Effect of nutraceutical and psychological interventions on cognitive functions of healthy human subjects

Shriharsh1 V, Chauhan1 P, Singh2 AK & Attrey2* DP

1Amity Institute of Behavioural (Health) and Allied Sciences, 2Amity Institute of Seabuckthorn Research
Amity University Uttar Pradesh, Sector-125, Noida-201303, UP, India
E-mail: dpattrey@amity.edu

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Present study aims to evaluate the effects of nutraceutical and psychological interventions individually and in combination, on various cognitive functions of healthy human subjects. Twenty four healthy subjects were recruited and subdivided into three intervention groups, i.e. nutraceutical, psychological and combined. Pre- (base line) & post-intervention performance levels of all the subjects were established for each cognitive function using neuropsychological tests. These were further compared to understand the effect of interventions on the cognitive functions. A polyherbal liquid formulation was administered as Nutraceutical Intervention. Twelve sessions of Cognitive Behaviour Therapy were given as Psychological Intervention. Combined intervention consisted of Nutraceutical & Psychological Interventions together. All the interventions were administered for a period of 3 months each. Results of the study indicate significant improvement in overall memory and attention in all the intervention groups. Immediate memory was also found to be improved significantly in psychological and combined intervention groups. However individual pre and post analysis indicated improvement in immediate memory in most of the subjects in all the intervention groups Combined intervention has shown significant improvement in all the cognitive functions except in cognitive processing speed, planning and organizing abilities. The findings of present study, thus, indicate that the nutraceutical and psychological interventions (used in this study) are likely to have positive influence on the cognitive functions of healthy human subjects. However, better results were obtained when used in combination.

**Keywords:** Polyherbal formulation, *Bacopa monnieri*, *Centella asiatica*, *Hippophae rhamnoides*, Cognitive function

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Cognitive functions enable us to know and gather information about our surroundings. The common cognitive functions are attention, comprehension, thinking, memory, problem solving, etc.1. Cognition can be affected by a number of factors like ageing, hypertension, Parkinson’s Disease (PD), Alzheimer’s Disease (AD), Schizophrenia, Cancer and HIV, etc.2-3.

Cognitive impairment is one of the major clinical problems, occurring in almost half of the population aged over 65 yrs. Due to complex & progressive nature of neurodegenerative disorders and lack of availability of suitable medicines in conventional therapy, use of herbal drugs seems to be more promising and acceptable4. Many medicinal plants have been reported in the Indian System of Medicine to improve memory functions5.

*Bacopa monnieri* (L.) Wettst. (BM) syn. *Herpestis monnieria* (L.) H.B. & K. is a small, creeping herb, commonly growing in marshy places throughout India, ascending to an altitude of 1,320 m. Stem obtuse-angular; leaves short-petioled, oblong-cuneate to obovate. 1.0-2.5 cm × 0.4-1.0 cm; flowers solitary, axillary, white or purple- tinged; capsules ovoid. It can be easily grown in damp areas and can be propagated by seed and also vegetatively. The entire plant constitutes the well known drug *Brahmi*. It is astringent, bitter and cooling, and is reported to improve the intellect. It is used in the indigenous systems of medicine for the treatment of asthma, hoarseness, insanity, epilepsy and as a potent nerve tonic, cardiotonic and diuretic. A clinical report showed that this drug is an anti-anxiety agent having adaptogenic effect.

The drug is one of them, which has been used to promote memory and to treat psycho neurological disorders. This plant has been studied extensively for its memory/cognition-enhancing activities. It is a well known drug in the Ayurvedic medical tradition in
India, and is used in many Ayurvedic herbal preparations. It has been traditionally used to treat asthma, insanity, epilepsy, and as a nerve tonic, cardiac tonic, and diuretic.

*Centella asiatica* (L.) Urb. (CA) is a prostrate, faintly aromatic, stoloniferous perennial herb, up 2 m long commonly found as a weed in crop field and other waste places throughout India up to an altitude of 600 m. Stem glabrous, pink and striated, rooting at the nodes; leaves fleshy, orbicular-reniform; crenate-dentate, base cordate and often lobed, long-petioled, smooth on the upper surface and sparsely hairy on the lower; flowers red, pink or white, in fascicled umbels; fruits oblong, dull brown, laterally compressed, pericarp hard and thickened, woody white.

The dug is another medicinal herb that grows in wet places throughout India. It is used in Ayurvedic preparations either as whole plant or as leaves in the fresh or extract form. In ancient Ayurvedic medicine, CA is reputed to restore youth, memory and longevity. Like BM, there are several reports indicating the use of CA in cognitive disorders. It has a long history of traditional uses in numerous medicinal systems dating back many centuries. In India, the plant has been used traditionally to treat dermatitis, diabetes, cough, cataracts and other eye conditions, and to improve memory.

Seabuckthorn (*Elaeagnus rhamnoides* (L.) A. Nelson syn. *Hippophae rhamnoides* L.; Family Elaeagnaceae) is a dioecious, usually spinescent shrub or a small tree up to 40 ft high with rough brown bark, occurring in the river beds of the drier ranges of the North-western Himalayas at altitudes of 7,000-12,000 ft. Leaves small, linear-lanceolate, covered on both sides with silvery scales; flowers very small, greenish or yellowish, appearing with new leaves: male in axillary clusters, female solitary; fruits enclosed by succulent receptacle, ovoid, c. 0.25 in. long, orange-yellow or scarlet; seeds oblong, testa crustaceous, shiny.

The drug has also been reported to show beneficial effects on cognition besides exhibiting unique properties of being an excellent antioxidant, immunomodulator and anti-inflammatory. Medicinal effects of Seabuckthorn have been suggested to be due to the presence of high antioxidant contents. It has a rich history of use in treating numerous medical conditions. It has been called a wonder plant in many Asian countries, including China, India, and Pakistan. Ancient Tibetan medical literature documents the use of this plant for fever, inflammation, toxicity, abscesses, cough, colds, clearing sputum, laxative effect, tumors (particularly in the stomach and oesophagus), and gynaecological diseases.

All the three plants used in this study have history of traditional use. They have been investigated scientifically for validation of their traditional claims from quite a few decades not only in India but almost all over the world.

There are several studies related to the clinical evaluation of effect of BM and CA extracts on various cognitive parameters. As per our knowledge, no such studies have been conducted on the use of SBT extracts for modulating cognitive functions in human subjects, except Dubey et al.

In view of the above, present study was carried out to assess and compare the effect of a polyherbal formulation (a nutraceutical formulation, prepared by using combined extracts of the above three plants) on various cognitive parameters of healthy human subjects with that of psychological intervention and also to see the effect of combined intervention, i.e. using both nutraceutical & psychological interventions simultaneously.

### Material and methods

#### Participants

Initially a sample population of 100 healthy individuals was identified for the study. After taking voluntary consent, 24 individuals (20 – 64 yrs) were selected through a screening tool consisting of 10 questions related to various cognitive functions to be examined. Prior approval of the human ethical committee was obtained to conduct the study as a part of a Research Project. The study was conducted in the pharmacy and psychology departments of the University.

#### Study design

Pre-Post experimental design was employed in this study. The selected subjects were randomly assigned to three experimental groups, viz. Nutraceutical Intervention (NI) group, Psychological Intervention (PI) group and Combined Intervention (CI) Group, each consisting of 8 subjects.

#### Independent variable (Interventions)

- **a. Nutraceutical Intervention (NI):** With a polyherbal nutraceutical formulation. Formulation was prepared in a GMP facility using simple syrup IP (66.67% w/v), as a base. Equal proportions of each
plant extract \[Bacopa monnieri\) (L.) Wettst. (BM), \[Centella asiatica (L.) Urb. (CA) \] and \[Elaeagnus rhamnoides \)(L.) A.Nelson syn. \[Hippophae rhamnoides\) L. (SBT)\] were added to the prepared syrup along with permitted additives. Standard extracts of BM and CA were procured from M/s Sanat Products Ltd, Sikanderbad, district Bulandshahar (UP). SBT extract was prepared and characterized in our laboratory, based on which the final SBT extract was prepared in a GMP certified facility.

**b. Psychological Intervention (PI):** Subject oriented intervention plan was prepared which consisted of 12 sessions of Cognitive Behaviour Therapy (CBT) @ 1 per week. This included the techniques such as identified cognitive errors, identified stressors, cognitive restructuring, desensitization, role play, stress burst out exercises, other exercises to improve cognitive functions (cognitive rehabilitation) and time management, etc.

c. Combined Intervention (CI): Both Nutraceutical and Psychological interventions simultaneously.

**Dependent variables (Cognitive Functions)**

These included Overall Memory (OM), Immediate Memory (IM), Delayed Memory (DM), Recognition (Rec), Cognitive Processing Speed (CPS), Executive Functioning (EF), Attention (At) and Planning & Organizing Abilities (POA).

**Procedure**

**Pre-Intervention/Base line scores**

These were established for all the subjects using various neuropsychological tests, viz. PGIMS (Post Graduate Institute Memory Scale) to measure OM\(^21\), TMT (Trail Making Test) A & B to assess CPS & EF respectively,\(^22\) LCT (Letter Cancellation Test) to measure At,\(^23\) PMT (Porteus Maze Test) to measure POA\(^24\) and RCFT (Rey Complex Figure Test and Recognition Test) to IM, DM & Rec,\(^25\) before the interventions. On the basis of pre-intervention/baseline standard scores, pre intervention/baseline performance levels (from 0 to 5 i.e. high to low); were established for all the subjects for all the cognitive functions.

**Note:** As the subjects were identified from the healthy population, the low scores on one or few of the cognitive functions did not indicate presence of any cognitive deficit as all the subjects were asymptomatic and their overall cognitive functions were intact.

**Intervention schedule**

Following baseline testing, each group was given interventions for 3 months as mentioned above. The NI group was given 10 ml of the polyherbal liquid formulation (containing 1.2 gm of combined extract) every day for three months. In the PI group, subjects were called individually for CBT. Each individual was given 12 sessions of CBT @ 1 hr/week. For the CI group, both the treatments (Nutraceutical & Psychological) were given in the similar manner simultaneously.

**Post-Intervention scores**

Post- intervention assessment of all the subjects was done to get raw scores on all the cognitive parameters. Further, these scores were converted in to post-intervention performance levels in the same manner as in case of pre-intervention analysis.

Thus, in various intervention groups, 8 individual were tested for 8 cognitive functions with the help of 6 Neuropsychological Tests. In this way two sets of results were obtained, viz. Pre- intervention performance levels and post intervention performance levels for each cognitive function of each subject. Pre- and post-intervention performance levels were compared to understand the effect of various interventions on the cognitive functions.

**Statistical analysis**

The Statistical Package SPSS 12.0 for Windows was used to analyze the data. Differences in the pre- and post-performance levels of the three intervention groups were analyzed using ‘Mean’ and paired \(t\) test analysis. Further, individual analysis was also carried out to compare the pre- and post- performance levels of same subject to see the effect of intervention individually also.

**Results**

After testing 8 individuals for 8 cognitive functions with the help of 6 neuropsychological tests in each intervention group, two sets of results, viz. Pre- intervention and post-intervention performance levels, were obtained for each cognitive function of each subject. Pre- and post-intervention performance levels were compared to understand the effect of various interventions on the cognitive functions.

Table 1 represents comparison of pre and post intervention performance levels of 3 groups on the basis of paired \(t\) test analysis. NI group showed significant improvement in OM and At whereas PI group showed significant improvement in OM, At and IM. However, CI showed significant improvement in all the parameters, except in POA.
Tables 2, 3 & 4 represent individual pre and post analysis for the 3 intervention groups.

Table 2 shows the results of the nutraceutical intervention on 8 cognitive functions among 8 subjects. Improvement/enhancement has been observed as under:

a. 4 subjects in OM (PGIMS)
b. 2 subjects in CPS (TMT A)
c. 2 subjects in EF (TMT B)
d. 4 subjects in At (LCT)
e. 4 subjects in POA (PMT)
f. 5 subjects in IM, 1 subject in DM and 4 subjects in Rec (RCFT)

It has been observed that there is no improvement in some of the cognitive functions of few individuals.

### Table 1—Paired t test analysis of pre- and post-performance levels of three intervention groups

<table>
<thead>
<tr>
<th>Cognitive parameters</th>
<th>Analysis</th>
<th>Group</th>
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<th>P</th>
<th>C</th>
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<td></td>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
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<td>Overall Memory (OM)</td>
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<td>3.969</td>
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<td>0.005*</td>
<td>0.017*</td>
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<td>Cognitive Processing Speed (CPS)</td>
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<td>0.033*</td>
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<td>Attention (At)</td>
<td>Mean</td>
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<td>1.5</td>
<td>3.125</td>
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<td>t value</td>
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<td>Sig. Level (p)</td>
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<td>0.019*</td>
<td>0.014*</td>
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<tr>
<td>Planning &amp; Organizing Abilities (POA)</td>
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<td>1.25</td>
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<td>0.875</td>
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<td>Immediate Memory (IM)</td>
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<td>Sig. Level (p)</td>
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<td>0.011*</td>
<td>0.003*</td>
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<td>Delayed Memory (DM)</td>
<td>Mean</td>
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<td>2.125</td>
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<td>t value</td>
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<tr>
<td>Recognition (Rec)</td>
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<td>t value</td>
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<td>Sig. Level (p)</td>
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<td>0.064</td>
<td>0.015*</td>
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</table>

*Significant improvement; ^Nutraceutical intervention group; ^=Psychological intervention group; ^Combined intervention group, i.e. Nutraceutical and psychological intervention simultaneously

### Table 2—Impact of nutraceutical intervention on various cognitive functions measured by 6 neuropsychological tests

<table>
<thead>
<tr>
<th>Subject</th>
<th>PGIMS</th>
<th>TMTA</th>
<th>TMTB</th>
<th>LCT</th>
<th>PMT</th>
<th>RCFT</th>
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<tr>
<td>No</td>
<td>OM</td>
<td>CPS</td>
<td>EF</td>
<td>At</td>
<td>POA</td>
<td>IM</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rec</td>
</tr>
</tbody>
</table>

(+): indicates Enhancement/Improvement; (=): indicates No improvement; (-): indicates Decline

PGIMS – Post Graduate Institute Memory Scale; TMTA – Trail Making Test A; TMTB – Trail Making Test B; LCT – Letter Cancellation Test; PMT – Porteus Maze Test; RCFT - Rey Complex Figure Test and Recognition Trial; OM – Overall Memory; CPS – Cognitive Processing Speed; EF – Executive Functioning; At – Attention; POA - Planning & Organizing Abilities; IM – Immediate Memory; DM – Delayed Memory; Rec - Recognition
in NI group (Table 2). A decline in existing cognitive performance level has also been noticed in 3 subjects (1 showing decline in CPS and Rec, 1 in IM and 1 in Rec).

Table 3 shows the results of PI on 8 cognitive functions among 8 subjects. Improvement/enhancement has been observed as under

- 7 subjects in OM (PGIMS)
- 2 subjects in CPS (TMT A)
- 2 subjects in EF (TMT B)
- 5 subjects in At (LCT)
- 1 subject in POA (PMT)
- 5 subjects in IM, 3 subject in DM and 5 subjects in Rec (RCFT)

It has been observed that there is no improvement in some of the cognitive functions of few individuals in PI group also (Table 3). A decline in existing cognitive performance level has also been noticed in 1 subject in Rec.

Table 4 shows the results of CI on 8 cognitive functions among the 8 subjects. Improvement/enhancement has been observed as under

- a. 5 subjects in OM (PGIMS)
- b. 3 subjects in CPS (TMT A)
- c. 4 subjects in EF (TMT B)
- d. 5 subjects in At (LCT)
- e. 3 subjects in POA (PMT)
- f. 7 subjects in IM, 7 subject in DM and 5 subjects in Rec (RCFT)

Table 3—Impact of psychological intervention on various cognitive functions measured through 6 neuropsychological tests

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>PGIMS</th>
<th>TMTA</th>
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<td>OM</td>
<td>CPS</td>
<td>EF</td>
<td>At</td>
<td>POA</td>
<td>IM</td>
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(+ indicates Enhancement/Improvement; (=) indicates No improvement; (-) indicates Decline
PGIMS – Post Graduate Institute Memory Scale; TMTA – Trail Making Test A; TMTB – Trail Making Test B; LCT – Letter Cancellation Test; PMT – Porteus Maze Test; RCFT - Rey Complex Figure Test and Recognition Trial; OM – Overall Memory; CPS – Cognitive Processing Speed; EF – Executive Functioning; At – Attention; POA - Planning & Organizing Abilities; IM – Immediate Memory; DM – Delayed Memory; Rec - Recognition

Table 4—Impact of combined intervention on various cognitive functions measured through 6 neuropsychological tests

<table>
<thead>
<tr>
<th>Subject No.</th>
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<td>CPS</td>
<td>EF</td>
<td>At</td>
<td>POA</td>
<td>IM</td>
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</tbody>
</table>

(+ indicates Enhancement/Improvement; (=) indicates No improvement; (-) indicates Decline
PGIMS – Post Graduate Institute Memory Scale; TMTA – Trail Making Test A; TMTB – Trail Making Test B; LCT – Letter Cancellation Test; PMT – Porteus Maze Test; RCFT - Rey Complex Figure Test and Recognition Trial; OM – Overall Memory; CPS – Cognitive Processing Speed; EF – Executive Functioning; At – Attention; POA - Planning & Organizing Abilities; IM – Immediate Memory; DM – Delayed Memory; Rec - Recognition
It has been observed that there is no improvement in some of the cognitive functions of few individuals in CI group also (Table 4). However, no decline has been observed in this Group.

**Discussion**

**Memory**

Results of present study indicate that the polyherbal formulation, used as nutraceutical intervention in this study, appears to enhance/improve Overall Memory (OM) in healthy human subjects when given orally for 3 months. Since, this formulation contains three plant extracts viz BM, CA and SBT, and all these plant extracts are having prior history of human use, especially for improving cognition, findings of the present study also support such other clinical studies\(^{9,15,26,27}\).

Further, much clearer picture emerges through individual analysis of NI group (Table 2), where in case of OM and Rec 50% (4/8, i.e. 4 subjects out of 8) and in case of IM & DM 62.5% (5/8) subjects were showing improvement. This indicates that polyherbal formulation may have a better positive impact on memory which needs to be investigated in more details further.

PI was found to show significant improvement in OM & IM (Table 1). Further, on individual analysis PI was found to show improvement in 87.50% (7/8) in case of OM, in 62.50% (5/8) in IM, in 37.5% (3/8) in case of DM and in 62.50% (5/8) subjects in case of Rec (Table 3).

CI was found to show significant improvement in OM, IM, DM and Rec (Table 1). In individual analysis also, CI was found to show comparatively better impact than the other two interventions on all types of memory investigated in the study like OM (5/8), IM (7/8), DM (7/8) and Rec (5/8) (Table 4).

From both types of analysis, i.e. the group and the individual analysis of all the three interventions, it appears that both NI & PI have positive impact on the memory parameters and that the memory can be comparatively improved further by the use of CI.

**Attention**

Jana *et al.* (2010) conducted a clinical trial using CA for 2 months. However, sample is consist of patients diagnosed with generalized anxiety disorder, the results showed enhancement in attention. After the use of CA extract, there were no side effects such as vertigo, nausea, dizziness or mental weakness\(^{28}\). Roxana *et al.* (2009) have also reported improvement in attention among middle aged healthy individuals due to use of CA extract\(^{27}\). In the present study also, all the intervention groups were found to show significant improvement in At and no side effect. Further in individual analysis, in NI group 50% (4/8) and in PI and CI groups 62.5% (5/8) subjects have shown improvement/enhancement in At.

**Planning and organizing abilities**

The individual analysis of NI & CI groups has shown improvement in 37.5% (3/8) human subjects (Tables 2 & 4). However, in PI group 12.5% (1/8) subjects showed improvement (Table 3). Whereas, for POA, none of the intervention groups showed significant improvement (Table 1).

**Cognitive processing speed and executive functioning**

Neither NI nor PI was found to show any significant improvement in these dimensions (Table 1). Further, even the CI showed significant improvement in 1 case only in executive functioning (Table 1). Individual analysis shows that both CPS & EF were improved in 25% subjects (2/8) in NI group (Table 2). Stough *et al.* (2001) has also reported improvement in CPS in a study using standard BA extract on the healthy human subjects\(^{27}\). Roxana *et al.* (2009) found improvement in EF after using CA\(^{27}\).

In the present study, PI (Table 3) also showed equal improvement (2/8, i.e 25%) as in the case of NI. However, in CI group, more subjects were observed to be benefited 37.5% (3/8) for CPS and 50% (4/8) for EF (Table 4). These results indicate that improvement/enhancement was equal in case of both NI & PI. However, CI has shown comparatively better improvement. Thus, the results indicate that NI exerts significant positive influence on OM & At; PI on OM, At & IM and the CI on OM, EF, At, IM, DM & Rec.

Individual analysis also indicates that NI has a higher positive influence on DM and IM (5/8); OM, Rec and At (4/8) while POA (3/8), CPS & EF (2/8) have also shown some improvement. Hence it appears that polyherbal formulation (NI) is likely to exert positive influence on some of the cognitive functions.

As is evident from Table 3, PI has shown more positive influence on OM (7/8), IM, Rec & At (5/8) and has also shown some improvement in DM, CPS & EF (2/8) and in POA (1/8). These results are indicative of positive influence on cognitive functions due to psychological intervention.
The individual analysis of results of CI (Table 4) indicate a higher positive influence on DM, IM (7/8); OM, Rec, & At (5/8). EF (4/8), POA & CPS (3/8) has also shown some improvement.

Thus, the above results are indicative of positive influence on the cognitive functions due to CI, which were better than the NI and PI individually.

It has also been observed that there is no improvement in some of the cognitive functions of few individuals in all the intervention groups (Tables 2, 3 & 4). However, out of 24 subjects in 3 experimental groups, 4 subjects have also shown an unexplained decline in the existing cognitive performance levels. In NI 1 subject showed decline in CPS & Rec both, 1 subject showed decline in IM and 1 in Rec. However, these 3 subjects of Nutraceutical group have shown improvement in EF (TMTB) and OM (PGIMS) simultaneously. In PI group only 1 subject has shown decline in Rec. However, the same individual has shown improvement in OM (PGIMS) simultaneously. None has shown any decline in the combined intervention group.

We can draw the following inferences from the above results:

a. Overall memory and attention have shown significant improvement in all the intervention groups.

b. In all the intervention groups there is improvement in immediate memory in most of the subjects. In Individual analysis, however, paired t – test reveals significant improvement in psychological & combined intervention groups but no significant improvement in NI group (p=0.06).

c. Significant improvement has not been observed in any of the intervention groups in cognitive processing speed and planning & organizing abilities.

d. Combined intervention has been observed to show significant improvement in all the cognitive functions except in cognitive processing speed and planning & organizing abilities.

Although enhancement/improvement in some of the cognitive functions due to various interventions has been indicated clearly, yet it is a matter of discussion whether the modulation observed in cognitive functions, as a result of intervention with the polyherbal formulation, is due to the individual effect of BM, CA or SBT extracts or their combined effect.

### Traditional significance of study to the researchers

Present study is based on the psychological observation of the effects of a polyherbal formulation based on 3 medicinal plants having history of medicinal use. It also compares the effects of this polyherbal formulation with psychological therapies and also with the combined effects of both. Findings of the present investigation support the traditional claims of these 3 plants. They also suggest that a larger sample size can be used for further scientific validation. Moreover, comparison of individual effects of these 3 plants can also be done through quantitative mode of investigation. Further, they can be investigated for understanding the mechanism of action. In view of all these things, it can be said that the findings of this study explore many ideas to be work upon for researchers.

### Conclusion

The findings of present study provide an indication that the nutraceutical (polyherbal formulation) and psychological interventions (used in this study) are likely to have positive influence on the cognitive functions of healthy human subjects. But, on combination they are likely to be more effective. However, these results are preliminary and need to be validated further using large sample size.

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