Chapter-2

Review of Literature
Recent evidences in more than 300 empirical articles described a relationship between psychological stress and immune system. Acute stressors were associated with potentially adaptive upregulation of some parameters of natural immunity and downregulation of some functions of specific immunity. Brief naturalistic stressors (such as examinations) tend to suppress cellular immunity while preserving humoral immunity. Chronic stressors were associated with suppression of both cellular and humoral measures. Effects of event sequences varied according to the kind of event (trauma vs. loss). Subjective reports of stress generally did not associate with immune change.

In some cases, physical vulnerability as a function of age or disease also increase vulnerability to immune change during stressors.(66)Recent survey on human reproduction shows that infertility affects 15–20% of couples in industrialized countries(67) compared to 7–8% during early 1960s. The concern over decreased sperm count and male reproductive capacity was triggered by a report (68)on the meta-analysis of 61 sperm count studies which showed a nearly 50% decrease in sperm counts between 1940 and 1990 world-wide and this decrease amounts to about two percent per year over the last two decades. (69)

Numerous studies demonstrate the interaction of environmental toxicants with steroid receptors and thereby causing interference with developmental and functional aspects of testis, epididymis and accessory sex organs. Induction of reactive oxygen species (ROS) by environmental contaminants and associated oxidative stress also have role in defective sperm function and male infertility.(70)

Apart from this the stress affects the physical structure of the epithelium which has been evolved to protect it from the damaging hydrogen ions. The
Management of Stress induced Ulceration, Depression and Sexual deficiency through M. pruriens and H. pruriens

mucosa has acquired a remarkable capacity to repair itself quickly. Ulcers arise when a number of external factors impact on these finely balanced protective mechanisms, resulting in acid-induced damage to the gastric mucosa. In other words, peptic ulcer is a multifactorial disease. While this basic concept has not altered over the past 20 years, and the dictum `No acid - No ulcer' still stands, what has changed is the discovery of new contributory external factors and the different opinions on the relative contribution of these effects on the gastric mucosa. In recent times, the impact of stress dominates the ulcer hypotheses, being supported by animal models.(71)

Chronic stress in animals results in elevated adrenocorticotropic hormone (ACTH) and glucocorticoid levels in plasma and elevated production of corticotropin releasing hormone (CRH). In addition, tyrosine hydroxylase (TH) gene expression in the locus coeruleus is elevated suggesting that stress activates the norepinephrine-containing neurons that play an important role in behavioral arousal. (72)

Recently, other work has extended these findings in animals to include observations of neurochemical changes in brain structures known to influence the HPA axis. These include GABA in the bed nucleus of the stria terminalis (BST), assessed by measuring the glutamic acid decarboxylase (GAD) mRNA levels, and several neurochemical markers in the hippocampus. An important link between depression and stress is established by the facts that the HPA axis and particular sets of 5-HT, norepinephrine, and GABA containing neuronal systems are involved both in the pathophysiology of depression and the neurobiology of stress.(73, 74)
Herbal treatment of stress induced sexual deficiency, ulceration and depression:

*M. pruriens*: The problem of infertility is closely related to stress, as a couple, failing to achieve the expected goal of reproduction, experiences the feelings of frustration and disappointment. These feelings only compound in couples experiencing infertility related problems requiring prolonged efforts to conceive. Previous studies have indicated that stress, especially psychological stress, has a negative impact on various parameters associated with semen quality, sperm concentration, motility and morphology. (75)

The recent study on human patients indicated the role of *M. pruriens* in preventing infertility in men under psychological stress. This study included 60 subjects who were undergoing infertility screening and were found to be suffering from psychological stress. Semen samples were collected from each patient twice and biochemically investigated before and after the treatment of *M. pruriens* extract initially and then after 3 months of treatment. The results demonstrated decreased sperm count and motility in subjects under psychological stress. Treatment with *M. pruriens* significantly ameliorated psychological stress and seminal plasma lipid peroxide levels along with improved sperm count and motility. Treatment also restored the levels of SOD, catalase, GSH and ascorbic acid in seminal plasma of infertile men. (76)

It has been observed that dopaminergic agents ameliorate the experimentally induced gastroduodenal mucosal injury, but no information is available about their effect on small intestinal mucosa. In addition, the effect of L-DOPA which is the key phytoconstituent of *M. pruriens* was observed on indomethacin-induced intestinal ulceration in rats. Ulceration was produced by s.c. injection of 30 mg/kg indomethacin, and the effect of L-DOPA administered 30 mins prior to the administration of indomethacin, was found to protect the small bowel mucosa against indomethacin-induced damage. The protective
effect is probably mediated through the stimulation of alpha-2-adrenoreceptors. (77)

Depression is one of the most common mental health problems experienced by people with Parkinson's disease. Although, effective medications are available to treat depression and the best medication depends upon an individual's situation, a class of medications most commonly used for depression are called as SSRIs (selective serotonin reuptake inhibitors). In contrast, the less often used antidepressants are tricyclic antidepressants such as nortriptyline are also effective. But, there was no such evidence to indicate that l-DOPA significantly increased or decreased the amount of depression in the patients. (78)

Based on the previous data, it can be concluded that M. pruriens not only reactivates the anti-oxidant defense system of infertile men but also helps in regulating gastric ulceration, stress and improves semen quality.

Hypericum perforatum: The most common male sexual dysfunction is premature ejaculation (PE) for which yet there are no approved effective therapy. An extract of H. perforatum, has been demonstrated pharmacologically to delay ejaculation in a rat model of PE. In addition sixteen men desiring longer sexual intercourse were treated with H. perforatum immediately prior to sexual activity where a significant rise in mean ejaculation time was observed [from 246±29 to 331±34 seconds, (p<0.002)] in subjects taking hypericum extract. (79)

Recent study indicate that H. perforatum oil extracts (HPE) (olive, sunflower and palm oil) of aerial parts of the plant have the protective activity in rat gastric mucosal injury induced by cold restraint stress (CRS). These oil extracts offered significant protection against gastric damaging action of CRS in rats, and the significance of this effect was found close to that achieved by quercetin (the most studied anti-ulcer flavonoid). This indicates that besides quercetin, other constituents of H. perforatum oil extracts play an additional role in complex gastro-protective activity. (80)
In addition, *H. perforatum* is a popular treatment for anxiety, depression, cuts, and burns. Recent research suggests the effectiveness of this herb in treating other ailments, including cancer, inflammation-related disorders, and bacterial and viral diseases, and as an antioxidant and neuroprotective agent. Its effectiveness as an antidepressant agent is well studied, but the underlying mechanisms are not well understood. (81)

Randomized, comparative treatment of depression was assessed between *H. perforatum* and an standard antidepressant fluoxetine HCl through the double-blind trial in 70 patients (mean age, 49.7 years) suffering from mild to moderate depression. Efficacy was determined according to the 17-item Hamilton Rating Scale for Depression (HAMD) and the von Zerssen depression scale (DS) where significant decreases (P<.001) of 50% in the Hypericumgroup and 58% in the fluoxetine group in the HAMD score and of 42% and 52% on the DS was observed respectively. Safety evaluations demonstrated only minor changes. Apparently, the Hypericumpreparation found therapeutically equivalent to fluoxetine and is therefore a rational alternative to synthetic antidepressants.(82)

**P-glycoprotein (P-gp): A key regulatory protein in the management of stress induced disorders**
Figure-3: Crystal structure of P-glycoprotein

The blood-testis barrier (BTB), one of the tightest blood-tissue barriers in the mammalian body, creates an immune-privileged site for post meiotic spermatid development to avoid the production of antibodies against spermatid-specific antigens, many of which express transiently during spermatogenesis and spermiation.

Though Pgp, an ATP-dependent efflux drug transporter is an integrated component of the occludin/zonula occludens 1 (ZO-1) adhesion complex at the BTB, structurally interacted with focal adhesion kinase (FAK), creating the occludin/ZO-1/FAK/P-gp regulatory complex. Interestingly, a knock-down of Pgp by RNAi was found to impede Sertoli cell BTB function, making the tight junction (TJ) barrier "leaky." However, the silencing of Pgp, is capable of impeding drug transport across the BTB and TJ permeability barrier function. Thus, Pgp is involved in BTB restructuring during spermatogenesis but that Pgp-mediated restructuring does not "open up" the BTB to make it freely permeable to drugs(83) hence the leaky barrier facilitate the movement of xenobiotics into the cells that causes cellular damage.(84)

Non steroidal anti-inflammatory drugs (NSAIDs) inhibit the activity of cyclooxygenase (COX), the key enzyme in prostaglandins (PG) production. COX exists in two isoforms, of which COX-1 is a constitutive enzyme expressed in many tissues including the stomach, and COX-2 is normally undetectable in most tissues, its expression being induced at inflammatory sites. It is well known that treatment with conventional NSAIDs causes a delay in the healing of gastric ulcers. This delay is associated with a reduction of the increased PG production in ulcerated tissues in rats and humans.(85) Recently, Mizuno et al. (1997) reported that COX-2 is induced by gastric ulceration in mice, resulting in an increase in PG production. Consequently, it is thought that COXs and PGs play important roles in gastric ulcer healing.(86) Thus, COX-2 plays an important role in the healing of gastric ulcers in rats. COX-2-selective inhibitors are
expected to be new NSAIDs without ulcerogenic effects, but they are likely to impair gastric ulcer healing if used in the early phase of the healing process. (85)

One of the several genes that were highly up-regulated by over expressed COX-2 is multi drug resistance 1 gene (MDR1). MDR1 is also called as Pgp, the product of the MDR1 gene, is implicated as the primary cause of multidrug resistance (MDR) where it acts as an efflux pump for chemotherapeutic agents. It is also expressed in normal tissues of the liver and kidney where it functions to actively transport lipophilic xenobiotics. Reverse transcriptase-PCR analysis confirmed the results of the microarray, showing increased mRNA levels for MDR1 in COX-2 overexpressing cells. This increase in mRNA translated to an increase in MDR1 protein expression, which was dose-dependent on COX-2 expression. (87)

Recent reports suggest that expression of the COX-2 enzyme may up-regulate the expression of MDR1/Pgp, an exponent of resistance to cytostatic drugs. In addition, a strict positive correlation between MDR1/P-gp expression detected with mouse anti P-gp antibody (primary, C219), (88) indicates the role of Pgp in healing mechanism of peptic ulcers. (89)

Cortical spreading depression (CSD) is a propagating wave of neuronal and glial depolarization and has been implicated in disorders of neurovascular regulation such as stroke, head trauma, and migraine. It has been found that CSD alters blood-brain barrier (BBB) permeability by activating brain MMPs. MMPs are a gene family of neutral proteases important in normal and abnormal brain function. They have been implicated in processes such as (a) opening of the blood-brain barrier (BBB), (b) invasion of neural tissue by blood-derived immune cells, (c) shedding of cytokines and cytokine receptors, and (d) direct cellular damage in diseases of the peripheral and central nervous systems where MMPs disrupt the BBB, which comprises endothelial tight junctions, pericytes, astrocytic end feet, and basal lamina. (90)
Major depression indicates both cognitive and affective disorders that are clinically characterized by cognitive impairments which may be due to the relevant molecules as the amyloid precursor protein (APP) and its derivatives including the amyloid beta-peptides (Aβ_{40} and Aβ_{42}). (91) Recent study suggests that soluble Aβ-treated rats show a depressive state, which is accompanied by alterations in the expression of neurotrophins and 5-hydroxytryptaminergic (5-HT) neurotransmission in selective brain regions without an impairment in working memory.

Although the relationship among soluble Aβ, brain neurochemistry and depression remains complex, several studies have demonstrated an increased risk for the development of AD in individuals with late-life depression, suggesting a prodromal state of AD. Interestingly, it is observed that soluble form of Aβ_{40} and Aβ_{42} significantly affected the rat behavior when they were placed in a cylinder of water, during the forced swim test (FST), a method for inducing a behavioral state resembling depression in rats. Aβ-treated rats exhibited a marked increase in FST-induced immobility time compared with controls, reflecting a state of behavioral despair or helplessness. The mechanism by which soluble Aβ peptide induces depressive-like behavior is not yet clear, but the test results raise the possibility that the modulation of 5-hydroxytryptaminergic neurotransmission is involved. (92)

In this regard, it is well known that impaired 5-HT neurotransmission in the prefrontal area is central to depressive disorders, but could also have an important role in the pathogenesis of several neurodegenerative diseases for eg. the risk of developing Alzheimers disease (AD) is higher in individuals with a history of depression. (92)

Neurovascular dysfunction is an important component of stress induced disorders including AD, leading to reduced clearance across the blood-brain barrier and accumulation of neurotoxic Aβ peptides in the brain. It has been observed that Aβ significantly reduces the Aβ transporters, Pgp, LRP1, and RAGE