regulation of homeostasis via several mechanism of action [43].

Suresh *et al.*, (2012) examined the anti-stress activity of *Murraya koenigii* in rat model of acute and chronic stress. The results indicated that leaf extract of *Murraya koenigii* had antistress activity.

Selvi *et al.*, (2012) explored the antistress activity of aqueous extract of leaves of *Centella asiatica* linn by *in vivo* methods in rats. The results indicated the extract had significant antistress activity as showed by its effects on different experimentally induced animal models.

Saxena and Saxena, (2012) investigated the antistress effect of *Cinnamon (Cassia zelynicum)* bark extract in cold restrained stress model in Albino rats. The results showed that *Cinnamon* was effective in minimizing stress response and beneficial in stress therapy.
Venkatesh *et al.*, (2012) studied the plants which containing anti-stress activity of ayurvedic origin. The results stimulated the researchers for further work medicinal plants containing anti-stress activity from ayurveda.

Anju, (2011) evaluated the adaptogenic property of an ethanolic extract of *Bacopa monnieri* against acute stress model in mice using swim endurance test. The results concluded that the ethanolic extract of *Bacopa monnieri* possessed a potent adaptogenic activity.

Atchley (2011) examined the time-course of the effects of stress in rodents. The results suggested that females were not more vulnerable to the effects a single restraint stress on the EPM (Elevated Plus Maze).

Debnath *et al.*, (2011) explored anti stress activity *of Terminalia chebula* fruits in various animal models, namely anoxia stress tolerance and forced swimming test in mice, as well as cold resistant stress and immobilization test in rats. The results suggested that ethanolic extracts of *Terminalia chebula* significantly increased the swim endurance, anoxia stress tolerance test and extract also reduced stress induced elevated levels of serum biochemical parameters in cold restraint stress and immobilization stress.

Desai *et al.*, (2011) explored antistress activity *of Boerhaavia diffusa* and a polyherbal formulation containing *Boerhaavia diffusa* using cold restraint stress model in Wistar rats. The results concluded that *Boerhaavia diffusa* had comparable antistress activity.

Ihne *et al.*, (2011) studied that C57BL/6J mice exposed to ten daily sessions of restraint stress exhibited increased exploration of the aversive light compartment in the light/dark exploration (LDE) test.The results elucidated that genetic and neural mechanisms mediating stress-induced changes in mouse 'emotion-relevant' behaviors and, ultimately, further understanding of the pathophysiology of stress-related neuropsychiatric disorders[44].

Joshi *et al.*, (2011) studied antistress activity of ethanolic extract of *Asparagus racemosus* willed roots in mice by swimming endurance test and restraint stress. The results suggested that antistress property of *Asparagus racemosus* in different model of stress.

Kavitha *et al.*, (2011) studied the antistress activity of *Momordica charantia* fruit extract on stress induced change in Wistar rats. The results showed that *Momordica charantia had* significant antistress activity.

Kothiyal and Ratan, (2011) evaluate the antistress potential of extracts of *Fagopyrum esculentum* on forced swimming endurance test. The results concluded that *Fagopyrum esculentum* hadsignificant anti stress activity.

Patel *et al.*, (2011) evaluated the antistress effect of hydroalchohalic extract of *Argyreia speciosa* by using swimming endurance test and anoxic tolerance test and cold restraint stress in mice and rats. The results indicated that *Argyreia speciosa* had significant antistress activity.

Saxena and Singh, (2011) examined the anti-stress activity of risperidone, atypical antipsychotic drug, in rat stress models. The results concluded that risperidone pretreatment showed significant anti-stress activity in the cold restraint stress.

Duraisami *et al.*, (2010) evaulated antistress and adaptogenic activity of standardized dried fruit extract of *Aegle Marmelos* using swimming endurance and post-swimming motor function test in Wistar rats. The results indicated that test extract increased the swimming endurance time along with motor function like rota rod falling time.

Lakshmi *et al.*, (2010) evaluated the anti-stress activity of *Cuminum cyminum linn* seeds extract by using swim endurance test. The results concluded anti-stress activity of the aquesous extract of *Cuminum cyminum* linn had the significant values at a dose of 400mg.

Mrudula *et al.*, (2010) showed the antistress and antioxidant effects of *Prunella vulgaris* leaves. The results suggested that it could be used for the treatment of oxidative stress induced disorders.

Ou and Li, (2010) evaluated effect of enhancing physical strength and antistress activity of flavonoids from the Chinese medicinal plant *Epimedium Koreanum Nakai* using in male ICR mice and Sprague dawely rats. The finding suggested that flavonoid from the *Epimedium Koreanum Nakai* had a effect on enhancing physical strength and antistress activity.

Tabassum *et al.*, (2010) studied the ameliorative effect of *Occimum sanctum* and *Camellia sinesis* on stress induced anxiety and depression in male Albino rat. The results concluded that *O.sanctum, C.sinesis* reduced immobility times of rat in forced swim test and tail suspension test.

Umukoro and Aladeokin, (2010) evaluated the anti-stress and anticonvulsant activities of the aqueous leaf extract of *Alchornea cordifolia* were investigated in mice. The results showed that *Alchornea cordifolia* protected against stress or fatigue
But the extract did not exhibit anticonvulsant activity.

Deore and Khadabadi, (2009) screened the antistress properties of *Chlorophytum borivilianum* tuber. The results indicated that *C. borivilianum* extract possessed significant antistress activity[45].

Kumar *et al.*, (2009) studied possible GABAergic mechanism in the protective effect of allopregnenolone against immobilization stress. The results suggested that allopregnenolone's protective effect could be due its interaction with γ-amino butyric acid receptor.

Meera *et al.*, (2009) evaluated antistress and immunomodulatory activity of aqueous extract of *Momordica charantia (MC)*. The results suggested that *Momordica charantia* had significant antistress and immunomodulatory activity.

Pacheco and Gonsebatt, (2009) studied the role of antioxidants and antioxidant-related enzymes in protective responses to environmentally induced oxidative stress. The results suggested that antioxidant responses elicited by environmental pollutants in humans and animal models.

Samson *et al.*, (2009) explored oxidative stress in brain and antioxidant activity of *Ocimum sanctum* in noise exposure in rats. The results indicated that *O. sanctum* had the potential for further evaluation as an ideal antioxidant for the noise induced oxidative stress.

Sumnath and Mustafa, (2009) evaluated antistress, adaptogenic activity of *Sida cordifolia* roots in mice using swim endurance test. The results showed that significant improvement in the swim duration and proved the antistress and adaptogenic property.

Singh *et al.*, (2009) evaluated the antistress effect of the hydro-alchohalic extract of *Eugenia caryophyllus* (clove) on anoxic stress induced convulsion. The results concluded that hydroalcholic extract of clove at doses of 100 and 200 mg/kg orally possessed good antistress activity.

Tiwari *et al.*, (2009) investigated anti-stress activity of standardised extract of *Marselia minuta* l. in rats. The results indicated that *Marsilea minuta* had significant anti-stress activity.

Verma and Khosa, (2009) explored effect of *Costus speciosus* and *Wedelia chinensis* on brain neurotransmitters and enzyme monoamine oxidase following cold immobilization stress. The results indicated the protective nature of the plant material on the brain tissues against the detrimental effect of noise stress.

Ishola *et al.*, (2008) investigated phytochemical component and antistress potential of aqueous root extract of *Alchrnea cordifolia* by using forced swim test and anoxic tolerance test in mice. The results showed that root extract of *Alchornea cordifolia* possessed antistress property.

Kulkarni and Juvekar, (2008) investigated the effect of stress and its modulation by methanolic extract of bark of *Alstonia scholaris* was studied using acute restraint stress model in mice. The results provided scientific support for antistress activity, antioxidant and nootropic activities of methanolic extract of bark of *Alstonia scholaris*.

Lyle *et al.*, (2008) evaluated stress modulating antioxidant effect of *Nardostachys jatamansi* in rats. The results suggested that the NJEE possessed significant antistress activity which might be due to its antioxidant activity [46].

Nirmal *et al.*, (2008) evaluated the behavioural and antioxidant activity of *Cytisus scoparius* link in rats exposed to chronic unpredictable mild stress. The result showed that *Cytisus scoparius* possessed anti-stress and moderate anxiolytic activity.

Singh *et al.*, (2008) evaluated anti-stress effects of *Geriforte*. The results suggested that *Geriforte* had antistress activity.

Adam and Epel, (2007) explored the stress, eating and the reward system. The results elucidated likely pathways for stress-eating, there was much progress to be made in trying to understand and prevent stress eating and non homeostatic eating in general.

Bartolomucci (2007) focused on studied conducted on laboratory and wild rodents where social factors such as dyadic interactions, individual housing and differential group housing were investigated. The results concluded that social factors in rodents was causally linked with immune disorders/disease susceptibility.

Grandi *et al.*, (2007) investigated the influence of peripheral nociceptin/orphanin FQ (N/OFQ) on cold restraint-induced gastric mucosal damage in the rats. The results suggested that N/OFQ counteracts acute stress-induced gastric mucosal damage by interacting with NOP receptor and by influencing mucous cell activity.
Ishola and Ashorobi (2007) explored antistress potential of aqueous root extract of *Cnestis ferruginea* by using forced swimming endurance test and anoxic tolerance test in mice. The results concluded that the root extract of *C. ferruginea* had antistress property.

Kenjale *et al.*, (2007) studied the antistress and antioxidant effects of roots of *Chlorophytum borivilianum* in rats. The results suggested that it could be used for the treatment of oxidative stress-induced disorders.

Sumnath and Mustafa, (2007) explored the ethanolic extract of roots of *Boerhaavia diffusa* for antistress, adaptogenic activity in albino mice by swim endurance test. The results indicated that roots of *Boerhaavia diffusa* possessed antistress and adaptogenic activity.

Dhir *et al.*, (2006) examined the effect of naproxen or rofecoxib in subchronic immobilization stress in mice. The results suggested that the use of COX-inhibitors (naproxen or rofecoxib) could be a useful neuroprotective strategy in the treatment of stress.
Sood *et al.*, (2006) investigated the effect of *Ocimum sanctum* linn. on cardiac changes in rats subjected to chronic restraint stress. The results showed that *Ocimum sanctum* protects the stress induced changes in heart.

Gupta *et al.*, (2005) studied the anti-stress and adaptogenic activity of L-arginine supplementation in rats using the cold hypoxia restraint model. The results suggested that L-arginine possessed potent anti-stress activity [47].

Patil *et al.*, (2005) studied antistress activity of roots *Rubia cordifolia* linn. The results suggested that *Rubia cordifolia* possessed antistress activity.

Sembulingam *et al.*, (2005) studied effect of *Ocimum sanctum* Linn on the changes in central cholinergic system induced by acute noise stress in rats. The results proved the protective nature of the plant material on the brain tissues against the noise stress.

Archana and Namasivayam, (1999) investigated antistresser property of *Withania somnifera* using adult Wistar strain albino rats and cold water swimming stress test. The results indicated that the drug treated animals show better stress tolerance.

Bhatwadekar *et al.*, (1999) investigated the antistress activity of water-soluble part of ethanolic extract of *Butea monosperma* on water immersion stress-induced ulceration, elevation of serotonin (5-HT) in brain and corticosterone in plasma in rats. The results concluded that *Butea monosperma* flowers possessed antistress activity.

Ahmed *et al.*, (1998) investigated the antistress activity of JM (Jawahir Mohra) preparation anti-stress activity against physical, chemical and metabolic stimuli. The results showed that the gems in JM contribute significantly to its anti-stress activity.

Grandhi *et al.*, (**1994)** compared the aqueous suspensions of roots of an Indian drug Ashwagandha and the Korean drug Ginseng were tested comparatively for 2 pharmacological activities, namely the anti-stress activity by the mice swimming endurance test and anabolic activity by noting gain in body weights and levator ani muscle in rats. The results evaluated that significant increase in body weights in the Ashwagandha treated group was better than Ginseng. Gain in wet weights of the levator ani muscle were also significant in Ginseng and Ashwagandha treated groups.

Singh *et al.*, (1988) studied *Dicspyros peregrina* (ethyl acetate extract) for the anti-stress activity in albino mice and rats. The results possessed that *Dicspyros peregrina* had significant antistress activity.

Bhattacharya and Bhattacharya, (1982) examined the effect of restraint stress on morphine antinociception in rats. The results suggested that serotonin and prostaglandins are involved in restraint stress-morphine interaction.

Tripathi *et al.*, studied effectiveness of *Spirulina* in sound stress induced biochemical changes in rat. The results indicated that *Spirulina* was effective in reducing sound stress induced biochemical changes.

1.4 REVIEW OF LITERATURE ON PLANT

Asham *et al.*, (2013) evaluated the preliminary screening of *Marsilea quadrifolia* extract for their antianxiety potential. The results showed that *Marsilea quadrifolia* possessed the anxiolytic activity.

E. Rolli *et al.*, (2013) evaluated that *in vitro* micropropagation of the aquatic fern *Marsilea quadrifolia* linn. and genetic stability assessment by random amplified polymorphic DNA (RAPD) markers. The results suggested that the *in vitro* HF (hormone free) micropropagation could be useful in the development of *ex situ* conservation programs of *Marsilea quadrifolia.*

Uma and Praveen, (2013) evaluated the in vitro cytotoxic activity of methanol, aqueous and ethyl acetate extracts of leaves of *Marsilea quadrifolia* on MCF-7 cell from human breast cancer. The finding indicated that methanol and ethylacetate extracts of *Marsilea quadrifolia* leaf possessed vast potential as medicinal drug especially in breast cancer treatment.

Ashwini *et al.*, (2012) studied the *Marsilea quadrifolia* plant extract against Alzheimer's disease in mice. The results proved the anti alzheimer's potential of *Marsilea quadrifolia*.

Mathangi, and Prabhakaran, (2012) evaluated the antimicrobial activity of the ethenolic extract of *Marsilea quadrifolia* against various bacterial pathogens. The results indicated that *Marsilea quadrifolia* had profound anti bacterial activity.

Bhadra *et al.*, (2012) studied the phytochemical profile of *Marsilea quadrifolia* and investigate its anti-cholinesterase potential. The results concluded that *Marsilea quadrifolia* might be a potential lead as an AchE inhibitor.

Manjula, and Mythili, (2012) investigated the improved phytochemical production using biotic and abiotic elicitors in *Marsilea quadrifolia*. The results showed that using elicitors the metabolite production can be increased.

Reddy *et al.*, (2012) evaluated the psychopharmacological studies of hydro alcoholic extract of whole plant of *Marsilea quadrifolia*. The results showed that *Marsilea quadrifolia* had significant psychopharmacological property.

Sahu *et al.*, (2012) investigated the anticonvulsive potential of *Marsilea quadrifolia* extract by using pentylenetetrazole (PTZ) induced seizure model in rats. The results proved that *M. quadrifolia* had anti convulsive activity.

Soni and Singh, (2012) studied the *Marsilea quadrifolia* Linna valuable culinary and remedial for its medicinal properties. The results found that *M. quadrifolia* Linn. is an important marketable species and used by tribals for its nerve relaxant nature and curative properties for various other ailments of nervous system and its nutritional value.

Nahar *et al.*, (2011) evaluated the possible analgesic and antidiarrhoeal potential of methanolic extract of *Marsilea quadrifolia* (MEMQ) in rats. The results indicated the potent analgesic and antidiarrhoeal effects of *Marsilea quadrifolia* extract on animal models which are comparable with those of standard drugs such as Indomethacin, Loperamide respectively and supports its traditional uses as medicine**.**

Zahan *et al.*, (2011) investigated the antidiabetic and antioxidant activity of the methonolic extract of *Marsilea quadrifolia* in rats. The results suggested that *M. quadrifolia* may be a potential source of natural oxidant with good hypoglycemic activity.

Kao and Lin, (2010) investigated the phototropic leaf movements and photosynthetic performance in an amphibious fern, *Marsilea quadrifolia*. The results concluded that diurnal phototropic leaf movement represents one of the plastic responses enabling this amphibious fern to grow under terrestrial conditions.

Bwzeanu and Banciu, (2009) perform the comparative studies regarding ultrastructure of *Marsilea quadrifolia* (pteridophyta) leaf mesophyll cells by *in vivo* and *in vitro* culture. The results concluded that plant regeneration and clonal multiplication did not affect the normal pattern of plant development.

Ripa *et al.*, (2009) studied the antibacterial, cytotoxic and antioxident activity of crude extract of *Marsilea quadrifolia.* The results indicated that the chloroform and ethyl acetate extracts of the aerial part of *M. quadrifolia have* got profound antibacterial, cytotoxic and antioxidant effect and may have potential use in medicine.

Lin *et al.*, (2005) evaluated abscisic acid regulation of heterophylly in *Marsilea quadrifolia* L.: effects of *R*-(−) and *S*-(+) isomers. The results suggested that two distinct mechanisms of action for (−)-ABA: either (−)-ABA is intrinsically active, or its activity is due to the stimulation of (abscisic acid) ABA biosynthesis.

Kim *et al.*, (2000) investigated the evolutionary history of expanism and their role in cell elongation in early land plants, isolated two α-expanisn genes respectively, from the semiaquatic ferns *Marsilea quadrifolia* and Regnellidium diphyllum Lindm. The results showed that α-expansions act as wall-loosening proteins in ferns,as had been proposed for angiosperms. In addition, Rd-EXPI may play role in mediating elongation of the rachis in submerged plants.

Lin and Yang, (1999) studied that blue light and abscisic acid independently induce heterophyllous switch in *Marsilea quadrifolia.* The results indicated that the blue light signal is not mediated by ABA (abscisic acid). Therefore, in the regulation of hetrophyllous determination,discrete pathway exixt in response to environmental signals.

Chernys and Kende, (1996) evaluated the ethylene biosynthesis in *Regnellidum diphyllum* and *Marsilea quadrifolia.* The results concluded that the formation of ethylene in both ferns occurs mainly, via an ACC-independent route.

Bordonneau and Tourte, (1994) studied the differential expression of parental genomes during formation of embryonic organs in the early development of the fern *Marsilea quadrifolia.* The results indicated that growth of the first organs was quite normal, indicating that they develop under the control of the maternal genome. The subsequent organs indicated that they are under the control of both parental genomes.

Lin and Raghvan, (1991) studied that lateral root initiation in *Marsilea quadrifolia* linn origin and histogensis of lateral root. The results showed that central axis of the root is not only a geometric centre, but also a physiological centre which determines the fate of the different cell types [48].

CONCLUSION

Stress is a global menace fortified by the advancement of industrialization and elicited by a variety of factors, viz., environmental, social or pathological phenomenon of life. Considerable evidence published in the last decade has focused on a constellation of neurochemical, biochemical and molecular effects caused by stress in the CNS, endocrine system, and immune system. Normally stress induced changes are self-limiting and adaptive until events override “threshold” limits, becoming irreversible and pathological. Advancements in the understanding of processes leading to the pathogenesis of stress-induced disorders cannot obscure the simple fact that the exhaustion of energy supply is still the basis for triggering the disorders and collapse of energy metabolism following glucose deprivation in the circulation. The desire to augment the coping mechanism has led to the emergence of the science of adaptation that focuses on elucidating mechanisms that may help to counteract excessive and unnecessary responses to stress.

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