INTRODUCTION

Stress is a broad, ambiguous, and often poorly understood concept. In its most simplified sense, stress is what one feels when life’s demands exceed one’s ability to meet those demands. Stress can be described as the sum of all the reactions of the body, which disturb the normal physiological equilibrium and results in a state of threatened homeostasis. Stress is an internationally recognized phenomenon fortified by advancement of industrialization and a demanding civilization. Modern life is full of hassles, deadlines, frustrations, and demands. For many people, stress is so commonplace that it has become a way of life. Thus, every person today faces stressful situations in day to day life. Stress represents reaction of body to stimuli that tend to disturb its normal physiological equilibrium or homeostasis and has been defined as non specific response of the body to any demand imposed on it [1]. For optimal survival of the individual it is important that bodily functions are subject to homeostatic control. Hence there is a continuous effort to maintain these functions within a certain range variable to demand by a process referred to as allostasis [2]. Just about everybody men, women, children and even foetuses suffer from stress. Relationship demands, chronic health problems, pressure at workplaces, traffic snarls, meeting deadlines, growing-up tensions or a sudden bearish trend in the bourse can trigger stress conditions. Stress isn’t always bad. In small doses, it can help you to perform under pressure and motivate you to do your best. But when you’re constantly running in emergency mode, your mind and body pay the price. As per the observations of American Institute of stress it has been reported that forty-three percent of all adults suffers from adverse health effects due to stress and if remain untreated more than 50% suffers from lifetime emotional disorders. Stress costs American industry more than $300 billion annually [3]

People react to stress in their own ways. In some people, stress-induced adverse feelings and anxieties tend to persist and intensify. When stress goes far beyond what one actually feels, causes predictable changes in immune function, hormone levels, enzymes, and gastrointestinal function. In fact, prolonged stress, whether a result of mental/emotional upset or due to physical factors such as malnutrition, surgery, chemical exposure, excessive exercise, sleep deprivation, or a host of other environmental causes, results in predictable systemic effects. All individuals have different capacities to perform and accommodate when faced with stress but ultimately we all have a breaking point; beyond which if total stress is added up then performance of body suffers. Stress that continues without relief can lead to a condition called distress (a negative stress reaction). Distress can lead to physical symptoms
including headaches, upset stomach, elevated blood pressure, chest pain, emotional symptoms such as, feeling overwhelmed, sense of loneliness, irritability, agitation and depression. Behavioural symptoms involving eating too much or too less, isolating yourself, neglecting responsibilities, and cognitive symptoms including memory problems, inability to concentrate, poor judgment, anxious or racing thoughts, constant worrying etc. This state of accumulated stress can increase the risk of both acute and chronic psychosomatic illnesses and weaken the immune system. Stress can cause diseases such as hypertension, asthma, diabetes, heart ailments and even cancer.[4]

In a challenging situation the brain prepares the body for defensive action called fight or flight response by releasing stress hormones, namely, cortisone and adrenaline.[5.-8] Potential disturbances from internal or external sources (stressors), which collectively are perceived by the individual as “stress” activate two systems that serve to normalize the disturbed functions: the sympatho-adrenomedullar system and the hypothalamo–pituitary–adrenocortical (HPA) axis. Activation of the former rapidly results in enhanced release of adrenaline and nor adrenaline, which through activation of the vagal nerve indirectly increases the activity of noradrenergic neurons in the nucleus tractus solitairus and the locus coeruleus [9] [4]. As a consequence noradrenaline (NA) levels elsewhere in the brain involving regions which receive projections from these nuclei will be temporarily elevated leading to functional changes in neurons carrying NA receptors. Stress activates the hypothalamic-pituitary–adrenal (HPA) axis, resulting in the release of corticotropin releasing hormone (CRH) from the hypothalamic paraventricular nucleus (PVN). CRH causes the anterior pituitary to secrete adrenocorticotrophic hormone (ACTH), which in turn stimulates the adrenal cortex to secrete corticosterone [10] [5] which due to its lipophilic nature easily enters the brain. Within the brain the hormone acts at those sites where corticosteroid receptors are expressed such as in limbic areas like the hippocampal subfields, lateral septum and central amygdala etc.[11,12] [6,7] In addition to NA and corticosterone, stress exposure also leads to enhanced release of neuropeptides in the brain, such as vasopressin and corticotrophin releasing hormone (CRH) [13-15].

Collectively, catecholamines, neuropeptides and corticosterone change (among other things) the electrical properties, shape and proliferative capacity of cells in the brain, thus giving rise to the central and behavioural stress and stress hormones also affect other aspects of brain function, such as bio-availability of neurotransmitters [16] and metabolic processes [17] each
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contributing to the dynamic range of cellular effects of stress. These changes in cellular activity translate into symptoms of stress.

Stress can have effects on other hormones, brain neurotransmitters, additional small chemical messengers elsewhere, prostaglandins, as well as crucial enzyme systems, and metabolic activities that are still unknown. Research in these areas may help to explain how stress can contribute to depression, anxiety and its diverse effects on the gastrointestinal tract, skin and various other organs. Understanding the above concepts is very important in evolving the pathophysiology of the diseases caused by stress and to develop the therapeutic agents for the management of stress and stress induced diseases.

Stress has been investigated as a root cause of many diseases like diabetes mellitus, hypertension, allergies, CCF, Alzheimer etc. Thus to avoid these serious consequences of stress drugs with anti stress effect need to be developed as preventive as well as curative measures. Due to lack of diagnostic tests to identify aetiology of stress, treatment is based only on symptoms. There is no firmly established treatment recommendations for this condition [18], and the available therapies in modern medicine are limited. Allopathic drugs used for treatment of stress mainly include use of benzodiazepines, antidepressants, Barbiturates etc. These drugs are mainly used for curing or controlling the neurological or psychiatric implications of stress. There are no drugs available to correct all together neuronal, endocrinal metabolic disorders caused by stress non specifically. The modern allopathic medicines used are only for symptomatic cure and can not be used for prevention therapy. They also carry serious liability of development of addiction and/or drug dependence [19] along with serious side effects on prolonged use. Also they are not proved to be very effective against chronic stress induced adverse effects on endocrinal system, immunity, behaviour and cognition. These drugs thus are mainly used for symptomatic control of acute stress however there is no reliable and safe pharmacotherapeutic agents available for treatment of chronic stress. Thus the exploration of potential alternative therapies from traditional medicine is prerequisite to overcome stress, and for overall prevention or cure of stress and stress related diseases.

In traditional systems of medicine the Indian medicinal plants have been used in successful management of various respiratory gastric, hepatic, cardiovascular, endocrinal & immunological disorders [20]. The medicinal use of plants is very old. The writings indicate that therapeutic use of plants is as old as 4000–5000 B.C. Traditional Chinese and Ayurveda medicine constitute the two major legacies for health and healing from the ancient world [21,22]. *Atharvaveda* (around 1200 BC), *Charak Samhita* and *Sushrut Samhita* (1000–500
B.C.) are the main classics that give a detailed description of over 700 herbs. Ayurveda, Siddha, Unani and folk (tribal) medicines are the major systems of indigenous medicines. Among these systems, Ayurveda is most developed and widely practised in India. Considerable research on pharmacognosy, chemistry, pharmacology and clinical therapeutics has been carried out on Ayurvedic medicinal plants [23]. Plants, especially used in Ayurveda can provide biologically active molecules and lead structures for the development of modified derivatives with enhanced activity and/or reduced toxicity. In some cases, the crude extract of medicinal plants may be used as medicaments. On the other hand, the isolation and identification of the active principles and elucidation of its structure and mechanism of action of isolated drug is also of paramount importance for the future development of novel drugs. Hence, research works in both crude traditional medicine and single isolated active compounds of plant origine are very important. Especially at times where the active molecule cannot be synthesised economically then the product must be obtained from the cultivation of plant material. The scientific study of traditional medicines, derivation of drugs through bioprospecting and systematic conservation of the concerned medicinal plants are thus of great importance.

The drugs of plant origin are gaining importance and are being investigated for remedies of a number of disorders including stress. It is believed, in Ayurveda, that the qualities of the rasa-dhatu influence the health of other dhatus (tissues) of the body. Hence any medicine that improves the quality of rasa (rasayanas) should strengthen or promote the health of all tissues of the body. These rasayana plants are said to possess the following properties: they prevent ageing, re-establish youth, strengthen life and brain power and prevent disease [24,25] all of which imply that they increase the resistance of the body against any onslaught. Traditionally, these agents are used against a plethora of seemingly diverse disorders with no pathophysiological connection according to modern medicine and hence appears to exhibit ability to combat with stress related diseases.

Since the introduction of adaptogen concept several plants have been investigated, which were used earlier as tonics due to their adaptogenic and rejuvenating properties in traditional medicine [26]. The problem of increasing non specific resistance of an organism to untoward influences of various origin is of great importance in development of drug with antistress activity. The idea of using tonic remedies to restore balance and health in a person is an ancient idea. The word and concept of an “adaptogen” is a relatively new way of describing a type of remedy commonly found in traditional Chinese (Qi tonic), African (Manyasi), Tibetan, Ayurvedic (Rasayana), and Cherokee medicine. The first great success achieved on the pathway to development of
medicinal remedies which increase non specific resistance was the ascertaining of similar properties in benzimidazol derivatives. N. V. Lazarev and his collaborators found 2-benzyl-benzimidazol (dibazol) to be effective in medication for damage to various regions of the nervous system and to increase non specific resistance to adverse influences in 1958 [27-29]. The theoretical basis for separation of a new group of medicinal substances was laid down by Lazarev [30,31], who phrased the concept of "a state of nonspecifically increased resistance" of the organism (SNIR). The medicinal substances causing SNIR were named "adaptogens.[32] Brekhman and Dardymov(1969) defined the general pharmacological properties of adaptogenic substances. [33] Medicinal plants such as *Eleutherococcus senticosus*, *Panax ginseng*, *Raponticum carthamoides* and *Rhodiola rosea*. were found to fulfil the criteria laid down by Brekhman and Dardymov and were claimed as adaptogens. These initial studies opened a vast arena for research both abroad and in India and thereafter substantial work has been carried out on plants such as *Acanthopanax sessiliflorum* and *Rhodiola rosea* [34] from Russia, *Albizzia julibrissin* and *Cicer arietinum* from Japan, *Codonopsis pilosula* [35] and *Panax ginseng* [34] from China as well as *Withania somnifera* [36-38] *Ocimum sanctum* [39-41], *Hoppea dichotoma* [42], *Alium sativum* [43,44] *Tinospora cordifolia* [45] and *Emblica officinalis* [46.] from India. Many of these plants were selected on basis of their therapeutic claims made in traditional systems of medicines. Herbs which were used as rejuvenators, restorers, vitalizers and tonics were thought to be capable of modulating stress related changes, might be by increasing the ability to resist stressors nonspecifically and adapt to surroundings. Several theories have been suggested to explain the effects of adaptogenic substances. One theory proposed by Dardymov and Kirkorian [47] argues that adaptogens function primarily due to their antioxidant and free radical scavenging effects. But it is inadequate to explain the complete effects of these medicines. More recent research postulates that adaptogens work primarily by affecting the Hypothalamic/Pituitary/Adrenal (HPA) axis and the Sympathoadrenal System (SAS) [48]. Thus, adaptogens modulate our response to stress (physical, environmental, or emotional) and help to regulate the interconnected endocrine, immune, and nervous systems. This re-regulation of a disordered or highly stressed system is achieved by metabolic regulators such as cytokines, catecholamines, glucocorticoids, cortisol, serotonin, nitric oxide (NO), cholecystokinin, corticotrophin-releasing factor (CRF), and sex hormones.[49-51]. This broad array of biochemical activators helps to explain why adaptogens also have antiinflammatory, antioxidant, anxiolytic, antidepressant, nerve, and amphoteric effects as well. So while most or all adaptogens are antioxidants however having antioxidant properties is not enough to
make a substance an adaptogen. Brekhman and Dardymov’s list of physiological actions of adaptogens states that adaptogens help to modulate system function and maintain homeostasis. So all adaptogens act as broad spectrum amphoterics to living organisms, but they rarely have a pronounced effect on only one specific organ or system.

In present research work efforts have been made to explore and evaluate antistress potential of various extracts of two medicinal plants namely Murraya koenigii which has been claimed as a tonic [52] and Ocimum sanctum. which has been traditionally regarded as possessing rejuvenating properties that contribute to longevity and a healthy life. To evaluate clinical efficacy of the effective plant extracts formulation has been developed and tested for stability as well as their invivo efficacy. Further efforts have been made to isolate the phytochemical constituent from Murraya koenigii extract demonstrating significantly potential antistress effect. by developing an economical easy precise method of isolation. The structure of isolated phyto-constituent has been elucidated by using various physical methods .The possibility of its contribution to the observed antistress effect has been evaluated by carrying out invitro testing. Thus our entire efforts have been directed for investigating novel and promisingly effective medicinal plant with antistress effect and isolating possibly therapeutically effective phytoconstituent from it. These efforts might throw some light on the development of potent therapeutic lead molecule useful for management of stress and related disorders in future.