SUMMARY

Extracts of MK and OS were found to be significantly preventing stress induced increase in serum corticosterone levels which is an important biomarker of stress.[715] Thus MK and OS might be executing their antistress effect by deactivating stress-messengers corticosteroids which are endogenous mediators of cellular communications, hence protecting the cells and whole organism from overreacting to the activating messengers or else preventing the down regulation of glucocorticoid receptors observed on exposure to chronic stress thus maintaining the function of glucocorticoid feed back mechanism intact and preventing surge rise in serum corticosterone levels in serum. Because of the elevated levels of glucocorticoids energy resources become depleted due to the catabolic action of the hormone. Extracts were also found to be normalizing stress induced perturbation in various biochemical parameters like glucose triglycerides and cholesterol levels due to stress by effectively regulating metabolic homeostasis. MK and OS extracts might have executed this homeostatic control on metabolism of energy substrate by enhancing the utilization of secondary sources of energy substrates like triglycerides and sparing rapid utilization of primary substrates like glucose and therefore glycogen there by maintaining the availability of ATP and thus energy to sustain with stress. This might have prolonged the period of resistance phase of GAS and delayed the onset of exhaustion state during stress as observed in increased endurance period and delayed onset of fatigue in WFS in treatment animals.

MK and OS were found to be effectively regulating serum levels of glucose in treated animals when subjected to different types of stress models by controlling glucose homeostasis and/or promoting the assimilation of glucose in to the tissues may be by preventing stress induced loss of insulin sensitivity in the tissues. These mechanisms might had made glucose available to the tissues especially to the brain for which the only source of energy is glucose. Availability of glucose to the brain during stress might be another mode of action responsible for preventing neuronal trauma. Especially in areas like hippocampus and amygdala involved in memory formation, this mechanism must be contributing to the observed effect of retention of memory of learned task in various memory paradigms. However on treatment with extracts prevention of stress induced deficit in negative feedback control on release of corticosteron at higher centers, there by restricting hypercorticosteronism might be considered as another central mode of action for decreased neuropathy in brain and for prevention of stress induced serum hyperglycemia and
simultaneously decreased demand of cholesterol for synthesis of corticosterone peripherally. Decreased neuronal damage in hippocampus due to restricted release of corticosterone during stress might be an important contributing factor for observed retention of memory. However at the same time MK and OS were also found to be reducing significant reduction in Ach content due to stress induced elevation of AChE activity in the discrete areas of brain in rats subjected to stress. Ach plays a cardinal role in process of memory formation [716]. Pretreatment with extracts MK and OS was found to conserve the concentration of Ach by reducing the degree of hydrolysis by choline esterase thus it is possible to be hypothesized that decreased rate of metabolism of Ach might be another possible mechanisms responsible for retention of the memory of learned tasks during stress. Thus on treatment with extracts loss of contextual memory observed in cooke’s pole, shuttle box and step down inhibitory avoidance tests as well as loss of spatial memory in Elevated plus maze and Morris water maze was found to be prevented due to combined effect of reduction in stress induced increased metabolism of acetyl choline and as well as by prevention of detrimental effects of corticosteroids on LTP in hippocampus by restricting stress induced hypercorticosteronism [717].

Due to regulatory effect of extracts on secretion of serum Glucocorticoids it was observed that its rate of synthesis in adrenal cortex might had reduced thus preventing hyperplasia of cortex responsible for stress induced adrenomegaly, also the rate of utilisation of precursor i.e. cholesterol and its uptake in adrenal gland and its release in blood might had reduced correspondingly. Thus Prevention in perturbations in levels of serum cholesterol during stress is a secondary effect to the primary control of restriction on hypersecretion of corticosterone executed on treatment with MK and OS extracts.

Extracts of MK and OS also exhibited a significant effect in preventing stress induced increased turnover of catecholamines such as Norepinephrine, 5HT and Dopamine as observed in restraint stress, foot shock and sleep deprivation models, thus avoiding occurrence of stress related psychological consequences of depression. Treatment with extracts was also observed to be significantly increasing body’s resistance to antigenic challenge presented by s.c injection n of raw cow milk. Degree of occurrence of Various stress correlates such as formation of ulcer, thymus atrophy, decrease in weight of spleen and adrenomegaly were found to be decreased on treatment with extracts.

Oxidative stress is commonly observed triggering factor for various stress induced neurodegenerative effects. MK and OS were found to possess significant anti oxidant...
Summary

potential both invivo as well as invivo. Treatment with MK and OS extracts prevented rise in levels of aggressive factors such as lipid peroxidation and lowering of defense mechanism such as GSH and Catalase in brain during oxidative stress induced by ECS, thus protecting the brain from oxidative stress injury. On phytochemical investigations Steroids flavonoids, alkaloids terpenes and tannins were found to be present in MK whereas glycosides steroids, tannins flavonoids and terpenes were found to be present in OS which might had conferred the ability to the extracts for scavenging Reactive oxygen species (ROS) generated during oxidative stress. This antioxidant effect thus might had prevented the stress induced excitotoxicity and possibly the resultant oxidative stress induced neurodegeneration. Thus antioxidant effect of extracts may be speculated as another mode of action supporting the prevention in rise in levels of corticosterone and offering protection against the detrimental effects of stress on neurons.

When bioactive extracts were put in to capsule dosage formulation, were found to be stable with significant invivo anti stress activity thus proving their clinical efficacy in future. An effective method for isolation of the pure phyto-constituent from bio activity guided effective extract has been developed successfully. The isolated phyto-constituent was confirmed to be Mahanimbine from structural elucidation studies Which was also found to be possessing significant antioxidant effect in vitro. This observed effect of isolated phytoconstituent has created a ray of hope to continue the exploration of Mahanimbine to further investigate its potential ability as antistress drug, which might lead to the development of a novel potent antistress molecule in future.