Review of Literature
Selye, (1956) defined stress as the nonspecific result of any demand upon the body, be it mental or somatic. Stress can be either positive or negative. The positive stress is called “Eustress” while the negative stress is called “Distress”. The possible cause for positive aspect of stress is suggested as many people perform best when they are under pressure; they concentrate, focus, and reach their peak efficiency. Stress becomes negative when one can’t meet the challenges. Chronic negative stress may lead to serious health related problems. Under stress, the body makes rapid physiological changes called the General Adaptation Syndrome (GAS) to deal with threatening situations, which is induced by stress and consists of an alarm reaction followed by a stage of resistance eventually leading to the state of exhaustion.

Selye, (1953) has described a generalized physiological response to stress, as Alarm, the “fight or flight” response, resistance phase, the source of stress is actively fought and the exhaustion phase.

American physiologist Cannon, (1929) referred the “fight or flight” response has a very real effect on the body virtually all systems are modified to meet the perceived danger and it also depends on the intensity, duration of stress exposure. It is classified in to phases.

- **The acute phase**: This is the phase in which stressful stimuli start to act on the brain to induce alteration in hormones to answer quickly.

- **The resistance phase**: This is the phase where the mental, emotional and physical consequences of chronic stress start to appear unless managed. Loss of concentration, emotional instability or depression, increase in heart palpitations, cold sweating and headaches are telltale signs, but most of the persons do not relate them to stress.

- **The exhaustion phase**: This is the phase when the organism capitulates to stress, and when organic and psychic alteration results in diseases.

One cannot avoid the environment around them so also the stress originating from it and hence the noise acts as an environmental stressor (Berglund and Lindvall, 1995; Passchier-Vermeer and Passchier, 2000).
Noise

Noise is generally defined as unwanted or undesirable sound that causes an uncomfortable feeling. Tsai et al., (2005) reported that sound those are unwanted, unpleasant or hurtful become noise and in this modern age noise has become an inescapable phenomenon. However, this definition is quite subjective because it varies depending on many different factors, including the time, the place, the conditions, as well as the emotional states of the individual. It is also depends on social and cultural backgrounds of the people exposed to the noise. Hence, there is no clear demarcation to define noise.

Sound levels:

Sound propagates from a source in all directions. In scientific terms, ‘Sound is the result of pressure changes in a medium (usually air), caused by vibration or turbulence’ (Suter, 1991). It has several important properties such as

- **Level or intensity (loudness) of sound** – it is the sound pressure level, which is measured in decibels (dBA) using a logarithmic scale.

- **Frequency or pitch** – The frequency of a sound, expressed in Hz, represents the number of cycles occurring in 1 sec and determines the pitch perceived by the listener.

The higher the number of sound waves, the higher the frequency and the higher the pitch of the sound. We can hear a wide range of sound frequencies, from 20 to 20,000 Hz with a wide range of intensities.

Classification of Noise

Noise is highly complex with components from a wide range of frequencies and for the purpose of noise measurement a filter, which accepts all audible frequencies, have been incorporated and adjusted to the ear’s sensitivity. The units are expressed in decibels

- **White noise** is defined as sound with equal power per Hz in frequency and its amplitude is constant throughout the audible frequency range. If the frequency spectrum is flat then the noise is called 'white', in which all frequencies are present with the same intensity. White noise is also the 'pure academic noise', whereas all the rest of the forms of noise are considered as pseudo-noise.
• **Pink noise** is filtered to give equal power per octave or equal power per 1/3 octave. Since pink noise has relatively more bass than white noise, it sounds more like the roar of a waterfall than like the higher hissing sound of white noise.

• **Black noise** is, paradoxically, just a specific form of white noise with opposite sign. It is the noise that cancels out white noise, or in a sense 'anti-noise'.

• **Brown Noise (1/f² noise):** This is a special form of noise that particular case the fluctuations occur like in a 'random walk' or in diffusion: The final result is white noise, but for a finite interval of time the numbers have a higher probability to stay close to the previous value than to move far away from it.

• **Shot-noise:** The amplitude of noise often depends on the intensity of the measured signal, because the noise of the background adds up with the noise from the measured property. Shot-noise increases linearly with the square-root of the (signal) intensity.

Hearing loss caused by exposure to non-occupational noise is collectively called sociocusis. It includes recreational and environmental noises (e.g., loud music, guns, power tools, and household appliances) that affect the ear the same as occupational noise. Different noises may also have different effects on physiological threshold and noise-response relationships (Edworthy and Hellier, 2000). The initial response may be annoyance. Annoyance can be defined as “the expression of negative feelings resulting from interference with activities, as well as disruption of one’s peace of mind and the enjoyment of one’s environment” (Suter, 1991). There is likely a considerable variation in people’s tolerance to noise levels and the different types of noise. This makes it difficult to quantify direct health effects. Predictability and controllability are clearly influencing factors in individual reactions to noise (Job, 1996). Noise sensitive people attend more to noises, discriminate between noises, find more noises threatening and out of their control, and react to, and adapt to noises more slowly than less noise sensitive people (Stansfeld, 1992). Various Sound Levels has its own effects on human beings and it has been given in Table 1 (Raju, 2003).
### Table 1
Various Sound Levels has its own effects on human beings

<table>
<thead>
<tr>
<th>Sound Source</th>
<th>Sound Level, dBA</th>
<th>Subjective Feeling</th>
<th>Effects on Human Beings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rockets and missiles, heavy explosives</td>
<td>150-160</td>
<td>Unbearable</td>
<td>Above 150 dBA may cause severe damage to the whole body such as loss of hearing of both ears, dizziness, nausea, disturbance of speech, confusion or psychosis</td>
</tr>
<tr>
<td>Jet planes and cannons, explosives</td>
<td>140</td>
<td>Unbearable</td>
<td></td>
</tr>
<tr>
<td>Aircraft propeller and machine guns</td>
<td>130</td>
<td>Unbearable</td>
<td></td>
</tr>
<tr>
<td>Diesel, steam engine and mills, crackers</td>
<td>120</td>
<td>Unbearable</td>
<td>Above 90 dBA may cause headache, dizziness, tinnitus, insomnia, deafness, heart disease, blood hyper-tension, gastric ulcers, neurosis, temporary hearing threshold shift.</td>
</tr>
<tr>
<td>Electric saws and looms, heavy trucks</td>
<td>110</td>
<td>Unbearable</td>
<td></td>
</tr>
<tr>
<td>Lorries, highway vehicles and very busy streets</td>
<td>90-100</td>
<td>Very noisy</td>
<td>50-90 dBA may cause various degrees of effects in sleeping, studying, working and talking.</td>
</tr>
<tr>
<td>Commercial place, air conditioners, loud voice and busy street</td>
<td>70-80</td>
<td>Noisy</td>
<td></td>
</tr>
<tr>
<td>Office complex, average loudness of voice</td>
<td>60</td>
<td>Noisy</td>
<td>Sense of noisy feeling</td>
</tr>
<tr>
<td>Ordinary room</td>
<td>50</td>
<td>Quiet</td>
<td></td>
</tr>
<tr>
<td>Silent night, library</td>
<td>30-40</td>
<td>Very quiet</td>
<td>Pleasant feeling</td>
</tr>
<tr>
<td>Hospital, bedroom at night, church</td>
<td>20-30</td>
<td>Very quiet</td>
<td>Serene feeling</td>
</tr>
<tr>
<td>Sound proof room, broadcasting studio</td>
<td>10-20</td>
<td>Very quiet</td>
<td></td>
</tr>
</tbody>
</table>
Stress and its consequence

The magnitude and the effects of noise are determined partly by individuals’ characteristics, lifestyle behavior and also mainly depend on the exposure duration. Further, the effects of noise vary depending on the characteristics of noise, such as intensity, frequency (Kjellberg, 1990), exposure time, form, individual age, sex, and health condition. Acute noise exposures activate the autonomic and hormonal systems, leading to temporary changes such as increased blood pressure, increased heart rate and vasoconstriction. When the noise exposure is temporary, the physiological system usually returns after the exposure terminates to the normal (pre-exposure) state within a time range of the exposure duration. If the exposure is of sufficient intensity, unpredictability and susceptible individuals may develop permanent effects, such as hypertension and ischemic heart disease associated with exposures to high sound pressure levels (Passchier-Vermeer and Passchier, 2000).

Physiology of Stress

According to Babisch (2002), noise activates the pituitary-adrenal-cortical axis and the sympathetic-adrenal-medullary axis. The general pattern of endocrine responses to noise is consistent with noise as a stressor stimulating short-term physiological responses (Stansfeld et al., 2000). Most of the cells in the body have adrenergic receptors to respond the stress hormones including epinephrine, norepinephrine apart from cortisol. Increased hippocampal glucocorticoid receptor binding in response to noise was observed in pigs (Kanitz et al., 2004). It has been reported that in real life even moderate environmental noise exposure can increase the acute release of stress hormones (Ising et al., 1990). However, it is relevant to point out that the physiological response and the noise threshold relationships may vary according to an individual psychology and the mind.

Physiological events that counteract stress impact on the body

Researchers reported that the auditory system has the fastest metabolic rate in the brain (Hudspeth and Konishi, 2000). It has also been found that noisy environments can cause psychological, physiological, and behavioral stress in people, as well as affect sleep, work efficiency and performance, and communication abilities (Belojevic et al., 2003). Noise stimulates the brain’s reticular activating system to induce
wakefulness. Neural impulses spread from the reticular system to the higher cortex and throughout the central nervous system (Suter, 1991).

As the effects of noise are complex and diverse, alterations induced by noise stress could be understood better, when they are classified as

I. Noise stress and auditory effects

II. Noise stress and non-auditory effects

I. Noise stress and auditory effects

There are three principle effects occurs during continuous exposure to loud noise:

• Temporary reduction in hearing acuity, which is referred to as temporary threshold shift (TTS)

• Permanent hearing loss referred to as a "Noise Induced Permanent Threshold Shift" or NIPTS

• Ringing in the ears, or tinnitus

Noise affects the mechanical and metabolic effect in the inner ear (Carlson et al., 2005). Exposure to loud sound above 85 dBA sound pressure level causes noise-induced hearing loss by damaging the cochlea, particularly the organ of Corti (Spoendlin, 1971). Pathology of noise-induced hearing impairment (Kawada, 2004) includes the degeneration and loss of the outer hair cells of the hair cells in the organ of Corti in the Cochlea, the degeneration of the intracellular organelles within the hair cells (Vlajkovic et al., 2004). Noise exposure leads to changes in the cells of the organ of Corti, including the alteration in F-actin distribution in the hair cells and supporting cells (Hu and Henderson, 1997). Further, the changes in the presynaptic region of the outer hair cells apposing the afferent nerve endings also reported (Canlon et al., 1993).

The development of deafness has been extensively studied by a number of scientists (Miller, 1974; Moller, 1977; Canlon et al., 1988) and they reported that hearing threshold shift occurs in noise exposed experimental guinea pigs. Threshold shift (hearing loss) may be temporary if the organ of Corti is able to recover or permanent (PTS) (Saunders et al., 1985) when the hair cells or neurons die (Borg et al., 1995). Mild damage in the synapses and/or hair cell stereocilia can be repaired. Intermittent noise is reported to cause TTS and less hair cell damage compared to continuous noise of the same intensity in laboratory animals (Clark and Bohne, 1999;
Fredelius and Wersall, 1992) and humans (Patuzzi, 1998). PTS is due to the hair cell loss, loss of supporting cells, and neuronal apoptosis. The PTS itself is a consequence of degeneration that is secondary to the initial hair cell loss (Bohne and Harding, 2000). Hearing thresholds in the experimental animals returned to pre-exposure levels by 8 weeks after the intense sound exposure.

Usually noise-induced hearing impairment is accompanied by an abnormal loudness perception, which is known as loudness recruitment (Berglund and Lindvall, 1995). With a considerable loss of auditory sensitivity, some sounds may be perceived as distorted (paracusis). Another sensory effect that results from noise exposure is tinnitus. Commonly, tinnitus is referred to as sounds that are emitted by the inner ear itself (physiological tinnitus). Tinnitus is a common and often disturbing accompaniment of occupational hearing impairment (Vernon and Moller, 1995) and has become a risk inducing greater intolerance to external sounds (Hebert et al., 2004). Noise-induced tinnitus may be temporary, lasting up to 24 hours after exposure, or it may have a more permanent character after prolonged noise exposure. The process of hair cell damage and death as a result of exposure to noise is appears to be mediated by reactive oxygen species (Henderson et al., 1999).

II. Noise induced non-auditory effects

The non-auditory health effects attributed to noise exposure may be mediated through a ‘physiological stress response’ and others through ‘psychological response’. Noise stress can induce not only acoustic disorders, but also cardiovascular, nervous, and endocrine alterations (Alario et al., 1987). Measurable sleep disturbance effects have been observed as levels exceed 35 dBA and increase with increasing noise level (Vallet et al., 1998). Acute exposure to occupational noise caused changes in the serum cortisol levels, sleep architecture and heart rate during sleep. The percentage fall in heart rate during sleep was decreased compared to baseline values (Geetanjali and Ananth, 2003). It has also been reported that the total time spent in rapid eye movement sleep (REM), slow wave sleep and REM onset latency were significantly decreased in the night after exposure to noise (Vallet et al., 1983).
Cardiovascular system

The World Health Organization (Whitworth, 2003) has recognized noise as one of the possible exogenous factors for the pathogenesis of essential hypertension. Noise has been recognized as one of the risk factors for cardiovascular diseases because it increases heart rate, peripheral vascular resistances and arterial blood pressure (Talbott et al., 1990; Altura et al., 1992). Saha et al., (1996) also reported a significant increase in heart rate, systolic and diastolic blood pressure. Elevation in systolic and diastolic blood pressure was seen in kindergarten children living in the noisy and very noisy environments (Regecova and Kellerova, 1995; Morrell et al., 2000).

Acute noise stress could increase the diastolic pressure, mean arterial pressure and peripheral resistance, with a reduction in stroke volume and cardiac output (Andren et al., 1980). After prolonged exposure, susceptible individuals may develop permanent effects, such as hypertension and ischemic heart disease (Passchier-Vermeer and Passchier, 2000).

Community exposure to aircraft noise may be a risk factor for hypertension (Rosenlund et al., 2001). A loud noise can induce the disorder of the Long QT Syndrome (LQTS) in which the electrical recovery of their heart takes longer than normal after each heart beat. Soldani et al., (1997) observed that albino rats subjected to white noise showed mitochondrial alterations and changes in atrial and ventricular myocardium, consisting of areas of enlargement in intercalated disc membrane and depressed density in sarcoplasm. Further Gesi et al., (1999) also observed mitochondrial damage in the rat myocardium after noise exposure.

Gastrointestinal system

Both acute and chronic exposure to noise increased food intake in rats (Armario et al., 1983). However, according to Bauman et al., (1997) the exposure to sub-lethal blast overpressure reduced the food consumption and exercise performance, with the consequence of damage to the gastrointestinal tract. Bijlsma et al., (2001) concluded that mild sub-chronic noise stress for 8 days could cause a decrease in intestinal barrier function by increasing the transcytosis of luminal antigens. According to Suter (1991), noise can influence glandular, cardiovascular, and gastrointestinal changes via the autonomic nervous system.
Immune system

The immune system is particularly sensitive to stress and specific effects of stress have been demonstrated by a number of studies (Ayala et al., 1996; Benschop et al., 1996; Wu et al., 2000). Acute stress generally has positive effects, while chronic stress typically provokes immunosuppression (McEwen, 2000; Mastorakos and Ilias 2000). According to Archana and Namasivayam (2000), acute noise exposure causes significant increase in the thymus cell count and weight. Noise levels above 120 dBA increase cortisol in humans (Ising et al., 1990). Stressful situations stimulate hypothalamo-pituitary-adrenal (HPA) axis to secrete cortisol, which may be one of the factor responsible for the alteration observed in the immune system during long exposures. Although the short-term effects of glucocorticoids are essential, the long-term effects lead to immunosuppression, along with the insulin resistance, catabolism and intestinal problems (Spreng, 2000). In addition, excess cortisol inhibits inflammatory responses and the activity of macrophages, which are normally released into the bloodstream by the thymus gland to kill invading bacteria (Sapolsky, 2000). Nocturnal noise also has been indicated as a health risk because of the disturbance to the distribution of sleep stages resulting in direct immunosuppressive effects (specifically inhibition of eosinophils and basophils which usually proliferate during sleep) (Thompson and Gales, 1996). Srikumar et al., (2006) observed a significant decrease in the neutrophil functions in the noise-stressed rats before as well as after an antigen challenge.

Alteration in the brain enzymes

Rats exposed to various noise intensities showed an increase in serum dopamine beta hydroxylase activity compared to controls (Okada et al., 1985). According to Singh et al., (1994), acute sound stress in rats induced an increase in tryptophan hydroxylase activity in midbrain and cortex. Boadle Biber et al., (1993) showed that the corticotrophin-releasing factor within the amygdale mediates the activation of tryptophan hydroxylase after sound stress. According to Das et al., (2000) acute immobilization stress enhanced the cognitive function in mice which may be attributed to a decrease in AChE activity that results in an increase in cholinergic activity in the brain. Acute, chronic-predictable and chronic-unpredictable stress caused significant decrease in AChE activity in the detergent soluble fraction of cortex, hippocampus and
hypothalamus. However, cognition was affected only after chronic-unpredictable stress (Das et al., 2005).

**Psychological and behavior disturbances**

Repeated exposure to noise over a longer time periods may be experienced as an uncomfortable disturbance or interference with the ongoing activities. This effect is traditionally referred to as annoyance (Rylander, 2004). Exposure to high levels of occupational environmental noise has been associated with development of neurosis, irritability and deteriorated mental health (Stansfeld et al., 2000). After acute noise exposure, the rats showed an increase in the open field behaviour, shortened motor latencies with a decrease in defecation score (Katz and Manik, 1984), whereas Armario et al., (1983) after chronic noise exposure observed a reduction in exploratory activity without any changes in defecation rate. Windle et al., (1997) noticed an increase in exploratory behavior (rearing) and displacement behavior (grooming) after noise exposure. Lai, (1987) reported that acute noise stress produced an activating behavior, while chronic noise stress exposure resulted in a state of depression. Exposure to inescapable foot shock induced a marked immobility with a further decrease in locomotion and rearing when compared to control rats (Van Dijken et al., 1992). Hence, it appears that the behavioral alteration may depend on the nature of stressor.

**Noise stress on psychology**

Gonlachanvit et al., (2005) reported that acute acoustic stimulation increased anxiety scores. Edsell, (1976) reported that environmental noise (intermittent white noise) and social interaction leads to a significantly stronger feelings of anxiety than those in quieter conditions. Terasaki, (1981) found that low anxiety subjects showed an increased error response than the higher anxiety subjects. Ponnusamy et al., (2005) reported that conditional stimulus with white noise along with moderate foot shock induces anxiety in rats. Anticipation of white-noises increases self-reported anxiety (Grillon and Ameli, 1998) and potentiates the startle response (Patrick and Berthot, 1995; Skolnick and Davidson, 2000).

Stansfeld et al., (1996) found an association between traffic noise and increased anxiety levels. Environmental noise impairs a number of cognitive and motivational parameters in children (Hygge et al., 2002). The central processing and language
comprehension, such as reading, attention, problem solving and memory, appear to be most affected after exposure to noise (Evans and Lepore, 1993; Hygge, 1994; Evans et al., 1995). Matheson et al., (2003) showed that chronic aircraft noise exposure could impair the children's cognition in terms of rearing, working and long-term memory. Stress-induced deficits in delayed-response performance were ameliorated by pretreatment with drugs that block dopamine receptors indicating that stress impairs cognitive function of the pre frontal cortex through a hyper dopaminergic mechanism (Arnsten and Glodman-Rkiec, 1998).

Increased hippocampal glucocorticoid receptor binding in response to noise was observed in pigs (Kanitz et al., 2004). Too much cortisol can prevent the brain from laying down a new memory, or from accessing already existing memories. Studies have strongly associated the prolonged exposure to cortisol (the major stress hormone) to shrinkage in the hippocampus, the center of memory.

Free radicals and noise

The term ‘Free radicals’ was defined as, “It is an atom or group of atoms possessing one or more unpaired electrons” (Leigh, 1990). Any molecule can become a free radical by either losing or gaining an electron. Molecules containing these uncoupled electrons are very reactive. The singlet oxygen is not a free radical but is nevertheless a molecular reactive oxygen species (ROS) and capable of causing tissue damage (Levine et al., 1985). It is essentially formed during the metabolic processes.

Once free radicals are formed, they tend to propagate by becoming involved in chain reactions with other less reactive species. These compounds generally have longer half-lives and therefore extend the potential for cellular damage. Free radicals are terminated or neutralized, by nutrient antioxidants, enzymatic mechanism, or by recombining with each other.

Free radicals can be either endogenous or exogenous sources. Endogenous sources of free radicals include those that are generated intracellularly, acting within the cell, but are released into the surrounding area. Exogenous sources of free radicals introduced in to the body due to irradiation, chemicals, air pollutants and some medications.
Free radicals play an important role, both in health and disease. Emotional stress can lead to increased production of free radicals (Kendler, 1995). Overpressure induced by blast lead to oxidative stress with the free radical reactions (Elsayed et al., 1997). Oxygen (O₂) is an essential gas for most life forms. O₂ is also used as substrate by numerous other enzymes. Many of these enzymatic reactions generate reactive oxygen species (ROS) as their products, including superoxide (O₂⁻) and hydrogen peroxide (H₂O₂). However, formation of reactive oxygen species is associated with the development of many animal and plant pathological conditions as well as natural aging (Beckman and Ames, 1998; Halliwell and Gutteridge, 1999). A free radical or ROS is a compound with one or more unpaired electron in its outer orbital (Jesberger and Richardson, 1991). Researchers have confirmed the role of oxidative stress in the potentiation of noise induced hearing loss (Fechter, 2005). Antioxidants can be broadly defined as any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly prevents or delays any oxidation of that substrate (Haliwell and Gutteridge, 1999; Halliwell, 1995).

A series of antioxidant compounds are present in the cells, they react with oxidizing agents and disarm them (Fridovich, 1995). The rate and selectivity of reactions involving free radicals depend on the concentrations of the species, delocalization of the single electron of the radical (thus increasing its life time), and on the absence of weak bonds in any other molecules present with which the radical could interact. Most biological molecules however, are non-radicals containing only paired electrons. The generation of free radicals in vivo is a constant phenomenon due either to physiological metabolism or pathological alterations. Oxygen plays a double role in the cell: it is essential for aerobic organisms, but it can also act as a free radical since it contains two relatively stable unpaired electrons. (Gatte et al., 1999). Free radicals of importance in living organisms include hydroxyl (OH⁻), superoxide (O₂⁻⁻), nitric oxide (NO⁻), and peroxyl (RO₂⁻). Peroxynitrite (ONOO⁻), hypochlorous acid (HOCl), hydrogen peroxide (H₂O₂), singlet oxygen (¹Δg) (often written as ¹O₂) and ozone (O₃) are not free radicals but can easily lead to free radical reactions in living organisms. (Aruoma, 1998; Halliwell and Gutteridge, 1999). Normally, when ROS are generated in living systems, a wide variety of antioxidants namely the superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), reduced glutathione (GSH), α-
tocopherols, ascorbic acid, flavonoids, uric acid, and numerous others try to counter act. The actions of these scavenging systems are given as Figure 1

Mates et al., (1999) suggest that the three primary endogenous scavenging enzymes involved in detoxifying the free radicals are SOD, CAT and GPx. The high metabolic rate of brain cells implies a high baseline ROS production. SOD may represent as much as 1% of total protein in brain; it converts highly reactive superoxide anion to H$_2$O$_2$ (Teixeira et al., 1998). Coling et al., (2003) reported that superoxide dismutases (SOD) form a first line of defense against damage mediated by the superoxide anion. Absence of Cu/Zn SOD has been shown to potentiate hearing loss related to broadband noise exposure. Catalase and glutathione peroxidase provide two important cellular systems for eliminating H$_2$O$_2$. CAT efficiently reacts with H$_2$O$_2$ to form water and molecular oxygen (Mates et al., 1999). Catalase is more abundant in astrocytes than in neurons and in white matter than in gray matter, but it can be induced in neurons by neurotrophins. There is substantially less catalase activity in brain than in other tissues, such as liver (Sigalov and Stern, 1998).

Ascorbic acid, effectively intercept oxidants in the aqueous phase before they attack and cause detectable oxidative damage (Beyer, 1994). The intracellular small molecular antioxidants GSH, vitamins C and E are interrelated with each other and they can be recycled (Arivazhagan et al., 2000). Humans, in contrast to most other animals, are unable to synthesize vitamin C and hence this important antioxidant must be derived entirely from dietary intake. Glucose-6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme in the GSH- and NADPH-dependent H$_2$O$_2$ elimination. Hashida et al., (2002) suggested the importance of G6PD in the antioxidant function of brain and pathogenesis of the oxidative stress-related diseases. However, oxidants and antioxidants must be kept in balance to minimize molecular, cellular and tissue damage (Packer et al., 1997). The alteration in these systems indicates that body is subjected to an oxidative stress.

Any stress response results in creation of ROS, e.g. H$_2$O$_2$, HO• and O$_2$–– that cause lipid peroxidation, especially in membranes and can play an important role in tissue injury (Kovacs et al., 1996). Oxidative stress leading to inactivation in various tissues, particularly in brain neurons has been reported (Lehotsky et al., 1999). Thus,
Figure 1

Free radical scavenging system

Redox cycling

(2)O₂⁻

(2H⁺)

superoxide dismutase

H₂O₂

Mⁿ⁺ Mⁿ⁺⁺⁺

·OH + OH⁻

catalase

H₂O + ½ O₂

NADP⁺

2GSH

glutathione reductase

NADPH + H⁺

GSSG

GSSG translocase

Excretion

Prot SH

Prot S-SG+GSH
the LPO level indicates not only oxidative stress but also membrane injury and alteration in the cellular functions. The membrane injury causes disruption of the tissue integrity (Bagchi et al., 1999).

Different tissues in the cochlea respond differently to the damaging effect of reactive oxygen species due to their dependence on endogenous antioxidant levels (Ohinata et al., 2000). An increase in gene expression of GSH and CAT synthesis after a noise stress exposure (Jacono et al., 1998) with an increase in the cochlear glutathione synthesis (Yamasoba et al., 1998) in animals. Deficiency of glutathione has been linked to increased susceptibility to noise-induced damage while replenishing tissue glutathione stores reduces its susceptibility (Yamasoba et al., 1998; Henderson et al., 1999). An elevated oxyradical generation, possibly related to altered sympathetic innervation, and hypothesized to be responsible for the induction and persistence of noise-induced cellular damage (Lenzi et al., 2003).

Brain cells are the most vulnerable to free radical damage because they are relatively deficient in the protective mechanisms compared with other organ systems (Olanow, 1990; Skaper et al., 1999; Contestabile, 2001). The high metabolic rate of the brain, the low concentration of glutathione and the high proportion of polyunsaturated fatty acids, makes the brain a tissue particularly susceptible to oxidative damage (Smith et al., 1996, 1998).

Glia and neurons, isolated from rat cerebral cortex, showed a similar pattern of the most important antioxidant enzymes and of their basal ROS production. However, glia is more resistant to "oxidative stress" (Cafe et al., 1995). Auditory stimulation in rats reportedly causes a wide pattern of brain activation as indicated by induction of c-fos mRNA (Quirk et al., 1997).

**Stress and diseases**

Exposure to hostile conditions (usually referred to as stressors) results in a series of coordinated responses organized to enhance the probability of survival. Stressors can be defined as conditions that endanger, or are perceived to endanger, the survival of an individual (Van de Kar and Blair, 1999). These coordinated responses, often referred to as "stress responses," are composed of alterations in behavior,
autonomic function and the secretion of multiple hormones including ACTH and cortisol/CORT, adrenal catecholamines, oxytocin, prolactin and renin (Van de Kar and Blair, 1999). Free radical reactions have been implicated in the pathology of many human diseases including atherosclerosis, ischemic heart disease, ageing process, inflammation, diabetes, immunodepression, neurodegenerative condition and other disease conditions (Maxwell, 1995). Sterling and Eyer, (1988) suggested that neuroendocrine systems, autonomic nervous system and immune system are mediators of adaptation to challenges in daily life, referred to as ‘allostasis’ (which means maintaining stability through change). Further, they added that when an individual is challenged repeatedly then the allostatic systems induced mediators could produce the ‘wear and tear’ effects on the body and brain. As their action on target cells are prolonged and that effect has been termed ‘allostatic load’.

**Stress and heat shock proteins**

In very simple terms, Hsps act as molecular chaperones and are important in processing of newly synthesized proteins or preventing the aggregation of denatured proteins by adenosine triphosphate (ATP)-dependent mechanisms (Bechtold et al., 2000). Their increase in response to a variety of stresses and pathophysiologic stimuli confers cytoprotective properties on the cell, such as against injury by free radicals or oxidative stress and other forms of neuronal injury (Gotohda et al., 2000; Kawamura et al., 2000). Hsp70 gene encodes a major stress-inducible heat shock protein (Hsp70), which plays an important role in protecting cells from deleterious stresses. The well-characterized program of gene expression, leading to the synthesis of Hsp which exerts the cytoprotective functions (Sorger, 1991). In particular, induction of Hsp70 has been linked directly to the accumulation of improperly folded or denatured proteins in cells and may be involved in the repair of damaged proteins (Ananthan et al., 1986). It has been reported that oxidative stress leads to a massive induction of heat shock proteins, which is partly mediated by the oxidatively damaged proteins (McDuffee et al., 1997). Hsp70 is produced in vulnerable brain cells in response to a number of different manipulations that induce cellular injury paradigms (Massa et al., 1996; Sharp and Sagar, 1994). These damaged proteins occupy chaperone-binding sites, and liberate the heat shock factor1 (HSF1) and this transcription factor is responsible for Hsp induction (Morimoto, 1999). Several reports suggest that inducible Hsp70 has a protective
function in the CNS (Lowenstein et al., 1991; Rordorf et al., 1991). The heat shock gene Hsp70 mRNA and HSP70 protein are induced by many types of injury to the brain, including focal and global ischemia (Gonzalez et al., 1991).

The noise exposure that induces Hsp70 also increases the level of glial cell line-derived neurotrophic factor in the cochlea (Altschuler et al., 2002). An increase in constitutive Hsp73 was observed in animals exposed to the 108-dBA noise when compared to the ambient-noise controls (Helfert et al., 2002).

**Stress and c-fos**

The expression of c-fos is induced by acute and repeated restraint stress, anxiety, conditioned and unconditioned stressors (Smith et al., 1992; Melia et al., 1994; Duncan et al., 1996) and after some forms of learning (McCabe and Horn, 1994; Radulovic et al., 1998; Wan et al., 1999; Vann et al., 2000). Accordingly, Fos expression is considered a mechanism by which brief stimuli can trigger long-term changes in gene expression and alter the structural and functional properties of nerve cells (Goelet et al., 1986; Morgan and Curran, 1991). Immunohistochemical labeling of c-Fos is a useful marker of neuronal activation, as neuronal depolarization initiates c-Fos expression (Sheng and Greenberg, 1990). Particular stressors increase brain c-Fos in a regionally specific manner.

Many factors are known to induce the c-fos gene, including calcium and growth factors, which may modulate the response of brain cells to injury. We have also shown a correlation between oxygen free radical production and hsp70 or c-fos mRNA expression following focal ischemia (Kamii et al., 1994a; Kamii et al., 1994b). Besides being markers of stress to the liver, c-fos and c-jun expression have been suggested to be associated with liver function after ischemia/reperfusion. Several studies have demonstrated that c-fos and c-jun are involved in tissue repair (Schiaffonati et al., 1990) and/or apoptosis (Smeyne et al., 1993; Gajate et al., 1998). An association between c-fos and c-jun expression and the severity of ischemia/reperfusion related insults as well as subsequent graft failure has been shown in rat liver transplantation (Goto et al., 1994).
Preventive measures

Prevention is always better than cure. Prevention means to avoid creating hearing loss. Conservation means to sustain the hearing that is present, regardless of whether damage has already occurred.

Many different ways are adapted to prevent hearing loss. Wearing ear plugs or using other protective devices is one very common way to prevent NIHL. When ear plugs or other hearing protection devices are worn correctly (available in the market), they can have a positive effect (Nash, 2000). With medical advancements, new treatments are being studied and may end up replacing earplugs and other protective devices. An oral steroid drug was tested for hearing loss prevention but was abandoned due to its numerous side effects (Borlik, 1998).


A combination first three options given below represents much of international ‘best practice’ in the management of noise.

- Elimination or reduction of noise at the source
- Elimination or disruption of the transmission path
- Isolation or insulation of the receiver from the noise

Compensatory treatment to eliminate its effects (Carroll, 2004).

As many people are exposed to hazardous noise levels at work are inevitable for some professionals. In such situations treating with compensatory measures is the only possible solution. With the surge in industrialization bound to grow further and noise abatement proving prohibitively expensive to minimize the impact of noise stress. In the recent past natural remedies and herbal preparations are gaining attentions from
The antistressors have a major role in limiting the noise induced stress effects.

The study by Kashif et al., (2003) has suggested the vitamine E can be used as a nutritinal supplimen to reduce oxidative stress. Many herbal antioxidants are also protmoted as nutritional supplements to prevent oxidative stress. One of them is Panax ginseng, which has been reported in literature to improve physical and mental health, increase nonspecific resistance of body, promote physiological funtions and augment cognition (Rege et al., 1999). Ocimum sanctum is another example with antistressor antioxidant, radioprotective and immunomodulatory actions (Archana and Namasivayam, 2000).

Thus the focus on plant research has increased globally and the large body of evidence collected shows the immense potential of medicinal plants. Perusal of literature recommend Acorus calamus Linn.(AC) could be ideal remedy for noise stress, as it is help manage a wide range of symptoms in the head, including neuralgia, epilepsy, memory loss and shock, rejuvenative for the brain, promote cerebral circulation, stimulating nervine antispasmodic (Nadkerani, 1976; Nishiyama et al., 1994a,b; Zhang et al., 1994). Based on these reports AC is selected for this study. Traditionally AC was used to treat the children for relieving abdominal flatulents in the Indian system of Medicine such as Ayurveda, Siddha and Unani.

**Taxonomy & Morphology of Acorus calamus L.**

The detail of the drug used is summarized below.

<table>
<thead>
<tr>
<th>Kingdom</th>
<th>Plantae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subkingdom</td>
<td>Tracheobionta</td>
</tr>
<tr>
<td>Superdivision</td>
<td>Spermatophyta</td>
</tr>
<tr>
<td>Division</td>
<td>Magnoliophyta</td>
</tr>
<tr>
<td>Class</td>
<td>Liliopsida</td>
</tr>
<tr>
<td>Subclass</td>
<td>Arecidae</td>
</tr>
<tr>
<td>Order</td>
<td>Arales</td>
</tr>
<tr>
<td>Family</td>
<td>Acoraceae</td>
</tr>
<tr>
<td>Genus</td>
<td><strong>Acorus L</strong></td>
</tr>
<tr>
<td>Species</td>
<td><strong>calamus L</strong></td>
</tr>
</tbody>
</table>
*Acorus calamus* Linn

**Other names:** Calamus root, sweet flag, rat root, sweet sedge, flag root, sweet calomel, sweet myrtle, sweet cane, sweet rush, beewort, muskrat root, pine root, racha, vacha, vasambu (India), cinnamon sedge, myrtle flag, myrtle grass, myrtle sedge, beewort. shih-ch'ang pu (China).

**Related species:** *Acorus gramineus, Acorus americanus*

**Plant description:** It is shown in Figure 2

Sweet flag is a grass-like, rhizome forming, perennial that can grow to 2 meters high, resembling an iris. This species inhabits perpetually wet areas like the edges of streams, areas around ponds and lakes, ditches and seeps. The pointed sheathing leaves are from 2 to 6 feet in height and about 1 inch in width. The small greenish-yellow flowers, which appear from May to July, are borne in a fleshy spike about 3 inches long. The long creeping rootstocks are thick and fleshy, somewhat spongy, and have numerous rootless. They have an agreeable aromatic odor and a pungent, bitter taste, which are retained after drying.

**Plant part used:** Dried rhizome of AC

**Composition**

From the volatile oil of AC, Baxter et al., (1960) isolated three active substances namely Asarone, trans and cis forms of α-Asarone in Figure 3 and β-Asarone, of 2,4,5-trimethoxy-1-propenyl benzene. Dandiya et al., (1959a) reported that AC oil is containing phenol, aldehyde and alcohol contents.

AC contains glucoside Acorin (C36H60O6) crystalline alkaloid, calamine, trimethyl amine and choline to exist in calamus root (Felter and Lloyd, 1898) Ninety one constituents were positively or tentatively identified in the oils- 55 in the rhizomes. Possible formation of calacorene hydrates is suggested for the first time on the basis of mass spectral data. β-Asarone [(Z)-asarone] was the major constituent in the leaves (27.4-45.5%), whereas acorenone was dominant in the rhizomes (20.86%) followed by isocalamendiol (12.75%). A higher content of some aliphatic and oxygenated monoterpenes was found in oils of the leaves at their earliest growth phase (May), while the β-asarone content was at its lowest level. (Venskutonis and Dagilyte, 2003)
Acorus calamus Linn

Rhizome of AC

Figure 3

α-Asarone

\[
\begin{align*}
\text{CH}_3 \\
\text{H}_3\text{C} - \text{O} \\
\text{C} - \text{H} \\
\text{H} - \text{C} \\
\text{CH}_3
\end{align*}
\]

2,4,5-trimethoxy-1-propenyl benzene
Ancient history

Use of AC is a traditional practice in India from ancient days and it was even administered to the newborn in very small amount after charring the rhizome. British Pharmaceutical Codex refers calamus has the action of an aromatic bitter. On account of the volatile oil, it also acts as a carminative, removing the discomfort caused by flatulence and checking the growth of the bacteria which give rise to it. Further, it is used to increase the appetite and benefit digestion. Eclectic Materia Medica (Felter, 1898) refers AC as carminative, sialagogue, excitant, and slightly tonic. It is used as 'breathe perfume,' and in flatulent colic, atonic dyspepsia, feebleness of the digestive organs; and in the form of syrup as an agreeable vehicle for less pleasant medicines. The root was also used by the ancient Greeks and included in the traditional remedies of many European cultures. During the middle ages, calamus was an admixture in several of the ancient, psychoactive, “witches flying ointments”, often being mixed with solanacious herbs. Other native tribes used it to treat a cough, made a decoction as a carminative.

LD 50 dose for AC

It appears that the LD 50 dose vary according to the component of AC taken for the study and the place. Normally the environment, soil as well as the root of administration and various reports available are given in the Table 2 form.

Action of rhizome of AC

In an earlier preliminary report, it was shown that rhizome of AC possesses sedative, analgesics, moderately hypotensive and respiratory depressant properties (Agarwal et al., 1956). Rhizome of AC in different doses (10,20mg/kg i.p.) exhibited negative ionotropic and chronotropic effects in frogs.

Action of volatile oil of AC

AC oil, containing phenol, aldehyde and alcohol, when given to animals induced sedation. The elimination of phenolic and aldehydic fraction from the AC oil resulted in an increase in the toxicity (LD_{50} 177mg/kg) of the oil as well as the sedative potentiation (Dandiya et al., 1959b). Acorus oil injected half an hour before the barbiturate significantly prolonged the sleeping time. However, it did not reduce the
<table>
<thead>
<tr>
<th>Animal</th>
<th>Route (mg/kg bw)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acorus oil</td>
<td>i.p. 221 ± 1.8</td>
<td>Dandiya and Cullumbine, 1959</td>
</tr>
<tr>
<td>Guinea-pig</td>
<td>i.p. 2.75</td>
<td>Chopra et al. 1957</td>
</tr>
<tr>
<td>Calamus oil</td>
<td>Oral 8 880</td>
<td>Opdyke, 1977</td>
</tr>
<tr>
<td>(Jammu)</td>
<td>Oral 777</td>
<td>Jenner, 1964</td>
</tr>
<tr>
<td>(Kashmir)</td>
<td>Oral 4331</td>
<td>Taylor, 1981</td>
</tr>
<tr>
<td>(European)</td>
<td>Oral 3497</td>
<td>Taylor, 1981</td>
</tr>
<tr>
<td>Calamus oil</td>
<td>i.p. 154.5 ± 1.1</td>
<td>Yabiku, 1980</td>
</tr>
<tr>
<td>(European)</td>
<td>i.p. 1 139</td>
<td>Yabiku, 1980</td>
</tr>
<tr>
<td>(European free of and β-asarone)</td>
<td>i.p.1709</td>
<td>Yabiku, 1980</td>
</tr>
<tr>
<td>α-Asarone</td>
<td>i.p. 225 ± 1.1</td>
<td>Yabiku, 1980</td>
</tr>
<tr>
<td>β-Asarone</td>
<td>i.p.184.2 ± 1.0</td>
<td>Yabiku, 1980</td>
</tr>
<tr>
<td>β-Asarone</td>
<td>Oral 1010</td>
<td>Taylor, 1981</td>
</tr>
</tbody>
</table>
mice and hence the sedative potentiation activity of this oil may
hypothermic action (Dandiya et al., 1959b).

Acorn oil was found to have a general depressant effect in mice, rat, dogs, cats
and monkeys (Dhalla and Bhattacharya, 1968) and none of the animals passed to
hypnotic stage indicating its action as a tranquilizer-sedative type. The high dose of AC
oil inhibited monoamine oxidase and stimulated both D and L-amino acid oxidases.

The essential oil of AC has been found to have relaxant and spasmyolytic actions
on various smooth muscles in different species of animals. This action mimics the
action of acetylcholine and hence the crude drug was used to treat asthma, colic and
diarrhea in Indian system of Medicine (Das et al., 1962). This is supported by the report
of Shoba and Thomas, (2001) which showed that aqueous and methanolic extracts of
AC rhizome had an antidiarrhoeal action against castor oil induced diarrhoea in mice.

Vohora et al., (1990) observed that AC extract exhibited a large number of
actions similar to α-Asarone but differed from the latter in several other respects like
responses to electroshock, apomorphine and isolation induced aggressive behavior,
amphetamine toxicity in aggregated mice, and behavioral despair syndrome in forced
swimming. These differences may be due to chemical substances present in the extract
other than α-Asarone. It has reported that Asarone treatment did not altered brain 5HT
or noradrenaline. However, it antagonizes the central excitatory effect of mice treated
with iproniazid before the administration of reserpine (Menon and Dandiya, 1967).

Hypocholesterolemic action of α-Asarone

Labarrios et al., (1999) reported that α-Asarone analogues related to Clofibrate
have been administrated to mice for 6 days act as hypocholesterolaemic agent. α-
Asarone administrated for 8 days decreased serum cholesterol in hypercholesterolemic
rats. α-Asarone has been reported to have inhibitory action over hepatic HMG-CoA
reductase and their by it excerts its hypocholesterolemic and cholelitholytic action.
Interestingly, α-Asarone affects serum LDL-cholesterol levels, leaving serum HDL-
cholesterol lipoproteins unaffected, with a consequent decrease of LDL/HDL ratio and
stimulated bile flow in hypercholesterolemic rats, increasing the secretion of bile salts,
phospholipids, bile cholesterol. It also decreases the cholesterol saturation index of bile
in the hypercholesterolemic rats (Rodriguez-Paez et al., 2003). Administration of AC (100 and 200 mg/kg) as well as saponins (10 mg/kg) isolated from the extract exerted a significant hypolipidemic activity (Parab and Mengi, 2002). This indicates that the crude extract contains more active principle than α-Asarone.

**Antibacterial action of AC**

The extracts of AC have been found to possess an antibacterial activity (Grosvenor et al., 1995; McGaw et al., 2002; Rani et al., 2003), although a lack of antibacterial activity has also been reported (De et al., 1999). β-asarone in AC rhizomes was demonstrated to have antibacterial activity (MacGaw et al., 2002). However, β-asarone concentrations vary markedly among the oil from AC variety. Phongpaichit et al., (2005) reported that extracts of AC have been found to possess an antibacterial and antifungal activity.

**Immunomodulatory action of AC**

Mehrotra et al., (2003) demonstrated that the ethanolic extract of AC has the antiproliferative effect on human peripheral blood mononuclear cells *in-vitro* after the mitogen (phytohaemagglutinin) stimulation. Further, it also inhibited the production of nitric oxide, interleukin-2, and tumor necrosis factor-alpha with the down regulation of CD25 expression. However, interferon-gamma and expression of cell surface markers CD16, on human peripheral blood mononuclear cells were not affected after the treatment with AC extract. Bains et al., (2005) reported that acorus lectins present in the AC significantly inhibited the growth of J774, a murine macrophage cancer cell-line and to lesser extent WEHI-279, a B-cell lymphoma.

**Action of AC on brain**

In rats, electrographic recording revealed that after AC treatment ‘α’ activity increased with an increase in norepinephrine level in the cerebral cortex but decreased in the midbrain and cerebellum after AC treatment. Serotonin level was increased in the cerebral cortex but decreased in the midbrain. Similarly, dopamine level was increased in the caudate nucleus and midbrain but decreased in the cerebellum (Hazra and Guha, 2002). Hazra et al., (2005) reported a significant decrease in epilepto genesis after chronic treatment with AC. Preconditioning the kindled animals with AC for 14 days markedly reduced the development of amygdaloid seizure, intensity of fit and duration
of after-discharge together with an increase in the norepinephrine, serotonin and decrease in dopamine content in discrete brain regions. These findings indicate that AC possibly modifies the brain functions by modulating the brain neurotransmitter levels.

Shukla et al., (2002) found that extract of the rhizomes of AC prevents neurobehavioral changes and hind limb paralysis when rats exposed to acrylamide. Cho et al., (2002) evaluated neuroprotective action and mechanisms of Asarone, α-and β-Asarone. The Asarone inhibits the excitotoxicity induced by the 300 μM NMDA exposure of cortical cultures. Furthermore, α-and β-Asarone exhibited more potent inhibitions of the NMDA-induced excitotoxicity than the isolated Asarone.


**Antioxidant activity of AC**

AC is a one of the ingredient of Chinese medicine (DX-9386) and chronic oral treatment reduced the elevated levels of lipid peroxidation in the serum and liver (Nishiyama et al., 1994a,b). The ethanolic extract of AC showed high antioxidant activity with the 1, 1-diphenyl-2-picrylhydrazyl free radical assay (Acuna et al., 2002). Rhizome of AC, when tested for antioxidant activity in-vitro, was found to be effective at the 0.2 g/ml concentration (Govindarajan et al., 2003).

Based on this available literature the current study was focused on the efficacy of AC as an antistressor.