Chapter-II

REVIEW OF LITERATURE

All the synthetic compounds (Donepezil, Rivastigmine, Galantamine, Tacrine DuP996, Ketanserin, Tryptophan, Velnacrinemaleate, Memantine, L- deprenyl, Cerebrolysin etc.) are being practiced to treat the dementia but none of them are devoid of their ill effects in the long run. The ill effects include slower heart rates, fainting episodes, dizziness, nausea, sedation, drowsiness, sleep disturbance, and weight loss (Bartus, Dean, Beer, and Lippa, 1982). As already mentioned in the last chapter, an alternative that is claimed to be safer is the discipline of Ayurveda that has existed in India from millennia. One of the practices of Ayurveda is to treat poor health with medicines obtained from herbs. These medicines are prepared from the leaves, roots, or other parts of certain plants. Since the aim of this study is to investigate the effect of Shankhpushpi on Dementia, which is an herbal medicine, the following section would deal with the studies that used the herbal medicines to treat dementia. These studies have been collected from various journals, last 20 years retrieval of literature from 1988 and also from the journals related to Ayurveda. The studies have been reviewed in a chronological manner.

An interesting study explains the efficacy of the Ginkgo biloba special extract EGb761 in patients with pre-senile and senile dementia, and multi-infarct dementia. Kanowski, Herrmann, Stephan, Wierich, and Horr (1996) conducted a randomized, double-blind, placebo-controlled study on presenile and senile primary degenerative dementia of the Alzheimer type (DAT) and multi-infarct dementia (MID). The patients received either a daily oral dose of 240 mg EGb761 or placebo for 24 weeks. Three tools were used i.e. Clinical Global Impressions (CGI Item 2) for psychopathological assessment, the Syndrom-Kurztest (SKT) for the assessment of the patient's attention and memory, and the Nurnberger Alters-Beobachtungsskala (NAB) for behavioral assessment of activities of daily life. Total 156 patients completed the treatment. The results showed that the two treatment groups differed significantly in favor of EGb761, with p < 0.005 in Fisher's Exact Test. Thus, the helping role of clinical extract EGb761 in the dementia of
Alzheimer's type and multi-infarct type was confirmed. The investigational drug was found to be well tolerated.

Le Bars, Katz, Berman, Ihl, Freedman, and Schatzberg (1997) studied the effect of EGb761, an extract of Ginkgo biloba on dementia. Out of 309 patients suffering from dementia, 202 provided evaluable data for the 52-week end point analysis. In the intent-to-treat analysis, the EGb761 group had an ADAS-cog (Alzheimer's disease Assessment Scale- cognitive subscale) score 1.4 points better than the placebo group (P= .04) and a GERRI (Geriatric Evaluation by Relative's Rating Instrument) score 0.14 points better than the placebo group (P= .004). It was concluded that EGb761 is safe and appears capable of stabilizing and, in a substantial number of cases, improving the cognitive performance and the social functioning of demented patients at least for the period taken up in this study i.e. from six months to one year.

EGb761 was observed having positive effect on learning and memory in dementia of the Alzheimer type in another study. In their study, Maurer, Ihl, Dierks, and Frolich (1997) found the favorable results of EGb761 on Alzheimer's disease among 20 patients. The oral treatment of 240 mg/a day of EGb761 was given for three months. The primary outcome variable was the sum score in the Speciality Knowledge Test (SKT) for the determination of attention and memory. Other psychometric tests (including Trailmaking Test, ADAS, and CGI) and electrophysiological investigations (EEG Topography) were evaluated descriptively. Although the active treatment group, with a mean sum score of 19.67 points in the SKT, had a poorer baseline level than the placebo group (18.11 points), it experienced an improvement to 16.78 points under treatment with EGb761 whereas the placebo group deteriorated to 18.89 points. The difference between the baseline and the final values gave a result favourable to EGb761, at a significance level of p<.03. in addition to this psychometric confirmation of efficacy, certain descriptive trends were found at the psychopathological (CGI) and dynamic functional (EEG findings) levels, which can be interpreted as evidence of effectiveness of Ginkgo biloba special extract EGb761 in mild to moderate dementia and of local effects in the central nervous system. Inter group difference in ADAS cognitive and non-cognitive subscales did not reach statistical significance, probably because of the small sample size.
In a favourable double-blind, placebo controlled study Scripnikov, Khomenko, and Napryeyenko (2007) used the *EGb761* doses on 400 patients of various types of dementia for 22-weeks. The patients scored at least 5 on the Neuropsychiatric Inventory (NPI). The patients received either *EGb761* (240 mg/day) or placebo. The main outcome measure was the Speciality Knowledge Test (SKT) and the secondary outcomes were NPI, measuring frequency and severity of neuropsychiatric symptoms and care-giver distress caused by such symptoms, the Activities-of-Daily-Living (ADL) subscale of the Gottfries Brane Steen overall geriatric assessment scale (GBS), total GBS score for intellectual, emotional and ADL subscales, Verbal Fluency Test, Clock Drawing Test (CDT), HAMD, and self-rated tinnitus and dizziness. The findings indicated that *EGb761* was found significantly superior to placebo. There was a statistically significant difference favouring *EGb761* over controls for main outcome measure and for all secondary outcomes. Between baseline and week 22, the mean composite score (frequency x severity) of the NPI dropped from 21.3±9.5 to 14.7±9.5 in the group treated with *EGb761* and increased from 21.6±9.9 to 24.1±12.8 in the control group. The mean care-giver distress score dropped from 13.5±6.7 to 8.7±5.5 in the *EGb761* group compared to an increase from 13.4±6.4 to 13.9±7.2 in the control group. Both these intergroup differences were statistically significant.

Dodge, Zitzelberger, Oken, Howieson, and Kaye (2008) conducted a research to assess the feasibility, safety, and efficacy of *Ginkgo biloba Extract (GBE)* on delaying the progression to cognitive impairment in normal adults aged 85 and above. In this randomized, placebo-controlled, double-blind study 118 cognitively intact subjects were randomized to standardized *GBE* (240 mg) 80 mg three times a day or placebo for 42 months. Kaplan-Meier Estimation, Cox proportional hazard, and random effects models were used to compare the risk of progression from Clinical Dementia Rating (CDR) =0 to CDR=0.5 and decline in episodic memory function between *GBE* and placebo groups. But there was no reduced risk of progression to CDR=0.5 (log-rank test, p=0.006) was found among the *GBE* group. There was no improvement found in the memory function among the *GBE* group (p=0.05). Researchers also reported a higher incidence of stroke in GBE group which requires further study to confirm.
Another fairly large study of *Ginkgo* extract drew headlines for concluding that it is ineffective to use *Ginkgo* as treatment of dementia (Van, Van, and Kessels, 2008). This was a community based, pragmatic, randomized, double-blind, and parallel-group study. A standardized extract of Ginkgo biloba (120 mg/day) or placebo was given to 176 mild to moderate dementic patients for 6 months. The assessment tools were Cognitive Functioning subscale of ADAS, and participant and carer-rated Quality of Life Scale (QOL-AD). Results indicated that Ginkgo biloba did not have a significant effect on outcome at 6 months neither on the ADAS-cog score (p=0.392), the participant rated QOL-AD (p=0.787) nor the carer-rated QOL-AD score (p=0.222). This was concluded that a standardized dose of high purity Ginkgo biloba conferred benefits in mild to moderate dementia patients only.

In a recent randomized, double-blind exploratory study Yancheva, Ihl, Nikolova, Panayotov, Schlaefke, and Hoerr (2009) found *EGb761* very effective while administered it on 96 Alzheimer’s patients. The patients were scored below 36 on the TE4D, a screening test for dementia, below 6 on the Clock-Drawing Test (CDT) and between 9 and 23 on the SKT, a cross-culturally validated cognitive test battery. They scored at least 5 on the 12-item Neuropsychiatric Inventory (NPI). *EGb761* (240 mg/day), donepezil (initially 5 mg, after 4 weeks 10 mg/day) or *EGb761* and donepezil combined (same doses) were administered on the patients for 22 weeks. Results showed changes from baseline to week 22 and response rates were similar for all the treatment groups. An apparent tendency in favour of combination treatment warranted further scrutiny. Compared to donepezil, the adverse event rate was lower under *EGb761* treatment and even under the combination treatment.

To conclude the studies related to Ginkgo biloba, it can be said that there are contradictory evidences. However, it is to be noted that in the studies, where *EGB761* was not found to be effective, the dose used is lower i.e. 120 mg/day than 240 mg/day used in earlier studies.

Another such medicine is *Huperzine A*, a plant derived chemical from a particular type of club moss (Huperzia seratta). Its effect also has been examined by researchers to conclude that it is a beneficial treatment for dementia of many forms including *Alzheimer* and *Multi-infarct types*. In a study Zhang, Tang, Han, Sang, Zhang, Ma, Zhang, and Yang...
(1991) administered *Huperzine A* on 56 patients of MIT and 104 patients of simple memory disorders. They used placebo-controlled design. The evaluation was done by Wechsler Memory Scale. The dose for multi-infarct dementia patients was 0.05 mg per day for 4 weeks, whereas for patients of simple memory disorders the dose was 0.03 mg per day for 2 weeks. Saline was used for control group. The findings indicated that *Huperzine A* is very helpful in improving the symptoms of dementia. Only a few patients felt slight dizziness and did not feel the therapeutic effects.

Xu, Gao, Weng, Weng, Du, Xu, Yang, Zhang, Tong, Fang, and Chai (1995) conducted a research on 103 Alzheimer patients. Out of them 50 patients were administered 0.2 mg (4 tablets) of *Huperzine-A*, and remaining 53 patients were given 8 tablets of placebo for the duration of 8 weeks. The patients were tested on Wechsler Memory Scale, Hasegawa Dementia Scale, Mini-Mental State Examination scale, daily living scale, treatment emergency symptom scale, and measured with BP, HR, ECG, ALT, AKP, BUN, Cr, Hb, WBC, and urine routine. Results explained about 58% (29/50) of patients treated with *Huperzine-A* showed improvements in memory (p<0.01), cognitive (p<0.01), and behavioral (p<0.01) functions. The efficacy of *Huperzine-A* was better than placebo (36%, 19/53) and it was significant (p<0.05). No severe side effect was found.

In a prospective, double-blind, parallel group, positive controlled and randomized study conducted by Xu, Cai, Qu, Yang, Cai, Wang, Su, Zhong, Cheng, Xu, Li, and Feng (1999) *Huperzine A* was administered on 60 patients of Alzheimer’s Disease. The patients were divided into 2 equal groups. Patients in capsule group received 4 capsules of *Huperzine A* (each containing 50 mg) and 4 tablets of placebo (lactose and starch inside), while the tablet group received 4 tablets of *Huperzine A* and 4 capsules of placebo twice a day for 2 months. The patients were evaluated with a lot of related rating scales, and physiological laboratory examinations. Findings indicated that there were significant differences (p<0.001) on all the psychological evaluations. The changes of oxygen free radicals in both the groups showed marked improvement.

There is another herbal medicine named *Acetyl-L-carnitine* that has been found to be having somewhat positive results in treating the dementia. Montgomery, Thal, and Amrein (2003) conducted a double-blind randomized controlled research on 82 mildly
impaired patients with Alzheimer’s disease by administering Acetyl-L-carnitine on them for 3, 6, or 12 months. The daily dose varied between studies from 1.5-3.0 gm/a day. The results indicated mildly positive effect of Acetyl-L-carnitine on Alzheimer’s disease. The effect was evaluated with various clinical tests and psychometric tests. The Clinical Global Impression of Change (CGI-CH) was calculated separately. Meta-analysis showed a significant advantage for acetyl-L-carnitine as compared to placebo for the integrated summary effect (ES all scales=0.201, 95% confidence interval=0.107-0.295) and CGI-CH (ES CGI-CH=0.32, 95% confidence interval=0.18-0.47).

Colistrinin, a substance derived from colostrums, has shown promising results for treatment of Alzheimer’s disease in the study conducted by Bilikiewicz and Gaus (2004). They took 105 patients of mild to moderate Alzheimer’s disease as the subjects. The patients received 100 mg of colistrinin in a day for duration of 15 weeks. The primary outcome measures used were Alzheimer’s disease Assessment Scale- Cognitive subscale (ADAS-cog) and Clinical Global Impression of Change (CGIC). Secondary outcome measures were Instrumental Activities of Daily Living (IADL), Mini-mental State Examination (MMSE), ADAS-non cognitive test (ADAS-non cog), and overall Patients Response. Analysis at week 15 showed a stabilizing effect of colostrinin on ADAS-cog (p=0.02) and on IADL (p=0.02). The overall patients response was also in favour of the active (p=0.03). Patients graded as mild on entry also showed a superior response of ADAS-cog compared with more advanced cases (P=0.01). The evidence from the study indicated an early beneficial effect on cognitive symptoms and daily function. Thus colostrinin has potential value in the treatment of dementia, specifically of Alzheimer’s Type. Patients also showed a superior response of ADAS-cog compared with more advanced cases (p=0.01).

Shankhapushpi is another plant which has been found helpful in enhancing mental functioning. It is claimed to be a brain tonic. It is reported to reduce mental tension. The plant is famous to be a prominent memory improving herb. This herbal medicine has not been reported to be used to treat dementia. Therefore the following section will deal with the studies indicating its effects on mental functioning, alertness and learning and memory or in any other related area. These have been reviewed in the following section. Firstly, its chemical composition would be reviewed.
Basu and Dandiya (1948) isolated an alkaloid from the plant, named as \( \text{C}_{17}\text{H}_{23}\text{NO}_3 \). They studied the effects of this isolated base on frog’s heart and found no action on the heart or vessels in a concentration of 1:5000. The same authors reported the presence of an essential oil in Shankhpushpi, while determining some of the physical constraints of this plant. However, the exact oil was perhaps not identified and there is no mention of the name and chemical properties of this oil, by them.

Another effort to understand the composition of Shankhpushpi was made by Basu and Bhan (1951). They confirmed the presence of \( \text{C}_{17}\text{C}_{23}\text{NO}_3 \) which is soluble in chloroform. Besides this very reported the presence of two other water soluble bases: one acetone-insoluble base \( \text{C}_3\text{H}_{14}\text{NO}_6 \), having m.p. 84°, hydrochloride m.p. 214°, picrate m.p. 176° and the second base was an acetone soluble base. This was not obtained in crystalline form. Some more derivatives were also prepared by them. These two derivatives were also bases, named as base hydrochloride, having m.p. 272° and base oxalate having a relatively lower m.p. 154°.

Singh and Mehta (1977) reported the psychotropic effect of Shankhpushpi. As a sample, 30 outdoor patients of anxiety neurosis were selected. After clinical diagnosis and basal evaluation these patients were subjected to a course of treatment with Shankhpushpi syrup in the dose of 30 ml per day in 3 divided doses (representing 50g. dry crude drug). They were instructed for uniform diet and regimen. The patients were reassessed on the following parameters to evaluate the effect of the treatment given after one month: (1) Clinical relief: the main symptoms scored in numbers by qualitative grading, (2) Psychological changes studied by (i) Total and differential anxiety level with the help of Middle Sex Hospital questionnaire, (ii) Neuroticism index as per MPI, (iii) Mental fatigue rate as per Joshi’s digit cancellation test, (iv) Immediate memory span as per Joshi’s digit renounce test, (3) Physiological changes viz. pulse rate, blood pressure and body weight, (4) Biochemical changes viz. plasma cortisol, urinary catecholamines.

A significant symptomatic relief was observed after one month of treatment as regard to the major symptoms like nervousness, palpitation, insomnia, weakness and fatigue, dyspepsia, and general feeling of not being well. The total and differential anxiety levels were found to be reduced after one month of the therapy. The free floating anxiety, obsessive compulsive neurosis, phobic features, somatic features, depressive features,
and hysterical features, were found to have reduced though the differences were statistically not significant except in case of hysterical features (p<0.05). The mental functions as estimated by (1) mental fatigue rate and (2) immediate memory span showed significant improvement. Thus the study confirmed the claimed effect of this herbal medicine as a brain tonic and memory enhancer.

In another study, Shukla (1979) used albino rats having five groups as the subjects. For the present study young growing healthy albino rats of known weight were selected. The animals were divided in five uniform groups. Group-1 was kept as control and was given no treatment except 1.5 ml water orally through a stomach tube. Group 2 was treated with a standard anti-anxiety drug, Diazepam in the dose of 1 mg/100 g body weight orally suspended in 1.5 ml of water. Group 3 was given total alcoholic extract of the dry whole plant of Shankhapushpi in the dose of 83.3 mg of dry extractive / 100 g body weight suspended in 1.5 ml of water orally through a stomach tube. Group 4 was given water soluble portion of total alcoholic extract and Group 5 was given water insoluble portion of the total alcoholic extract, in doses proportionate to that given in Group 3. A standard barbiturate hypnosis potentiation test was applied to the animals in all the groups, using Nembutal 2.5 mg/100g body weight intraperitoneally 30 minutes after administration of single doses of the respective test drugs. The onset and the total duration of sleep in case of each animal following the injection of Nembutal were recorded in minutes. The drug Diazepam showed statistically significant barbiturate hypnosis potentiation effect as a result. The total alcoholic extract of Shankhapushpi and its water soluble and insoluble fractions showed a lesser degree of effect. The activity was more in water soluble portion.

Shankhapushpi is commonly used as a tranquilizer. To test the immediate and cumulative tranquilizing effects of this herb, neurohumoral changes were recorded as an index to study the status quo of brain by Mudgal, Rai, Singh and Udupa (1977). The aerial parts of Shankhapushpi were collected and the test extracts were prepared. Twenty-four young albino rats weighing 100 ± 10gm, acclimatized to laboratory conditions for 10 days, were divided into four groups comprising of 6 rats in each group.

Two types of experiments were as follows:
(a) Short term experiments: (i) control receiving only distilled water, (ii) treated
group receiving one single injection of water soluble alcoholic extract of leaves and
flowers of Shankhapushpi in the dose of 300mg/kg weight intraperitonially one hour
earlier to sacrifice.

(b) Long term experiments: (i) control receiving only distilled water, (ii) treated
group receiving the drug in the dose of 1.20g/kg weight orally once in a day, for a period
of 10 days. These rats were sacrificed on the 10th day.

In the short term experiment Shankhapushpi treated groups showed significantly
lower levels of acetylcholine and histamine. Statistically there was no significant change
found in the level of catecholamine in control and treated ones. Shankhapushpi treated
groups showed significantly lower levels of all the three neurohumors than control. This
indicates a direct influence of Shankhapushpi on the central nervous system by way
neurohumoral responses, thus strengthening the claim of Charak Samhita stating
Shankhapushpi as the best neural tonic.

A study based on 60 young albino rats of 100-110 gm of weight was conducted
by Singh, Mehta, Sarkar, and Udupa (1977). The animals were trained with a simple T-
maze up to a criterion of mastery. After optimum training they were divided into three
equal groups. Group 1 was given 50 mg dose/100gm body weight of the total alcoholic
extract of the dry Shankhapushpi plant. Group 2 was given a psychotropic drug, named as
triflupromazin in the dose of 2 mg/110 gm body weight. Group 3 was used as control and
only 1 ml water was given to them through stomach tube once a day. The experiment was
of duration of 10 days. As a result, there was found a reduction in the activity of
Shankhapushpi treated group in terms of increased time and errors while walking in T-
maze. The use of triflupromazin showed a relatively more pronounced reduction in the
activity of the animals. Later on the rats were sacrificed by deception. The whole brain
tissue was dissected out and subjected to the determination of 5-HT, acetylcholine,
catecholamines, and histamine. A significant barbiturate hypnosis potentiation effect was
observed in Shankhapushpi group. The biochemical studies showed an increase in the
levels of histamine and 5-HT in treated animals as compared to controls. The
acetylcholine and catecholamine contents were found to be reduced in Shankhapushpi
treated group.
Ali (1998) found that Shankhapushpi contains volatile oil, n-triacontane, higher fatty alcohols, kaempferol, its 3-D-glucoside, 2,3-dihydroxycinnamic acid B-sitostosterol, carbohydrates such as glucose, rhamnose, sucrose, starch and potassium chloride, which enable the plant to be a brain tonic, in hypertension and as tranquilizer. The study provides scientific support for the antioxidant activities of extracts of Shankhapushpi substantiates the traditional claims for the usage of these drugs in stress-induced disorders.

Indurwade and Biyani (2000) found that Shankhapushpi showed promise as a safe, effective remedy for anxiety. They conducted the research on 110 adults of age group 25-45 years. The Ss were divided into two groups- one as experimental group and received Shankhapushpi treatment, whereas the other group was control and received placebo. The treatment of was continued for 4 weeks with doses of 120 mg daily. The assessment was done with the help of Hamilton Anxiety Scale (HAS) in before and after conditions. The findings showed that the experimental group experienced reduced anxiety than the control group.

In another empirical study, people suffering from anxiety were given Shankhapushpi for six weeks and claimed to have slept better, have more energy and better concentration. The researcher gave 28 people diagnosed with anxiety 50 mg daily of an herbal formula with Shankhapushpi as a primary ingredient. After six weeks of treatment, 91 percent of the patients had more energy and 60 to 70 percent could sleep and concentrate better (Shaughnessy, 2002).

Siripurapu, Gupta, Bhatia, Maurya, Nath, and Palit (2005) evaluated crude ethanolic extract of Evolvolus alsinoides (EA) for its adaptogenic and memory enhancing properties in rodents. Adaptogenic activity was assessed in rats subjected to acute and chronic unpredictable stress. Male Sprague-Dawley rats, weighing 180-200 g were immobilized for 150 min once only in acute stress (AS) model, whereas in chronic unpredictable stress (CUS) model rats were subjected to different types of stressors daily for 7 days. Stress exposure induced gastric ulceration with increase in adrenal gland weight, plasma creatine kinase (CK), and corticosterone level in AS and CUS. However, plasma glucose was increased only in AS. Rats were treated with graded doses of crude ethanolic extract of EA (100, 200 and 400 mg/kg p.o.) for 3 days and subjected to AS on
3 day after 45 min of last dose. In CUS, EA at a dose of 200 mg/kg p.o. found effective in acute studies was administered 45 min prior to stress regimen for 7 days. EA reduced the stress induced perturbations similar to Panax quinquefolium (PQ) (100 mg/kg p.o.), a well known adaptogen. EA (100 mg/kg) administered orally for 3 days in adult male Swiss mice, was effective in decreasing scopolamine induced deficit in passive avoidance test. The improvement in the peripheral stress markers and scopolamine induced dementia by EA in the study indicates the adaptogenic and anti-amnesic properties of EA.

In a study related to anxiety treatment researcher (Ernest, 2006) gave 28 people of age group 28-50 yrs diagnosed with anxiety 50 mg daily of an herbal formula with Shankhapushpi as a primary ingredient. The patients were diagnosed with Walmyr Clinical Anxiety Scale (WACS). After six months of treatment, 91 percent of the patients felt reduced anxiety and 60 to 70 percent could sleep and concentrate better. Symptoms like nervousness also decreased.

In a pre-post, randomized, placebo-controlled study conducted by Cerevenka and Jahodar (2006), 30 patients with anxiety were given 30 ml of Shankhapushpi syrup daily for three months. Testing was done three times i.e. after 1 month, 2 months, and after 3 months of the treatment with the help of Hamilton Anxiety Scale (HAMA). After one month, their anxiety levels decreased by 20 percent, after 2 months the effect of treatment was more visible and the patients felt significantly better, after the third testing, the anxiety level of the patients was reduced by 56 percent. This was concluded that the herb Shankhapushpi is more effective when given for longer duration.

Gupta, Siripurapu, Ahmad, Palit, Arora, and Maurya (2007) studied purification of n-BuOH soluble fraction from the ethanol extract of Evolvulus alsinoides resulted in the isolation of two new compounds, 2,3,4-trihydroxy-3-methylbutyl 3-[3-hydroxy-4-(2,3,4-trihydroxy-2-methylbutoxy)-phenyl]-2-propenoate (1) and 1,3-di-O-caffeoyl quinic acid methyl ester (2) along with six known compounds, caffeic acid (3), 6-methoxy-7-O-beta-glucopyranoside coumarin (4), 2-C-methyl erythritol (5), kaempferol-7-O-beta-glucopyranoside (6), kaempferol-3-O-beta-glucopyranoside (7) and quecetine-3-O-beta-glucopyranoside (8). The structure of new compounds 1 and 2 were elucidated by spectroscopic analysis, while known compounds were confirmed by direct comparison of their NMR data with those reported in literature. This is the first report of the presence
of phenolic constituents in Evolvulus alsinoides. The isolated compounds 1-5 and 8 were screened for anti-stress activity in acute stress induced biochemical changes in adult male Sprague-Dawley rats. Stress exposure has resulted in significant increase of plasma glucose, adrenal gland weight, plasma creatine kinase (CK), and corticosterone levels. Compound 1 displayed most promising antistress effect by normalizing hyperglycemia, plasma corticosterone, CK and adrenal hypertrophy, while compounds 2 and 3 were also effective in normalizing most of these stress parameters, however compounds 4, 5 and 8 were ineffective in normalizing these parameters.

A study published in 2007 by Saeed, Bloch, and Antonacci examined the effect of herbal medicine Shankhapushpi on insomnia. Researchers gave 10 mg dose of diazepam (an anti-anxiety drug), a placebo, or one of several forms of Shankhpushpi to 25 albino rats. The rats that received an alcohol extract of Shankhapushpi slept for 74 minutes, significantly longer than those who were given the placebo (52 minutes) and only seven minutes less than those who took diazepam (81 minutes). Other forms of Shankhapushpi were not so effective.

These studies show that Shankhapushpi has the properties which help in reducing the anxiety and stress, along with leading to better sleep and other psychotropic effects.

An investigation was made to evaluate the role of Convolvulus pluricaulis root extract in the regulation of hyperthyroidism by Panda and Kar (2001). L-Thyroxine treatment was administered on 20 mice for 30 days. The increased serum concentrations of thyroxine (T4) and triiodothyronine (T3) were noted as a result. The activity of hepatic 5'-monodeiodinase (5'-DI) and glucose-6-phosphatase (G-6-Pase) was also enhanced. On the other hand, administration of the plant extract either alone or with L-T4, decreased serum T3 concentration and the activity of hepatic 5'-DI and G-6-phase, without marked alteration in hepatic lipid peroxidation, indicating the possible regulation of hyperthyroidism by the plant extract. It appears that the action of the plant extract on thyroid function is primarily mediated through the inhibition of 5'-DI enzyme activity.

Shankhapushpi has been found to play a very important role in learning, memory and other cognitive functioning. Following is the review of such studies:

Dubey, Pathak, and Gupta (1994) studied the confirmed effect of *Brahmi* (*Bacopa monniera*) and *Shankhapushpi* (*Convolvulus pluricaulis*) on memory and overall learning.
ability. Sixteen school going children (aged 10-19 years) selected on the basis of their poor educational performance were given these substances in doses of 200 mg daily. An equal number of children served as control and received only placebo. After six months of treatment, a significant improvement in memory was observed in the Shankhapushpi treated group. None of the children showed any adverse effects.

In an empirical study, Priyanka and Batra (2003) investigated the role of Shankhapushpi in memory enhancement. This was a pre-post double-blind, placebo-controlled parallel-group design based study. Sixty four subjects of age group 19-26 years were administered either Shankhapushpi or placebo for the period of 15 days and 30 days. The testing was done with the help of Forward Digit Span task and Backward Digit Span task, 30 words recall test and serial learning task before and after treatment. Results indicated that Shankhapushpi enhanced STM, LTM, Retrieval and storage of the treated group. T-values applied to pre-post scores were significant in all experimental groups at even 0.05 level of significance. The placebo group's score was found insignificant on all the tests in both the durations. The study indicated that even 15 days were enough to see the improvement due to administration of Shankhapushpi.

In another double-blind, placebo controlled multi-group study, Priyanka and Batra (2004) administered 3.5 gm/day of Shankhapushpi on 200 normal adults of age group 19-25 years. The participants were divided into 10 groups (5 controls and 5 experimental groups). There were 20 Ss in each group. The treatment was continued for different durations (i.e. 15 days, 30 days, 60 days, 120 days, and 180 days). Tasks taken were Forward Digits Span (FDS) and Backward Digits Span (BDS) taken from Wechsler Adult Intelligence Scale - Revised (WAIS-R), 30 words recall test, and serial learning task. A memory enhancement (of both STM and LTM) after the duration of 30 days was observed. Results of the treatments for 120 and 180 days were found to be the best. The improvement went on increasing with an increased duration of administration of Shankhapushpi. It was concluded that Shankhapushpi enhanced memory and cognitive functions such as attention, storage and retrieval capacity of short term memory and long term memory, speed of learning, encoding for items to get registered in LTM. A residual effect was also observed after 60 days of the administration of Shankhapushpi except the complex task of serial learning, up to 2 months only. For complex task a residual effect
after 120 days administration was observed up to 2 months. It is also very important to be noted that there was found no side effect of Shankhapushpi even used for longer durations i.e. 180 days or up to six months even in a single subject.

Dhingra and Valecha (2007) studied the effect of total ethanolic extract of Convolvulus pluricaulis Choisy on depression. The petroleum ether (25, 50 mg/kg), chloroform (25, 50, 100 mg/kg), and ethyl acetate (25, 50, 100 mg/kg) fractions were administered orally for 10 successive days to separate groups of 15 Swiss young male albino mice. The effects of the extracts on the mice’s immobility periods were assessed in the forced swim test (FST). The effects of reserpine (2 mg/kg i.p.), sulpiride (50 mg/kg i.p.), prazosin (62.5 microg/kg i.p.), and p-chlorophenylalanine (100 mg/kg i.p.) on the extracts’ antidepressant-like effect in TST was also studied. The findings suggested that chloroform fraction of the total ethanolic extract of Convolvulus pluricaulis elicited a significant antidepressant-like effect in mice by interaction with the adrenergic, dopaminergic, and serotonergic systems.

In a recent study, Nahata, Patil, and Dixit (2008) noted the significant improvement in learning and memory. The research was based on 23 albino rats of 100-120 gm of weight. The ethanolic extract of Convolvulus pluricaulis and its ethyl acetate, and aqueous fractions were evaluated for their memory enhancing properties. Two doses (100 and 200 mg) of the ethanolic extract, ethyl acetate, and aqueous fractions were administered on separate groups of animals. Activities using Cook and Weidley’s Pole Climbing Apparatus, passive avoidance paradigms and active avoidance tests were used to test the learning and memory of the animals. Both the doses of all the extracts significantly improved learning and memory. Furthermore, these doses significantly reversed the amnesia induced by scopolamine (0.3 mg). Convolvulus pluricaulis exhibited potent memory enhancing effects in the step-down and shuttle-box avoidance paradigms.

Batra (2008) investigated the effect of Shankhapuspi on mentally challenged population. 5 male mentally retarded Subjects from old-age-home in Rohtak were selected out of 20 such Ss on single and successive command tests in DRS-II (Dementia Rating Scale-2) by Steven Mattis. Selected subjects were those 5 Ss who could follow these commands. These Ss were administered upon FDS and BDS task to assess their

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short term memory. Quality of life scale by Meryl Brod was also employed. Now these Ss were given Shankhapushpi daily and retested after 10 days and 45 days. The results clearly showed an improved memory and wonderful quality of life. The Ss were also tested after 40 days of discontinuing the consumption of Shankhapushpi to study the residual effect.

Batra, Kumar, Rawat, and Batra (2008) conducted a study based on a sample of 20 Ss studying in IX and X was selected. They were given 3.5 g of Shankhapushpi powder for 40 days. These subjects were tested on FDS, BDS and Serial Learning Task before and after the administration of Shankhapushpi. The post test was taken after 20 and 40 days. Results indicated an improvement in both FDS & BDS. The number of trials taken in Serial Learning Task reduced. A retention test after 24hrs of Serial Learning Task was also taken in both pre & post testing. There was an improvement in the number of items recalled. These results indicate that the Shankhapushpi improves both the Short Term Memory and Long Term Memory. The rate of improvement after 20 days of consuming Shankhapushpi was higher than the rate of improvement between 20 and 40 days.

To conclude the review of various studies, although limited has proved that Shankhapushpi is hypotensive and tranquilizing. Its components like protein, glucose, fructrose etc. all are such substances that play an important role in cognitive functioning.

This background may now proceed towards the formulation of problem and hypotheses for the present research.