9. SUMMARY

Traditional medical systems popularly known as Complementary and Alternative Medicine (CAM) are burgeoning globally. Over 80% of developing countries depend on traditional healing systems. In developed countries the use of CAM has come to focus in recent years. CAM has in last few decades attracted world-wide attention because of its widespread use in some countries, their costs and unknown effects. The medical community has become interested in learning more about CAM from the patients’ perspective, which includes the presumption that CAM is natural, has scientific basis and promote spirituality. But the major lacuna for all these medical systems is lack of proper scientific evidence based on allopathic (modern) medical system. The present scenario of growing popularity to alternative medical systems encouraged us to take up pharmacological study of some of the drugs from ayurveda, unani and herbs used by folklore medicine.

Drugs were selected for two chronic central nervous system disorders, namely, epilepsy and depression. The drugs selected for testing their efficacy in epilepsy were Panchagavya Ghrutham (Ayurveda), Hab-e-Jund (Unani) and Cynodon dactylon (Herbal drug). The drugs selected for testing their antidepressant activity were Kushmanda Lehyam (Ayurveda), Itrifal Kishneezzi (Unani) and Barleria cristata (Herbal drug). The formulations were used as received and methanolic extracts were prepared for the plants selected.
All the drugs were subjected to preliminary phytochemical screening, acute toxicity studies using OECD guidelines, neuropharmacological profile test using Irwin’s test and antioxidant activity by DPPH radical scavenging and Fe$^{2+}$ metal chelating methods.

In addition, Panchagavya Ghrutham (PG), Hab-e-Jund (HJ) and Cynodon dactylon (CD) were tested for their antiepileptic activity and Kushmanda Lehyam (KL), Itrifal Kishneezi (IK) and Barleria cristata (BC) were tested for their antidepressant activity.

The Institutional Animal Ethics Committee approved the study protocol for all the drugs (IAEC/SUCP/01/2007, IAEC/SUCP/01/2009, IAEC/SUCP/09/2009).

The results of preliminary phytochemical screening revealed the presence of phenolic compounds and flavonoids and volatile oils. Eventhough extensive heating is involved in the preparation of the formulations, volatile oils remain in them similar to flavors retained in Indian curries even after extensive cooking. Gums and mucilages were not found in any of them.

Acute toxicity studies revealed that PG was relatively safer than the other drugs, followed by IK, HJ and KL. This could be explained by the higher therapeutic doses in humans and the formulations and large quantities of safer substances like clarified butter, honey, candy sugar, etc. Convulsions with higher doses of CD supports its use in folklore medicine.
for diabetes. Higher doses of PG, HJ and KL showed sedation whereas IK and BC showed anxiety, writhing, palpitation and tremors.

In Irwin’s test PG, HJ, KL and IK showed negligible actions at 30 mg/kg body weight. At higher doses the drugs showed certain behavioral, neuronal and other changes suggesting the course to be taken for further studies. PG, HJ and CD showed CNS depression, besides PG and CD showed significant analgesic activity. CD showed severe tremors and convulsions at higher doses indicating CNS stimulating &/or hypoglycemic activity. With these observations further studies for antiepileptic activity were taken up. KL, IK and BC showed CNS stimulation. But KL at higher doses showed CNS depression. KL, IK and BC showed potent analgesic activity. IK increased the volume and frequency of defecation. The drugs were studied for their antidepressant activity.

The drugs in our study showed varying degrees of dose dependent antioxidant activity. Literature survey of the ingredients of the formulations and preliminary phytochemical screening revealed that the drugs were rich in phenolic and flavonoids content. The antioxidant activity of the drugs could be attributed to this high phenolic and flavonoids content.\textsuperscript{[250]}

All the drugs showed varying degrees of dose dependent increase in free radical scavenging except Hab-e-Jund, which showed dose independent scavenging activity. DPPH\textsuperscript{*} radical scavenging method is widely used because of its simplicity and shorter duration required when compared to other methods.\textsuperscript{[251]} DPPH\textsuperscript{*} is considered to be a model of lipophilic radicals which initiate lipid auto oxidation.\textsuperscript{[244]}
All the drugs including Hab-e-Jund showed dose dependent Fe$^{2+}$ chelation. Flavonoids besides free radical scavenging can also chelate trace metals.$^{[251]}$ All the drugs including Hab-e-Jund showed dose dependent Fe$^{2+}$ chelation. Flavonoids besides free radical scavenging can also chelate trace metals.$^{[251]}$

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PG, HJ, CD showed antiepileptic activity in different models of epilepsy. PG protected the mice against MES, PTZ, Lithium-Pilocarpine and Strychnine induced convulsions indicating that it is a very good antiepileptic drug useful in grand mal epilepsy, absence seizures, status epilepticus and through inhibitory spinal reflexes of glycine.$^{[266,267]}$ It also antagonized the effect of the selective GABA$_A$-BZD receptor antagonist, flumazenil. PG antagonized the effect of flumazenil a BZD antagonist, it is understood that PG has a BZD like GABA enhancing activity. The effect of the selective GABA$_A$-BZD receptor antagonist, flumazenil on the anticonvulsant activity of the drugs indicates the probable involvement of GABA$_A$-BZD receptors.$^{[259-261]}$

BZDs act by enhancing presynaptic/postsynaptic inhibition by binding to specific BZD binding site (interface of α and γ subunits) on GABA$_A$ receptor-Cl$^-$ channel complex. The modulatory BZDs increase the frequency of Cl$^-$ channel opening induced by submaximal concentrations of GABA. BZDs have only GABA facilitatory but no GABA mimetic action.$^{[19-23]}$
Thus PG might be acting by multiple mechanisms of BZD like enhancement of central GABA ergic activity, by increasing brain acetyl choline content\cite{61,262} and enhancing strychnine sensitive inhibitory spinal reflexes of glycine and probable involvement of glycine receptors.\cite{266,267} These observations support its use in ayurveda for grand mal epilepsy, chronic and severe epilepsy. As the study also indicates its benefits in status epilepticus, it also could be added to the therapeutic regimen of the same.

HJ antagonized MES, PTZ and Lithium Pilocarpine induced convulsions and did not effect flumazenil action and strychnine induced convulsions. GABA enhancing activity of HJ is not a BZD action but may be mediated through other mechanism. HJ showed very good protection against Lithium Pilocarpine induced status epilepticus in accordance with its use in Unani for febrile convulsions.

CD like PG showed protection in all types of epilepsy (at higher doses for Lithium-Pilocarpine and strychnnine induced convulsions). But the higher doses of CD (300mg/kg and above) significantly reduced blood glucose levels.\cite{160} Thus CD is useful in grand mal and absence seizures and isolation of specific constituent would be much more beneficial.

The immobility in rodents subjected to unavoidable and inescapable situations induce behavioral despair that correlates with human depression.\cite{268,269} Apomorphine is a dopaminergic agonist. At noradrenergic terminals apomorphine acting through D\textsubscript{2} receptors prevents Norepinephrine release. It produces hypothermia that is mediated through dopaminergic and serotonergic mechanisms.\cite{287-292} It is reported that