DISCUSSION

Depression is a dreadful disease, which not only affects the individual creativity, but also disturbs basic natural balance of inter personal relationships at social level. The origin of depression is in the evolutionary process of human beings. Whenever man failed to accomplish the next step of evolution, he was affected by the natural emotion ‘depression’. Still he proceeded and struggled with all the adverse factors came on his way of development. But when the conditions made him so helpless, he started getting disabled, lost his interest towards all worldly pleasures which he previously enjoyed and this persistent ‘melancholy’ was named as ‘depressive disorder’. W.H.O. reports that it will be Second largest disorder all over the world by the year 2020. Full credit goes to throat cutting competition of modernization, improper life style and dietary habits. This disorder has threatened the modern world and forced the scientists to search the solution to ‘increase happiness’.

Since Chittavasada is not evident with any specific signs symptoms; clinical features inferred from the various definitions of Vishada and Avasada given by commentators in the classical texts were used as subjective criteria of Chittavasada. Another important thing noted was regarding the difference between the two synonyms ‘Avasada and Vishada’. A critical analysis of the literature revealed the basic components behind mentioning two different terms for depression. Vishada is mentioned in the list of Vataja Nanatmaja Vikara by Charaka and with special reference to imbalance of Vata dosha at various places in the classics. Chakrapani stated it as happening due to depletion of Vata dosha in the body. Although it is mentioned in the classics that depleted Dosha can’t produce a disease, it is an obvious thing that they have the potential to disturb the Samya avastha (homeo stasis) in the body. And this Dosha Vaishamya (named as Vyadhi) if remain persistent can lead to a full formed disease. Thus the principle of treatment in Vishada can be Shamana chikitsa which will correct the imbalance of dosha without aggravating others. On the other hand, Avasada is one of the Kapha vriddhijanya Lakshana i.e. arose due to aggravation of Kapha dosha. It is also one of the indications for Shodhana karma (purificatory procedures). Thus vitiation of Kapha dosha is the main aetiopathological factor in Avasada. Its prime treatment will be Shodhana i.e. to eliminate first and then pacify the aggravated Kapha dosha.
According to recent advances, Neurochemical basis of depression lies in the depletion of Serotonin and Norepinephrine at the synaptic level. These neuro transmitters control various drives of mood, sex, sleep and appetite. Some eminent ayurvedic scholars tried to find the neurohumoral basis of the Tridosha theory (Singh et.al.). However establishment of such theory for depression will be a matter of debate and further critical study can be carried out in same direction. Another worth vile thing to mention here is about unique concept of Manas Prakriti described in Ayurveda. Ayurvedic scientists narrated the characteristics of Sattvika Rajasika and Tamasika manas prakriti depending upon the dominance of Manas guna respectively. Modern science is on the edge to find the genetic basis of each emotion through ultra modern technologies of Genomics and Proteomics. The concept of Manas prakriti can provide the expected direction for fundamental research in psychiatry. Thus this study has provided new scope for interdisciplinary approach in the development of Ayurvedic Psychiatry.

**Pharmacognostical & Pharmaceutical study:**

The microscopic characters of transverse section of flax seed show epidermis, pigment layer, cotyledon consist protein mass with aleuron grains and abundant globule of fixed oil. Histochemoical study of transverse section showed presence of lignified sclerides and oil globules in the cells of endosperm and cotyledon. Powder microscopic characters of flax seed include lignified sclerides, aleurone grains & fatty oil globules etc. Physicochemical parameters of flax seed revealed fixed oil content (42.05%), whereas the physicochemical parameters of flax seed oil revealed loss on drying (0.19 %w/w), Refractive index (1.48), specific gravity (0.92), Acid value (0.33), Iodine value (170.90), Saponification value (192.8). Thin layer chromatographic study of the unsaponified matter of flax seed oil showed the presence of seven and four spots in short UV, long UV respectively. The information generated by this particular study provides relevant pharmacognostical and physicochemical data needed for proper identification and authentication of flax seed and flax seed oil. The strength of single drugs and those of formulations at a later stage assumes importance for the effective enforcement of the provision of the Act. Though the groundwork requisites for the standardization of Flax seed oil are covered in the current study, quantitative analysis of Omega 3 fatty acids (ALA, EPA & DHA) which is the active chemical constituents of flax seed oil is required to be done additionally to substantiate the clinical study.
Pharmacological study

Recent researches in psychopharmacology approve the validity of animal models for studying the antidepressant effects of drug because of strong resemblance between stressed animals and depressed humans in terms of changes in the regulation of endocrine systems, changes in learning and memory, changes in histology of certain parts of the brain, changes in behavior and other changes between stressed animals and depressed humans. Therefore stress-induced brain changes in animal models of depression may validly represent the brain changes in humans and antidepressant induced changes in animal models may validly represent antidepressant mechanism in depressed humans. The potential association between omega-3 fatty acids and psychiatric disorders has received considerable interest. The family of omega-3 fatty acids includes alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), but it is unclear at this time whether there are differences in their potential roles in treating depression or other psychiatric disorders. Omega-3s promote transmission of the chemical messengers that facilitate communication between nerve cells and are associated with emotional stability (e.g., serotonin) and positive emotions (e.g., dopamine). Further it also affects brain derived neurotrophic factor (BDNF), which encourages synaptic plasticity, provides neuroprotection, enhances neurotransmission and has antidepressant effects.

Flax seed is the best plant source of omega 3 fatty acids which is rich in ALA which can be endogenously converted into EPA & DHA. Ashwagandharishta, an Ayurvedic classical formulation is the treatment remedy for Apasmara (epilepsy), Shosha (tuberculosis), Murchha (syncope), Unmada (Psychosis), Mandagni (poor digestive power) etc. Ashwagandha (Withania somnifera D.,) a main ingredient of Ashwagandharishta has antistress and anxiolytic activities. It works as antidepressant by enhancing 5 HT neurotransmission. So the objective of the present study was to assess the psycho-neuro-pharmacological profile of Flax seed oil and Ashwagandharishta on suitable experimental models. A range of parameters were employed to assess the CNS activity, anxiolytic activity and antidepressant activity, anticonvulsant activity etc. of
both the test drugs. Further, a possible protective role of flax seed oil was also assessed as an adjuvant to Ashwagandharishta. The study has provided the evidences for antidepressant, anxiolytic, anticonvulsant action of both Ashwagandharishta and flax seed oil. The data generated are carefully analyzed, interpreted and discussed below.

The efficacy profile observed with respect to different types of parameters employed during the study has been summarized in tabular form (Consolidated statements) for easy comparison in following paragraphs.

The following is the key to the abbreviations employed in the tables depicted below:

NSE - No Significant Effect, SD - Significant Decrease, SI - Significant Increase, NSI – Non Significant Increase, NSD - Non Significant Decrease; HSD – Highly Significant Decrease; HSI – Highly Significant Increase

1. Effect on gross behavior:

In this test, only features of CNS depression (hypoactivity) were observed in Flax oil treated group, Ashwagandharishta administered group and also in combined (Flax + Ash) group. The onset of hypoactivity was occurred at 1h of drug administration and persisted up to 5h. Surprisingly administration of milk (Vehicle) also showed features of CNS depression by exerting hypoactivity. However no previous research reports are available on CNS depressant property of milk, hence further research is needed to explore the exact cause. The CNS depression feature in terms of hypoactivity observed in flax seed oil may be due to influence of milk which was added as vehicle during administering as no previous reports are available to support the CNS depression activity of flax seed oil.

The ingredients of Ashwagandharishta like Ashwagandha (Withania Somnifera (L) Dunal.)\textsuperscript{10}, Haridra (Curcuma longa Linn.)\textsuperscript{11}, Daruharidra (Berberis aristata DC.)\textsuperscript{12}, Musta (Cyperus rotundus Linn.)\textsuperscript{13}, Krishna Sariva (Cryptolepis buchananii Roem. & Schult.)\textsuperscript{14}, Rakta Chandana (Pterocarpus santalinus Linn.f.)\textsuperscript{15}, Vacha (Acorus calamus Linn.)\textsuperscript{16}, Chitraka (Plumbago zeylanica Linn.)\textsuperscript{17}, Maricha (Piper nigrum Linn.)\textsuperscript{18}, Pippali (Piper longum Linn.)\textsuperscript{19}, Nagakesar (Mesua ferrea Linn.)\textsuperscript{20} are proven CNS depressants.
The exact mechanism behind the observed CNS depressant effect needs to be elucidated. The probable mechanism could be due to synapses block of the afferent pathway or due to the overall CNS depressant action\textsuperscript{21,22}. The ingredients present in the Ashwagandharishta may contain psychoactive substances that are CNS depressant in nature.

2. Effect on hypnotic potentiation:

Table – 1: Consolidated statement related to effect on hypnotic potentiation

<table>
<thead>
<tr>
<th>Hypnotic potentiation</th>
<th>VC</th>
<th>Flax + Milk</th>
<th>Ash</th>
<th>Flax + Ash</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Latency onset of sleep</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
</tr>
<tr>
<td>b. Duration of sleep</td>
<td>NSI</td>
<td>SI</td>
<td>NSI</td>
<td>SI</td>
</tr>
</tbody>
</table>

It is generally accepted that the sedative effects of drugs can be evaluated by measurement of pentobarbital sleeping time in laboratory animals. The prolongation of pentobarbitone hypnosis is a good index of central nervous system depressant activity\textsuperscript{23}. In the present study, Flax seed oil alone and Flax seed oil + Ashwagnadharishta administered groups significantly potentiated the pentobarbitone sleeping time. Further, when Flax oil was combined with Ashwagnadharishta, it showed better effect than that of individually given; evidencing the role of Ashwagnadharishta in potentiating the sedative effect of Flax seed oil. Prolongation of pentobarbitone-induced sleeping time might be due to tranquilizing action as well as CNS depressant action of both Ashwagandharishta and Flax seed oil. The observed sedative activity of these formulations may be through modulation of cannabinoid system or stimulation of inhibitory neurotransmitter like GABA or inhibition of neurotransmitter like dopamine. It is also possible that the effect may be mediated through inhibition of catecholaminergic receptors at discrete sites in the CNS. However this needs further detailed investigations.
3. Anti-depressant activity (Behavioral despair test):

3.1 Behavioral despair test:

Table – 2: Consolidated statement related to effect on behavioural despair test

<table>
<thead>
<tr>
<th>Behavioral despair test</th>
<th>VC</th>
<th>Flax + Milk</th>
<th>Ash</th>
<th>Flax + Ash</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immobility time</td>
<td>NSD</td>
<td>SD*</td>
<td>SD*</td>
<td>SD*</td>
</tr>
</tbody>
</table>

* - In comparison to both normal and vehicle control

The behavioural despair test was selected as the immobility displayed by rodents when subjected to unavoidable stress such as forced swimming is thought to reflect a state of despair or lowered mood, which are thought to reflect depressive disorders in humans. In addition, the immobility time has been shown to be reduced by treatment with antidepressant drugs. Further this model is valid for a broad spectrum of antidepressants mainly including tricyclics and MAO inhibitors, which significantly decrease immobility time in forced swimming test\(^{24}\). The test model is based on the observation that rats or mice when forced to swim in a restricted space from which there is no possibility of an escape, eventually cease to struggle, surrendering themselves (despair or helplessness) to experimental conditions. This state considered as the state of depression\(^{25}\). The depressant drugs increases immobility time, decreases swimming depending upon the concentration, type and time of administration of drug. Conventional anti-depressants drugs reliably decrease the duration of immobility in animals during this test. This decrease in duration of immobility is considered to be a good predictive value in the evaluation of potential antidepressant agents\(^{26}\). The successive 5 days treatment with the test drugs significantly reduced the duration of immobility of mice in comparison to both normal control as well as vehicle control groups. Further, the observed effect is much better in Flax alone treated group in comparison to Ash alone and Flax + Ash proving the Flax seed oil is a potent antidepressant drug.

Previous research has revealed that Ashwagnadha produces an anti-depressant and anti-anxiety effect in rodents comparable to the anti-depressant drug imipramine and the anti-
anxiety drug lorazepam (Ativan)\textsuperscript{27}. It acts as an antidepressant by enhancing 5-HT neurotransmission\textsuperscript{28}. Haridra (Curcuma longa Linn.)\textsuperscript{29} and Shunthi (Zingiber officinale Rosc.)\textsuperscript{30} are known antidepressants. Evidences have demonstrated that Berberine, an alkaloid isolated from Berberis aristata Linn possesses central nervous system activities, particularly the ability to inhibit monoamine oxidase-A, an enzyme involved in the degradation of norepinephrine and serotonin (5-HT)\textsuperscript{31}. Chronic treatment of piperine which is a constituent isolated from black pepper (Piper nigrum Linn.) or long pepper (Piper longum Linn.) enhances the serotonin level in the hypothalamus and hippocampus\textsuperscript{32}, Vacha works as potential antidepressant probably through interaction with adrenergic, dopaminergic, serotonergic and GABAergic systems\textsuperscript{33}. So antidepressant effect of Ashwagandharishta might depend on the augmentation of the neurotransmitter synthesis or the reduction of the neurotransmitter reuptake. Antidepressant properties might be mediated via the regulation of serotonergic system. Further the observed effect may be attributed to blockage of 5-HT reuptake or MAO inhibition. The conventional theories on mode of action of anti-depressant suggest that anti-depressants act either by inhibiting reuptake of monoamines or by inhibiting the breakdown of monoamines or by increasing the reuptake of serotonin\textsuperscript{34}. The neurobiological basis of depression lies in the imbalance of certain neurotransmitters such as 5-hydroxy tryptamine (5-HT), norepinephrine (NE) and dopamine (DA)\textsuperscript{35,36,37}. In depression these biogenic amines are so markedly depleted at presynaptic level that they could not perform their normal functions of regulating essential drives of appetite, sex, mood, sleep, emotions, reaction to stress, concentration and motivation. Mono amine oxidase (MAO) is a mitochondrial enzyme involved in the deamination of biogenic amines like adrenaline, NE, 5-HT and DA. Two iso-enzymes forms of MAO have been identified: 1) MAO-A preferentially deamines NE and 5-HT. It is found in peripheral adrenergic nerve endings, intestinal mucosa and human placenta and 2) MAO-B preferentially deaminates phenylethylamin and predominates in certain area of brain and platelets. Liver contains both isoenzymes. MAO inhibitor antidepressant drugs noncompetitively and irreversibly inhibit MAO, allowing NA, DA and 5-HT to accumulate in their respective neurons in brain and periphery\textsuperscript{38}. Thus the effective
antidepressant should inhibit degradation, enhance storage, block the reuptake and somehow maintain the normal level of amines at synapses\textsuperscript{39}. The other group of antidepressant i.e. Tri-cyclic antidepressant (TCA) inhibit active uptake of biogenic amines NA and 5-HT into their respective neurons and thus potentiate them. This results in increased concentration of the amines in the synaptic cleft in the CNS and periphery.

In nut shell, the anti-depressant activity of Ashwagandharishta is mediated either by enhancing serotonin and norepinephrine levels or by inhibiting their uptake and deamination by MAO at synaptic level, thus potentiating antidepressant effect. Comparatively administration of flax oil along with milk as vehicle showed better effect than that of Ashwagandharishta. The same mechanism may be involved in the observed activity profile and also as reported above omega-3 fatty acid affect brain derived neurotrophic factor (BDNF), which encourages synaptic plasticity, provides neuroprotection, enhances neurotransmission and has antidepressant effects. This may be attributed to observed better effect in this group.

3.2. Anti- reserpine test:

<table>
<thead>
<tr>
<th></th>
<th>VC</th>
<th>Flax + Milk</th>
<th>Ash</th>
<th>Flax + Ash</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catatonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1h</td>
<td>SD</td>
<td>SD</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>3h</td>
<td>NSD</td>
<td>SD</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>5h</td>
<td>NSD</td>
<td>NSD</td>
<td>NSE</td>
<td>NSE</td>
</tr>
<tr>
<td>Sedation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1h</td>
<td>NSI</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>3h</td>
<td>NSI</td>
<td>SD</td>
<td>NSI</td>
<td>NSI</td>
</tr>
<tr>
<td>5h</td>
<td>NSE</td>
<td>SD</td>
<td>NSE</td>
<td>NSE</td>
</tr>
<tr>
<td>Ptosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1h</td>
<td>NSE</td>
<td>NSD</td>
<td>SD</td>
<td>NSD</td>
</tr>
<tr>
<td>3h</td>
<td>NSE</td>
<td>NSE</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>5h</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
</tr>
</tbody>
</table>

Reserpine is a vesicular re-uptake blocker, which depletes catecholamines or lowers noradrenaline turnover in the brain to produce a depression like syndrome in animals\textsuperscript{40}. 
Discussion

Reserpine is a well known monoamine depleting agent that blocks transmission of monoamines in the synaptic vesicles. In the present study, Flax oil decreased the reserpine induced sedation and catatonia at 1st h and 3rd h whereas Ashwagandharishta and combined (Flax+Ash) group exerted their effect only at 1st h. Ptosis was antagonized only by Ashwagandharishta. Thus, the flax seed oil was proved a potent antidepressant even in reversing the reserpine induced effects. Anti-depressant effect of Ashwagandharishta and combined group was found to be time dependent. Since reserpine induced depressive state is found to be significantly reversed by Flax seed oil at all most all time intervals it is tempting to suggest that the drug acts by increasing the amount of biogenic amines at the synaptic cleft.

3.3. L- Dopa potentiation test:

<table>
<thead>
<tr>
<th>Intensity of activity</th>
<th>VC</th>
<th>Flax + Milk</th>
<th>Ash</th>
<th>Flax + Ash</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 minutes</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
</tr>
<tr>
<td>60 minutes</td>
<td>SI</td>
<td>SI</td>
<td>NSE</td>
<td>SI</td>
</tr>
<tr>
<td>90 minutes</td>
<td>NSI</td>
<td>NSI</td>
<td>NSI</td>
<td>NSE</td>
</tr>
<tr>
<td>120 minutes</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
</tr>
<tr>
<td>180 minutes</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
</tr>
<tr>
<td>240 minutes</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
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</tr>
<tr>
<td>300 minutes</td>
<td>NSE</td>
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<td>NSE</td>
</tr>
</tbody>
</table>

Catacholamines (CA) are known to be critically involved in motor activity. Both NA and DA appear to normally facilitate movement. L-DOPA the immediate precursor to both DA and NA enhances motor activation and both CA are involved in this effect, although an intact DA system is needed for all behavioural expression including that of NA systems. In the present study administration of vehicle (milk) itself caused significant L-Dopa potentiation at 60min. Similar set of observations were made in Flax + Milk and Flax + Ash treated groups. Both flax seed oil and Ash did not potentiate L-dopa induced behavioural changes in comparison to milk control group. It should be noted that both the vehicle and its combination with flax and Flax and Ash combination produced short lived potentiation. This shows that DOPA potentiation may partly contribute to the observed anti-depressant activity of the test formulations.
To summarize, flax seed oil when administered with milk as vehicle was found to be excellent anti-depressant activity in behavioural depression model as well as against reserpine induced depression. However it failed to exert similar effect in L-Dopa potentiation test. This may be because of dose and duration of its administration in the present study. The period of administration was not sufficient for drugs to exert the effect at lower doses in these clinically relevant models. Antidepressants generally require several weeks to exhibit their efficacy in clinical use, but the effect was evaluated with only 5 days of administration in the present experiment. Further contrary to our expectation, when flax seed oil was combined with Ash, comparatively lesser anti-depressant activity was observed in comparison to flax seed oil administered group. The reason for this may be related to pharmacokinetic aspects and is to be further elucidated.

4. Anti-psychotic activity:
The test formulations were evaluated for antipsychotic activity by noting their effect on d-amphetamine induced stereotypy in mice and were further tested in tunnel board instrument to ascertain their effect on exploratory behaviour of mice and the conditioned avoidance behaviour in cook’s pole climbing apparatus.

4.1. d-Amphetamine stereotypy:

<table>
<thead>
<tr>
<th>d-Amphetamine stereotypy</th>
<th>VC</th>
<th>Flax + Milk</th>
<th>Ash</th>
<th>Flax + Ash</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Rearing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20min</td>
<td>NSI</td>
<td>NSD</td>
<td>NSD</td>
<td>NSI</td>
</tr>
<tr>
<td>40min</td>
<td>NSI</td>
<td>NSE</td>
<td>NSE</td>
<td>NSD</td>
</tr>
<tr>
<td>60min</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
<td>NSD</td>
</tr>
<tr>
<td>120min</td>
<td>NSI</td>
<td>NSD</td>
<td>NSE</td>
<td>SD</td>
</tr>
<tr>
<td>180min</td>
<td>NSD</td>
<td>NSD</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>240min</td>
<td>NSD</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>b. Grooming</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20min</td>
<td>SI</td>
<td>NSD</td>
<td>NSD</td>
<td>SD</td>
</tr>
<tr>
<td>40min</td>
<td>NSE</td>
<td>NSD</td>
<td>NSD</td>
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</table>
**Discussion**

<table>
<thead>
<tr>
<th></th>
<th>NSI</th>
<th>NSE</th>
<th>NSI</th>
<th>NSI</th>
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<tr>
<td>120min</td>
<td>NSI</td>
<td>NSD</td>
<td>NSE</td>
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<tr>
<td>180min</td>
<td>NSE</td>
<td>NSD</td>
<td>NSE</td>
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<td>240min</td>
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**c. Sniffing**

<table>
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<tr>
<th></th>
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<th>NSD</th>
<th>NSD</th>
<th>NSD</th>
</tr>
</thead>
<tbody>
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<td>20min</td>
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<td>40min</td>
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<tr>
<td>60min</td>
<td>NSD</td>
<td>NSD</td>
<td>SD</td>
<td>SD</td>
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<tr>
<td>120min</td>
<td>NSE</td>
<td>NSE</td>
<td>SD</td>
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<tr>
<td>180min</td>
<td>NSD</td>
<td>NSD</td>
<td>SD</td>
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</tr>
<tr>
<td>240min</td>
<td>NSD</td>
<td>SD</td>
<td>SD</td>
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</tbody>
</table>

Inhibition of amphetamine induced stereotyped behaviour is a predictive test for antipsychotic action. There is considerable evidence which suggests that d-amphetamine is an indirectly-acting sympathomimetic agent whose stimulant actions are mediated by brain dopamine and noradrenaline. Thus, agents which interfere with the synthesis of these catecholamines have been shown to attenuate the stimulant properties of the drug. In addition, d-amphetamine increases the synaptic release of catecholamines and inhibits their subsequent re-uptake. D-amphetamine exerts its behavioural effects indirectly through its action on brain catecholamines. In the present study, Ashwagnadharishta significantly attenuated the sniffing at 60, 120, 180 and 240 min. as well as grooming at 180 and 240 min and rearing at 240 min. Flax seed oil significantly inhibited rearing and sniffing only at 240 min. When both the drugs were combined, results were encouraging as it mitigated rearing at 120, 240 min; grooming at 20, 120, 180 and 240 min. and sniffing at 60, 120, 180 and 240 min. Taken together, these results suggest that flax seed oil potentiated the effect of Ashwagandharishta in inhibiting the stereotype behavior induced by d-amphetamine although both the test drugs exert some common effects on the amphetamine behavioral response. The observed effect may be attributed to CNS depression by depleting the dopamine level in the CNS. It is also possible that drug may be having direct inhibitory effect on dopamine receptor. The exact mechanism requires to be worked out. However, this inference is to be made in the context that the combination has low level of DOPA potentiating effect which is short lived. This type of activity profile is not seen in either classical anti-psychotics or anti-depressants. This may be due to multi-component nature of the herb based formulations which may contain both types of active principles which may get expressed in particular given condition. If the activity profile can be obtained in clinical condition it would be a great advantage in treating bi-polar depression.
4.2. Conditions Avoidance Response test (Cook's Pole Climbing):

<table>
<thead>
<tr>
<th>Inhibition of conditional avoidance response</th>
<th>VC</th>
<th>Flax + Milk</th>
<th>Ash</th>
<th>Flax + Ash</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSE</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
</tbody>
</table>

Conditioned avoidance response (CAR) is one of most important preclinical animal models in the study of antipsychotic drugs (APDs). From a neurochemical perspective, it has been established that the blockade of the dopamine D2 receptor is strongly implicated APD-induced disruption of avoidance. In the present study, in Flax + Milk administered group inhibition of CAR was observed in 3/6 (50%) animals, while in both Ash and Flax + Ash administered groups inhibition of CAR was observed in 3/5 (60%) animals in comparison to both normal control and vehicle control group. Blockade of this response is attributed to blockade of post synaptic DA receptors in nigrostriatal and mesolimbic dopaminergic system. This test may be considered as further evidence for direct modulatory effect of test formulation component on dopamine receptor as shown in previous experiment.

4.3. Exploratory behavior:

<table>
<thead>
<tr>
<th></th>
<th>VC</th>
<th>Flax + Milk</th>
<th>Ash</th>
<th>Flax + Ash</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of diff. tunnels</td>
<td>NSI</td>
<td>NSI</td>
<td>NSD</td>
<td>NSI</td>
</tr>
<tr>
<td>entered in 1st min.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of diff. tunnels</td>
<td>NSI</td>
<td>NSE</td>
<td>NSI</td>
<td>NSD</td>
</tr>
<tr>
<td>entered in 5 min.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of tunnels</td>
<td>NSE</td>
<td>NSE</td>
<td>NSI</td>
<td>NSD</td>
</tr>
<tr>
<td>entered in 5 min.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

An apparent increase in the number of tunnels entered during first min was observed in vehicle and flax oil administered group in comparison to control group, the increase was however found to be statistically non-significant. Similar increase was also observed with respect to the number of tunnels entered during the 5 min observation period and total no. of tunnels entered in 5 min. Administration of Ashwagandharishta alone failed to show any impact on these parameters. However flax seed oil combined with Ashwagandharishta administered group shows an apparent increase in the number of tunnels entered during first minute and decrease in number of tunnels entered during the
5 min observation period and total number of tunnels entered in 5 minutes. This activity profile is contrary to the anti-psychotics activity profile most of which suppress exploratory behavior. The observed mild increase in the exploratory behavior may be indicative of locomotor activity. This may be as mentioned above may be due to the multi-component nature of the formulations.

Analysis of the data obtained from all the three experiments related to anti-psychotic activity clearly indicates that Flax seed oil has complex CNS activity in which mild to moderate anti-psychotic activity is one of the components. Though Ash alone has better anti-psychotic activity the activity is quite good in combination (Ash+Flax).

Evidence suggests that fatty acid deficiencies or imbalances may contribute to neurodevelopmental disorders warrants investigation on the therapeutic efficacy of omega-3 fatty acids in prodromal schizophrenia and other psychoses (Berger et al, 2006). A randomized, double-blind, placebo-controlled trial testing the effects of 1.5 g/day omega-3 fatty acids (0.84 g/day eicosapentaenoic acid, EPA; 0.7 g/day docosahexaenoic acid, DHA) administered as a supplement in 81 adolescents (mean age=16.4, SD=2.1, range=13-24 years) with sub-threshold symptoms at incipient risk for progression to a first-episode psychosis establish potentially important role for omega-3 fatty acids as treatment in sub-threshold states. In a recent study, researchers based in Australia, Austria and Switzerland sought to assess the impact of omega-3 fats in individuals deemed to be at very high risk of ‘psychotic disorder’ aged 13-25 (psychotic disorders are generally severe mental illnesses that include schizophrenia). Long chain ω-3 PUFAs reduce the risk of progression to psychotic disorder and may offer a safe and efficacious strategy for indicated prevention in young people with sub-threshold psychotic states. Flax seed being a rich plant based source of omega 3 fatty acids, may have contributed its therapeutic efficacy as a anti-psychotic, when combined with Ash it showed better activity profile, may be due to its enhanced bio-availability. The mechanism involved may be through modulation of central dopamine receptor or decreased DA transmission.
5. Anti-anxiety activity:

Table – 4: Consolidated statement on anti-anxiety activity

<table>
<thead>
<tr>
<th>1. Open field behavior test</th>
<th>VC</th>
<th>Flax + Milk</th>
<th>Ash</th>
<th>Flax + Ash</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Number of Square crossed</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
</tr>
<tr>
<td>b. Rearing</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
</tr>
<tr>
<td>c. Freezing time</td>
<td>SD</td>
<td>HSD</td>
<td>HSD</td>
<td>NSD</td>
</tr>
<tr>
<td>d. Pellet excreted</td>
<td>NSD</td>
<td>NSD</td>
<td>NSD</td>
<td>SD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Elevated plus maze test</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Latency of first entry to closed arm</td>
<td>NSE</td>
<td>NSE</td>
<td>SI</td>
<td>NSE</td>
</tr>
<tr>
<td>b. Time spent in open arm</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
</tr>
<tr>
<td>c. Number of entries from closed to open</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
</tr>
</tbody>
</table>

a). Effect on spontaneous motor activity (Open field behavior test):

The open-field model examines anxiety-related behaviour characterized by the normal aversion of the animal to an open, brightly lit area. Animals removed from their acclimatized cage and placed in a novel environment express anxiety and fear, by showing alteration in all or some parameters, such as decreases in ambulation and exploration, and immobilization or freezing due to augmented autonomic activity\textsuperscript{52}. In the OFT, the confrontation with the situation induces anxiety behavior in rodents. The anxiety behavior is triggered by two factors, i.e., individual testing as the animal was separated from its social group and agoraphobia, as the arena is very large, relative to the animals breeding or the natural environment. In such situations rodents show thigmotaxic behavior identified by spontaneous preference to the periphery of the apparatus and reduced ambulation\textsuperscript{53}. Anxiolytic treatment decreases this anxiety-induced inhibition of exploratory behavior.

In the present study, both the test formulations when administered individually as well as in combinations did not affect the number of squares crossed and number of rearing. Both the formulations when given individually significantly decreased the freezing time, however when given combined could not exert significant decrease in the freezing time. Both the test formulations when administered individually as well as in combinations apparently decreased the number of faecal pellets passed, however only the observed
effect in Flax + Ash combination is found to be statistically significant. This may be indicative of presence of anxiolytic activity with both Ashwagandharishta and Flax seed oil.

Open field activity is one of the behavioural assays of drug induced dopaminergic actions. Dopamine is mainly implicated in locomotor and exploratory activity and it has been repeatedly found that decreased activity in central dopaminergic systems of adult animals produced hypoactivity. This observation again is evidence for the effect of test formulation on central dopamine receptor or DA transmission or both. However in this experiment contrary to our expectation, Flax oil alone and Ash alone administered groups showed better result than that of their combination. Conversely, in combination they showed excellent anxiolytic activity by decreasing the fecal expulsion.

b). Elevated plus maze test: The elevated plus maze test is a well-established animal model for testing anxiolytic drugs. This is a model which uses the natural fear of rodents to avoid open and elevated places. The EPM test is based on a premise where the exposure to an EPM evoked an approach-avoidance conflict that was considerably stronger than that evoked by the exposure to an enclosed arm. The decreased in aversion to the open arm is the result of an anxiolytic effect, expressed by the increase in time spent and entries in to the open arms. In the present study administration of test formulations prior to exposure to elevated plus maze did not affect any parameter except in Ash alone given group in which significant decrease in latency of first entry was observed. This shows some kind of pro-anxiety effect of Ash. The results were compared to a group administered with the benzodiazepine lorazepam for anxiolytic activity.

Several partial agonists of 5HT1A receptors have been explored for potential utility both in anxiety disorders and in milder cases of mixed anxiety depression. The 5- HT 2c serotonin receptor is prominent in limbic forebrain and cerebral cortex. This receptor subtype has been postulated to be a reasonable therapeutic target for depression or anxiety. The possibility of Ash acting on 5-HT receptors cannot be ruled out. The conformation of this possibility requires further studies.
8. Anti-convulsant activity:

Table – 6.68: Consolidated statement on anti-convulsant activity

<table>
<thead>
<tr>
<th>Anti-convulsant activity</th>
<th>VC</th>
<th>Ash</th>
<th>Flax + Milk</th>
<th>Flax + Ash</th>
<th>RS</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Flexion</td>
<td>SD</td>
<td>SD</td>
<td>HSD</td>
<td>HSD</td>
<td>HSD</td>
</tr>
<tr>
<td>b. Extension</td>
<td>NSE</td>
<td>NSE</td>
<td>SD</td>
<td>NSE</td>
<td>HSD</td>
</tr>
<tr>
<td>c. Convulsion</td>
<td>NSD</td>
<td>NSD</td>
<td>NSD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>d. Stupor</td>
<td>NSD</td>
<td>SD</td>
<td>SD</td>
<td>NSD</td>
<td>HSD</td>
</tr>
<tr>
<td>% protection</td>
<td>7.65%</td>
<td>-</td>
<td>76.44%</td>
<td>7.48%</td>
<td>81.20%</td>
</tr>
</tbody>
</table>

The MES test is the most frequently used animal model for identification of anticonvulsant activity of drugs like phenytoin for the generalized tonic-clonic seizures\(^{59}\). The MES test serves to identify compounds which prevent seizure spread, corresponding to generalized tonic-clonic seizures in humans. This model is based on observation of the stimulation by repeated electrical pulses induce in different neuronal structures\(^{60}\). Phenytoin is effective in therapy of generalized tonic-clonic and partial seizures have been found to show strong anticonvulsant action by increasing brain content of GABA in MES test\(^{61,62}\).

In the present study, a significant reduction (p<0.05) in the time taken for post ictal depression was noted in Ashwagandharishta treated group of animals. It also shortened the flexion phase of MES induced seizures; but failed to decrease the tonic extensor phase. Various ingredients of Ashwagnadharishta have proven anticonvulsant activity. Ashwagandha (Withania somnifera Dunal) itself possess antiepileptic properties\(^{63}\). The major bioactive chemical principles of Withana somnifera appear to be the glycol-withanolides (WSG)\(^{64, 65, 66, 67}\). WSG has been shown to inhibit ibotenic acid-induced cognitive deficits in rats by reversing rat brain frontal cortical and hippocampal decreases in acetylcholine, choline acetylase and cholinergic muscarinic receptors produced by the neurotoxin and also exerts significant antioxidant effect in various rat brain areas, including striatum. The other ingredients of Ashwagadharishta like Cyperus rotundus\(^{68,69}\), Curcuma longa\(^{70,71,72,73,74}\), Terminalia chebula\(^{75,76}\), Acorus calamus\(^{77,78,79,80}\), Pueraria tuberosa\(^{81,82}\), Glycyrrhiza glabra\(^{83,84}\) are also proven to be effective against experimentally induced seizure models. Non-observation of significant anti-convulsant activity in this model with Ash may be due to the multi component nature of the formulation because of this the anti-convulstant principle may not be present in significant quantities.

Flax seed oil exhibited significant anti-convulsant activity by decreasing the duration of tonic extensor phase (p<0.05), flexion phase (p<0.001) and recovery time (p<0.05) with 76.44%...
Discussion

This observation confirms the protective effect of Omega 3 fatty acid against the seizures as reported earlier.\(^8^5\) It has been also reported that chronic treatment with omega-3 promotes neuroprotection and positive plastic changes in the brain of rats with epilepsy\(^8^6\), with a decreased in neuronal death in CA1 and CA3 subfields of the hippocampus. This could be attributed to n-3 PUFAs ion channel modulation\(^8^7,8^8,8^9\), and anti-inflammatory action. In in vitro studies, DHA (docosahexaenoic acid) has been reported to inhibit epileptiform activity and synaptic transmission mainly through the frequency-dependent blockade of Na+ channels in the rat hippocampus\(^9^0\), and to stabilize neuronal membrane by suppressing voltage-gated Ca\(^{2+}\) currents\(^9^1\) and Na\(^+\) channels.

Contrary to the expectations, pre-treatment with Flax seed oil as an adjuvant to Ashwagandharishta failed to decrease the tonic extensor phase, however it significantly decreased the flexion phase (p<0.001) and duration of the convulsion (p<0.05). The reason for this observation needs further investigations and also can be tried in other animal models representing epilepsy.

The present study reveals that Flax seed oils exhibits moderate anti-epileptic activity; while good anti-post-ictal depression effect was observed with both the test formulations. The observed anti-convulsant activity in Flax seed oil may be mediated through inhibition of voltage dependant Na+ channels or by blocking glutaminergic excitation mediated by the n-methyl-D-aspartate (NMDA) receptor. However further detailed investigations are needed to explore the exact mechanism involved. Further, both the drugs can play a major role as an adjuvant therapy with modern anti-epileptic drugs, however this needs detailed investigations.

9. Muscle relaxant activity:

Table – 6.69: Consolidated statement on muscle relaxant activity

<table>
<thead>
<tr>
<th>Muscle relaxant activity</th>
<th>VC</th>
<th>Flax + Milk</th>
<th>Ash</th>
<th>Flax + Ash</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage reduction in motor coordination</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
<td>NSE</td>
</tr>
</tbody>
</table>

The increased muscle tone is a common feature of anxiety states in humans. Thus the test formulations were tested for their effect on muscle coordination and balance in the rota rod test. Oral administration of test formulations did not produced any significant myorelaxant effect.
Thus,

- Flax seed oil + Ashwagnadharishta – exhibit hypnotic potentiation – mechanism involved may be - modulation of cannabinoid system or stimulation of inhibitory neurotransmitter like GABA or inhibition of neurotransmitter like dopamine or inhibition of catecholaminergic receptors at discrete sites in the CNS.

- Flax seed oil when administered with milk as vehicle was found to produce good anti-depressant activity in behavioural depression model as well as against reserpine induced depression, however when flax seed oil was combined with Ash, it showed comparatively lesser anti-depressant activity – Mechanism involved may be enhancement of serotonin and norepinephrine levels or by inhibiting their uptake and deamination by MAO at synaptic level.

- Flax seed oil has mild to moderate anti-psychotic activity, while Ash alone has better anti-psychotic activity. However the combination (Ash+Flax) shows good anti-psychotic activity. The mechanism involved may be through modulation of central dopamine receptor or decreased DA transmission.

- Ash alone and Ash+Flax exhibit anxiolytic activity - possibility of Ash acting on 5-HT receptors.

- Flax seed oils shows moderate anti-epileptic activity - may be mediated through inhibition of voltage dependant Na+ channels or by blocking glutaminergic excitation mediated by the n-methyl-D-aspartate (NMDA) receptor.

- Test formulations did not produce any significant myorelaxant effect.

- The presence of both anti-depressant and anti-psychotic is not common; presence of such an effect in the test formulations indicates that they may have potential benefit effect in the treatment of bi-polar depression in which both depression and mania are observed.
Survey Study:

While evaluating the consumption of dietary articles containing Omega 3 fatty acids, less numbers of depressive patients were observed consuming fish, egg, sesame seeds, almond, basil fresh, cloves, pepper, soya beans, green leafy vegetables, pumpkin, citrus fruits like orange, lemon and other fruits like kiwi, strawberry etc. compared to non-depressive healthy volunteer whereas more numbers of depressive patients were observed consuming deep fried foods, sweet articles, saturated fat containing articles like butter, ice cream etc. and trans fat containing articles like packaged snack foods, chips, buns etc., and cottonseed oil compared to non-depressive healthy volunteers which are known factors for hampering the conversion rate of ALA to EPA & DHA. But Omega 3 fatty acid deficiency can not be proved merely by saying that less no. of depressive patients were consuming Omega 3 articles and more no. of depressed subjects were habituated to consume the articles hindering the conversion rate of ALA to EPA and DHA. So for assessing the deficiency, frequency score and quantity score were developed for each article containing omega 3 fatty acids and articles hampering the conversion rate of ALA to EPA & DHA and by summing up both the mean score of consumption (M.S.C.) was calculated. Then M.S.C. of both depressed and non-depressed healthy subjects were compared by applying proper statistical tools. Thus, while evaluating the difference in mean score of consumption of dietary articles containing ω-3 fatty acids between depressed and non-depressed persons showed highly significant difference in consumption of dietary articles like egg, sesame seeds, almond, figs, all the spices (like basil fresh, cloves, pepper, fennel seeds), pumpkin, green leafy vegetables, tomatoes, mango, citrus fruits like orange, lemon and other fruits like kiwi, strawberry etc. evidencing that intake of these articles was in less amount by depressive patients in comparison to non-depressive healthy volunteers.

Along with being source of Omega 3 FA; these all articles are also the source selenium, zinc, tryptophan, anti oxidants, folic acid, serotonin, vit. B₁₂. Deficiency of these nutrients is also linked with depression as well as with the status of Omega 3 fatty acids.
Egg: Source of selenium\textsuperscript{92}, increases serotonin concentration\textsuperscript{93}

Almond: selenium\textsuperscript{94}, zinc\textsuperscript{95}, calcium & tryptophan\textsuperscript{96,97}, folic acid & Vit B\textsubscript{12}\textsuperscript{98}, source of dopamine\textsuperscript{99}

Walnut: selenium\textsuperscript{100}, tryptophan\textsuperscript{101}, increases serotonin\textsuperscript{102}, rich in Omega 3 fatty acids\textsuperscript{103}, contains glutathione\textsuperscript{104}

Cashew nut: Selenium & zinc\textsuperscript{105}, tryptophan\textsuperscript{106}

Figs: zinc\textsuperscript{107}, tryptophan\textsuperscript{108}, moderate serotonin concentration\textsuperscript{109}

Sesame seeds: high in zinc\textsuperscript{110}, magnesium, calcium which helps in serotonin production\textsuperscript{111}, source of dopamine\textsuperscript{112}

Fennel seeds: tryptophan\textsuperscript{113}

Cabbage: selenium, zinc\textsuperscript{114}, vit B12 & folic acid\textsuperscript{115}, rich in vit C

Green leafy vegetables: vit B\textsubscript{12} & folic acid\textsuperscript{116}, calcium & magnesium\textsuperscript{117}

Tomatoes: serotonin\textsuperscript{118}, folic acid & glutathione\textsuperscript{119}

Citrus fruits: selenium\textsuperscript{120}, folic acid\textsuperscript{121,122}, magnesium, Calcium & vit C\textsuperscript{123}

Kiwi: Serotonin\textsuperscript{124}, calcium & folic acid\textsuperscript{125}
Zinc deficiency:
A number of studies have shown that zinc levels are lower among patients with depression and a recent study found that 25 mg zinc supplementation may improve depressive symptoms\textsuperscript{126}.

Selenium deficiency:
Lowered levels of selenium have been associated with negative mood scores in at least 5 studies. Selenium plays a significant role in the human antioxidant defense system. In addition, selenium deficiency can interfere with the normal conversion of ALA into EPA and DHA, and results in an increase in the omega-6:omega-3 ratio\textsuperscript{127}.

Folic acid deficiency:
Regarding folic acid, a growing body of research has documented the low levels of folic acid among patients with depression. In addition, there are small clinical trials showing a beneficial effect of folic acid in depression, and its ability to enhance the effectiveness of antidepressant medications at just 500 mcg. Folic acid has been shown to increase omega-3 status when supplemented, and decrease omega-3 status when it is in deficiency in the animal model. In addition, a folic acid deficient diet can enhance lipid peroxidation. Higher levels of serum folate have been linked to fewer mood swings and negative moods. High folate levels can improve other depression treatments.

Antioxidants:
In patients with MDD there are in fact signs of oxidative stress and lipid peroxidation. A recent human study found that depressive symptoms are independently correlated with lipid peroxidation. Dietary antioxidants are known to influence the antioxidant defense system, and new research suggests that dietary antioxidants can influence omega-3 status. Omega-3 fatty acids have been shown to decrease lipid peroxidation in vivo, and antioxidant supplementation can prevent the negative influence of saturated fat on BDNF levels and cognitive function in animals.

Vitamin B\textsubscript{6}, Tryptophan, Serotonin
Tryptophan is a precursor of Serotonin. Tryptophan derived form food is transported to the brain to make the neurotransmitter serotonin. At the appropriate place inside a brain cell, two enzymes and vit B6 transform tryptophan to serotonin\textsuperscript{128}.
Omega 3 Fatty acids

Essential fatty acids necessary for serotonin production are the Omega 3’s\(^{129}\). Thus, Omega 3 fatty acid deficiency may lead to depression by hampering serotonin production.

Deficiency of nutrient co-factors that support function of conversion enzymes are vitamins B3, B6, and C, plus minerals zinc and magnesium\(^{130}\) so deficiency of these nutrient co factor contributes in hampering the conversion of ALA to EPA & DHA and ultimately leads to depression.

While evaluating the difference in mean score of consumption of dietary articles interfering with the conversion of ALA to EPA & DHA between depressed and non-depressed persons demonstrated highly significant difference in consumption of dietary articles containing saturated fat like butter, ice-cream and trans fat like packaged snack foods, chips, buns, deep fried foods like bhajiya, bread rolls etc. and sweet articles substantiating that intake of these articles was in more amount by depressive patients in comparison to non-depressive healthy volunteers.

Sweet:
Overeating of carbohydrates and sugars can lead to decreased sensitivity to serotonin, leading to negative mood and physical side effects like obesity.

Saturated fat - Trans fat
Fats compete for the conversion pathways. Consumption of saturated and hydrogenated fats cause a double whammy to body’s ability to convert good fats to DHA and EPA.
Trans-fatty acids (found in hydrogenated vegetable oils in shortenings, deep fat fried foods, and processed foods) cripple the conversion enzymes irreparably. Tissues have to manufacture brand new enzymes to replace those damaged by trans-fats.

Widespread use of cotton seed oil was noted in depressed subjects in their routine diet which leads to much greater intake of omega 6 to 3 fats. Since the conversion enzyme for Omega 3 & Omega 6 to their long chain metabolites are common; hogh intake of Omega 6 preoccupies these enzymes and they are remain no more available for converting
Omega 3 to their long chain fatty acids i.e., ALA to EPA & DHA. This imbalance can lead to the conversion enzymes getting used up for omega 6, restricting omega 3 conversion. The ideal balance is (depending who you talk to) around 3 to 4 parts omega 6 to one of omega 3.

Omega-3 fatty acids, and EPA in particular, are well documented inhibitors of proinflammatory cytokines such as IL-1 β and TNFα. In addition, it has recently been suggested that the anti-inflammatory role of omega-3 fatty acids may influence brain derived neurotrophic factor (BDNF) in depression. BDNF is a polypeptide that supports the survival and growth of neurons through development and adulthood. Serum BDNF has been found to be negatively correlated with the severity of depressive symptoms. Voluntary exercise can enhance BDNF, while diets high in saturated fat and sucrose, and psychological stress inhibit BDNF production.

While evaluating the life style factors, more numbers of depressive patients were found addicted to Alcohol, smoking and tobacco compared to non-depressive healthy volunteers. Researchers have made bold claims about cigarette smoking leading to depression. It has long been known that smokers have higher rates of depression than nonsmokers. There is a cause and effect relationship between smoking and depression in which cigarette smoking increases the risk of symptoms of depression. This linkage may arise from the effects of...
nicotine on neurotransmitter activity in the brain, causing changes to neurotransmitter activity and leading to increased risk of depression\textsuperscript{135}. Smoking causes depression because of the withdrawal from a physically and psychologically addictive substance, called nicotine. Nicotine which acts as a receptor for the neurotransmitter, acetylcholine, indirectly stimulates the release of another neurotransmitter, dopamine, in the brain’s reward or motivation center. Eventually the brain becomes so much adapted to the presence of the drug that it no longer functions normally without it. After 20-30 minutes of smoking the last cigarette, nicotine withdrawal begins. This leads to anxiety, which is very closely related to depression. Smoking as well as quitting smoking, both cause depression. Depression occurs when the smoker tries to abstain himself from smoking\textsuperscript{136}. Too much caffeine from coffee and tea and nicotine from smoking cigarettes and even sugar can set the body into a downward spiral of artificial stimulus that just results in an ever increasing psychological and eventual physiological addiction. The result is just more stress on your body and reduced chance of optimal conversion of DHA and EPA. They can lead to higher levels of insulin in the body another potential stumbling block for conversion. A number of studies have shown that alcohol abuse increases the risk for depression. This connection may be because of the direct neurotoxic effects of heavy alcohol exposure to the brain. Researchers know that heavy alcohol consumption can lead to periods of depression\textsuperscript{137}. Alcohol abuse also can have serious repercussions on a person's life, leading to financial and legal troubles, impaired thinking and judgment, as well as marital stress. Alcohol abuse poisons conversion enzymes.

History of stress, disturbed sleep, and sedentary life style was observed in more number of patients compared to non-depressive healthy volunteers. Stress is a total catch 22 situation for body. It is the constant state of emergency for energy which diverts the body’s focus from digestion, absorption, and complex nutrient conversion. The result is no matter how much flax one eats, but body could be too busy keeping one awake, heart beating, blood flowing with eyes open and ears listening to be bothered with converting omega 3 fatty acids ALA to DHA and EPA.
Lack of sleeping negatively affect brain neuronal signaling, including responds to serotonin. Sleep deprivation has been shown to desensitize serotonin pathways.

Very less numbers of depressive patients were spending time for mindful relaxation, hobby, recreational activities and doing exercise or any other physical activity compared to non-depressive healthy volunteers. In one research study meditation was reported to increase release of dopamine. Hobby, Recreational activities, Time for Mindful relaxation are the tools for self induced change in the mood. Researches have shown that self-induced changes in mood can influence serotonin synthesis. This raises the possibility that the interaction between serotonin synthesis and mood may be two way, with serotonin influencing mood and mood influencing serotonin. Exercise can boost moods and make one feels better may be through increasing serotonin. Several lines of research suggest that exercise increases brain serotonin function in the human brain. It increases extracellular serotonin and 5-HIAA in various brain areas, including the hippocampus and cortex. Moreover, it releases endorphins which elevates the mood. Persons following sedentary lifestyle and not doing exercise or any physical activity essentially shut off the supply of endorphins. Increased levels of exercise have been shown to increase neuron production, giving out brains better ability to utilize serotonin boosts and improve moods. Moreover, exercise also allows brain cells to function better by making them more flexible i.e., by neuroplasticity, leading to better responses to all neurotransmitters, including serotonin.

In the present survey study, depressed patients were found more deficient in ω-3 fatty acids offered by seeds and nuts, spices and fruits as highly significant difference was observed in ingestion of these articles between depressed and non-depressed persons (p<0.001). Moreover, they were consuming significantly (p<0.001) high amount of trans fat, deep fried foods and sweet articles in comparison to non-depressed healthy volunteers. Overall results of the survey shows that depressive patients were ingesting significantly less amount of ω-3 fatty acids compared to non-depressive healthy volunteers. Moreover, they were consuming significantly high amount of diet articles interfering with the conversion of ALA to EPA & DHA which makes them more prone to depression.
Clinical Study:

Total 130 patients were listed for the study. In which 40 received the trial drug Ashwagandharishta, 50 received Ashwagandharishta & Atasi Taila and residual 40 were managed with Atasi taila only. Among 40 patients in Group A; 35 successfully accomplished the treatment period and 5 had to withdrawn the study in between. In Group B; 45 completed the course of treatment and 5 were dropped out whereas in Group C; 20 completed and 20 dropped out.

Reason for Drop out

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drop out</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashwagandharishta</td>
<td>5/40</td>
<td>1 – fracture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1- cataract surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 – family problems</td>
</tr>
<tr>
<td>Ashwagandharishta + Flax oil</td>
<td>5/50</td>
<td>1 – H/o peptic ulcer developed hyperacidity*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 – H/o Prostatitis developed burning micturition*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 – Abdominal heaviness, bloating,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>decreased appetite**</td>
</tr>
<tr>
<td>Flax oil</td>
<td>20/40</td>
<td>7 – Abdominal heaviness, bloating,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>decreased appetite**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 – students due to tight schedule</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 – failed to turn up after 1st week so the reason is unknown</td>
</tr>
<tr>
<td>Reason: *Ushna, **Guru Properties of Flax seed oil</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

None of the patients reported Adverse Drug Reaction.

Moreover, Montgomery Asberg Depression Rating Scale, Hamilton Anxiety Rating Scale, Hamilton Rating Scale for Depression, Beck Depression Rating Scale and DASS – 21 were also used as subjective criteria in the work. S. cortisol which is a marker for stress and HsCRP - a marker for inflammation has been taken as biomarker for the depression in the present work. DSM IV criteria for Major Depression was taken as diagnostic criteria.
Critical analysis of Demographic data:

The major part of existing populace comprises of male (66.92%). This finding is in accordance with the previous study\textsuperscript{138,139,140,141} but contrary to general report revealing females are twice more susceptible for depression than males due to basic body composition\textsuperscript{142}. In general women tend to be more emotionally expression than men and therefore display sadness or unhappiness more easily than men. Therefore the incidence is reported more in women. But Males are prime bread winners of the society without whom there would be severe hardship to the family. They have to bear more mental and physical burden. Still males are the most responsible and productive persons in family as compared to females. As depression results in decreased productivity first, it is obviously more apparent in working persons. So it is possible that it may remain in recessive state, unrecognized and unreported in females. Males have high ambitions, worried regarding future and embarrassed for the settlement of their life which may lead them to the stressful situation resulting into the condition of Chittavasada (depression).

Depression can affect at any age, but incidence seems to be higher after age of twenty which is the beginning of self-realization of individual, familial and social responsibilities. In view to the age prevalence, maximum numbers of the patients were found in their 3\textsuperscript{rd} (25.38\%) and 4\textsuperscript{th} (32.31\%) decade of the life which is most vulnerable to depression due to various stressors like job crisis and economic problems etc. Social factors appear to place younger persons at greater risk that the elderly. Moreover, genetic factors may have their greatest influence at this age. According to Sharangdhar; Buddhi (intellect) starts decaying from 4\textsuperscript{th} decade of life. Thus, on one side, stress affects due to increased responsibilities, expectations for maximum productivity and on other side the body begins to show changes of declining adaptability which may contribute to depression.

People following Hindu ethnicity and believes were dominating in this study (96.15\%). But interpretation of this as people from Hindu community are more prone to develop depression will be certainly a false statement, as this prevalence of Hindu population in the present work is due to majority of Hindus in the general population of Jamnagar.
vicinity/Gujarat. But the lifestyle prototype and food trend followed by certain community from centuries can be the basis for prevalence of depression and similar condition in the same society.

Likewise, the study consists of more married people (74.62%) which is again in accordance with the previous studies carried out in this institute on depression. Marriage is the social system made for fulfillment of third principal object of life i.e. ‘kama’ by union of two opposite sexes. It can also provide highest emotional contentment and support at psycho-sexual plane throughout life time. Though matrimonial status is neither an etiological factor nor a risk factor for depression but still marriage is one of the positive stressors enlisted. It can affect in both positive and negative way on overall human being. Positively, this provides physical and mental satisfaction and support throughout the adversities which is most important in coping with stress but surplus amount of stress and increased familial responsibilities beyond capacity affect negatively in disturbed relationship and may drag both individuals towards depression. Married people require significant adaptation to other family members in sharing life moments which may drain psychological energy. In general, unipolar and biopolar depression occur more often in divorced and separated individuals or in persons who have impaired interpersonal relationship. On critical analysis, marital life of nearly 30% of the married patients was found disturbed in the present study due to various reasons like extra marital affairs of spouse, conflicts in interpersonal relationship, lack of understanding, no love, care and affection from spouse or other family members, no support from spouse, spouse being non-accommodative, irritable, suspicious and angry in nature. There were so many problems in their marital life and it was completely disharmonized which may be the core reason for present finding.

Educational status is a prime milestone formative of excellence and standards of any living population. In present study, most of the patients had good educational status. The patients who achieved their bachelor degree comprise the largest cluster (29.23%) in the present study populace. Researches indicate that highly educated people show high score of happiness than those with low education and they are enlisted in the list of most happy persons, means they have least stress or may be due to high education they learn the
Discussion

adaptation quickly so the depressive illness is more prevalent among low educated and illiterate. But present study seems limited to establish such relationship between education and depression. On the contrary, data of the present study reveals that depression was more common among graduated people and even severity of depression was found significantly more among them compared to illiterate depressed subjects. The present study revealed the odds of being affected by severe depression for Post graduated and middle educated patients about more 37 times of that of illiterate. The rate of severely depressed patients was 52 times for higher secondary educated and 126 times for graduated for that of illiterate. Thus, the severity was significantly high in graduated depressed subjects followed by higher secondary educated, middle educated and post graduated in comparison to illiterate depressed patients. Thus, there was positive relation found between education and severity of depression may be because with increasing education expectation of job etc. increases from others and of course from the self and if not fulfilled may drag patient with the more severity of the symptoms. Positive relation between education and severity of depression was established in the present study. One reason may be that educated people have more awareness of the symptoms of depression and they take it as mental health problem and use the mental health services. So may be the prevalence of depression is more in low educated people but because of lack of awareness about the mental health services and of course lack of knowledge of the severity of the disease (if remained untreated), the cases reported are few in number as compared to high educated people.

The difference in prevalence of depression in high educated and low educated people may be that the urban verses rural lifestyle has some basic differences in terms of timings of diet and work schedules. Rural life is observed to be less stressful, more nature prone & eco-friendly which may prevent the persons against the adverse effects of stress. Urban life is probably more stressful and less eco-friendly which makes person prone to various stresses and vulnerable to diseases like depression. One more reason is that highly educated people usually live in rich environments and sedentary living atmosphere or engaged with white color jobs due to which they are physically inactive and have to bear more mental pressure leading them more prone to mood disorder like depression.
In the present study, variety of work types are studied, as it was not limited to a specific working group. Housewives (25.38%), businessmen (22.31%) and servicemen (21.54%) were found more incidents in studied population. With respect to job satisfaction history, 54.28% patients were not satisfied with the work they were doing. Moreover, they had feeling of competition (42.31%). Work plays a great role in life as nearly one third of adult life is spent at work place, indulged in work. Being housewife, also involves the psyche and soma equally to maintain the family and perform duties within the stipulated time limit. In service and business professionals, the key holders are their bosses and customers to whom they have to satisfy for their bread and butter, which play the role of stressors in patient’s life. The work satisfaction directly relates with psychological and spiritual health, which has an impact on mental health. The content of work shows positive influence on overall performance of the individual. In the present study, the data is an indicative of negative influence of psycho-physical nature of work. Many studies have shown that stress at work place, discontent towards work lead to increasing stress and ultimately results into mental health disturbance.

Patients belong to middle socio-economic ranks were comparatively more (44.62%) in the study. Middle class is the strata in struggling and developing stage, which is expecting more to earn, more to work and has less for leisure. This stage is more prone to stress. Apparently, the time, awareness, and attention towards personal physical, mental, emotional and spiritual health is less to this community. This ultimately results in poor status of overall health and nutrition. Due to strive for development they invite a lot of physical and mental stress and make person prone to depression.

Maximum patients i.e., 23.08% were reported with chronicity between 1 to 5 years. and history of previous episodes of depression was found positive in 25.38% of the patients. Most of the patients think that their depression will be relieved as soon as the tragedy is alleviated. It is true that if the feeling of sadness is associated with a stressful life events in life, one could get out of it soon enough. However, if the depression is ongoing for 6 months or long, then the brain chemistry may have been changed as a result of persistent/prolonged sadness so one could be clinically depressed. Interestingly, animal
Discussion

research shows that whereas stress-induced changes in the hippocampus gradually reverse after the removal of the stress, stress-induced changes in the amygdala do not reverse for weeks or longer. In fact, the persistence of amygdalar changes may explain why depressed humans overreact to stress in a trait-dependent way, why current depression begets future depression, why life events have a cumulative effect in the predisposition to depression and even why physical and sexual abuse of children predisposes to depression during adult life.

Multiple logistic regression analysis to identify the socio-demographic risk factors associated with severity of depression demonstrated age, socio-economical status and educational qualification, occupation, Manasika prakriti, Sattva as important predictors for severity of depression.

Age: Severity of depression was significantly high in patients of age group between 60-70 yrs. as compared to patients between the age 15-30 yrs.

Occupation: severity of depression was significantly high in laborers in comparison to housewives, businessmen and servicemen

SES: The odds of being affected by severe depression for lower middle class is about 15 times of that for very poor.

Prakriti: Odd ratio shows that severity of depression was found more in patients of Pittaja prakriti followed by Kaphaja prakriti and then Vataja prakriti. Pitta prakriti persons are kleshasahishnu and they may hyper react to the mild pain or adverse situation due to less tolerance.

Sattva: The rate of severely depressed patients was 4 times more in avara sattva compared to madhyama sattva, odd ratio is 4.178 (95% CI, 1.194 to 14.62). Persons with Avara sattva are susceptible to fear, grief, greed, delusion and ego.

Thus, the data of the present study reveals significant relationship between severity of depression and different socio-demographic factors.
Family history of psychiatric illness was found positive in 22.31% of the patients. Genetic risk factors for depression produce a “prekindling” effect rather than increase the speed of kindling. The “kindled” state, wherein depressive episodes occur with little provocation, may be reached by two pathways: many previous depressive episodes, perhaps driven by multiple adversities, and high genetic risk\textsuperscript{144}. It has been reported that genetic factors are of less significance in patients presenting with depression for the first time later in life. Case controlled familial study done by Maier et al\textsuperscript{145} 41 clearly established that late onset depression (LOD) has a higher familial risk than age matched controls but this familial risk was less than that seen in early onset depression (EOD). Those with a parent or sibling who has had major depression may be 1.5 to 3 times more likely to develop the condition than those who do not\textsuperscript{146}. Just because a person inherits a gene that predisposes him or her to a depressive illness, it does not mean that he or she is destined to develop major depression or bipolar disorder. It is believed that a genetic influence is only partially responsible for causing depression. Other factors may also play a role. One possibility is that individuals learn to adapt to their strengths and weaknesses, and in mid-life quell their infeasible aspirations.

**Dashavidha Pariksha**

In Dashavidha pariksha, *Sharirika Prakriti*wise, maximum no. of the depressive patients were found with *Kapha-Pitta prakriti* whereas at *manasika prakriti* level, maximum numbers of depressive patients had *Raja-Tama* followed by *Tama-Sattva prakriti* proving the involvement of *Kapha* and *Tama* in aetiopathogenesis of depressive illness. Maximum patients of depression were found having Kapha-pitta prakriti (25.38%) which is in accordance with the concept that the persons are more affected to the disease of their own prakriti and as discussed before Chittavasada – depression is a kaphaja disorder. Maximum patients of depression were of Rajasika (46.92%) & Tamasika prakriti (30%). Rajas is related with Sanga i.e. affection towards the objects and Tamas with the Moha i.e. allurements of worldly things. Both are prime causative factors in Chittavasada capable of slowing various mental activities. The combination of Rajas & Tamas is as psychic constitution leads to most unstable state of mind. This composition disturbs mind and results into many psychiatric
disorders including depression. Maximum patients of depression in the present study were found having Avara sara (46.92%) followed by Madhyama sara (44.62%). Ojas is considered as the bridge between the mind and body. As an effect transformation on each other by body and mind is mediated through Ojas. Oja vriddhi leads to mental satisfaction and bodily good built. On the contrary in the patients of depression, Oja kshya is caused by many of the mental factors like chinta, bhaya, shoka, kroha etc. Oja being the essence of all dhatus, oja kshaya may represent patients of depression with Avara sara. Maximum patients of the present study had Avara sattva (69.23%). Patients having low mental capacity are unable to accomplish various competitive tasks and ultimately getting trapped by depression. The individuals having inferior mental faculties, neither by themselves nor through others sustain their mental strength and even if possessed of plump or big physique, they cannot tolerate even mild pain. They are susceptible to fear, grief, greed, delusion and ego.

**Dietary habits & Life style**

In the type of diet, maximum patients (90%) were pure vegetarians. This may be mainly due to studied population within a particular territory. Taking into account some considerations quote in ancient wisdom, Bhagavad Geeta quotes the relation between Ahaara and Sattva, Rajas and Tamas in mind\(^\text{147}\). The flashy food is related to increase Rajas and Tamas, which are stemmed at the causation of stress in psyche. Vegetarian diet increase Sattva-the good quality in mind which helps to cope up with stress\(^\text{148}\). In contrary to this, recent researches and modern literature shows quantity of essential nutrients for maintaining neurotransmitter balance at synaptic level is more in non-vegetarian diet\(^\text{149}\). A study reported a very strong negative correlation (r = -0.84) between fish consumption and major depression in a cross-national depression database\(^\text{150}\). It seems that whatever the type of diet it may be, the quality of diet and nutritious components will matter the most for preventing depression and increasing stress endurance at physical and psyche level because now a days omega 3 fatty acid deficiencies is linked with mood disorders.
Faulty dietary habits like vishamashana (54.62%), adhyashana (44.62%) were observed to be followed by majority of patients. The timing of taking diet was irregular and not specific in maximum cases. Ayurveda has deeply dealt with the effect of diet on body and mind by laying down certain rules of taking diet and dietary habits. It has also been quoted that the status of body and mind as well as the disease originates from and depends upon quality and quantity of diet. It has been quoted as “Vishamashanam Agnivaishamyakaranam” & “Ajeernaadhyashanam grahanidushtikaranam”. Thus not following the rules lead to impaired agni producing disease. It also deteriorates the digestion process, leading to poor nutrition to body tissues, landing into impaired health status and enhancing the risk of depression. Furthermore, in other way, stress may lead to worsening of condition forcing the patient to follow improper dietary habits. Stress and lifestyle adaptation has an influence on dietary habits and vice versa. Classical references are available pointing towards the result of faulty diet, poor quality diet as etiological factors for psychiatric and psychosomatic disorders. “Viruddhadushtashuchibhojanani…” i.e., incompatible, unhygienic food is the cause of Unmada. “Ahita-Ashuchibhojanat…” i.e., improper, unhygienic diet leads to Apasmara. Another quotation emphasizing on the calmness of mind while taking diet, states that the diet though taken in proper quantity and of good quality remain undigested, if the mind is in disturbed status of anxiety, grief, fear, anger etc. therefore for proper digestion, peace of mind is of utmost important. The present data shows the negative impact of improper diet and dietary habits to worsen pathology of depression.

Lack of exercise and absence of required physical activity was observed in maximum fraction (93.08%) of study populace. Exercise is known to increase the physical and mental endurance to stress (dukkhaha, Kleshasahishnuta). It has got a positive psychological benefit as Ayurveda quotes that it gives stability to body and mind. Many reports have noted the beneficial activity of exercise as anti-stress through its impact on neuro-endocrinal axis. Moreover it can show many health benefits on cardiovascular system, immune system, brain functions and depression. A study reports that frequent and regular aerobics exercise has been shown to help prevent or treat serious life
threatening chronic conditions such as high blood pressure, obesity, heart disease, type 2 DM, insomnia and depression\textsuperscript{159}.

Disturbed sleep (73.08\%) and insomnia (22.31\%) were some of the common problems related to sleep in the study subjects. Sleep is essential for good health and considered as one of the tree pillars of life. Nidra depends upon the natural retirement of mind and sense organs owing to fatigue\textsuperscript{160}. Improper sleep is a cause as well as effect of stress pushing person into a vicious cycle. As per the quotation “Ratrua Jagaranam Ruksam”, inadequate sleep can vitiate Vata-pitta dosha and kapha at physical level and at mental level, it can disproportionate Rajas, Tamas and Satva quality\textsuperscript{161}. Various study support the finding that improper sleep can adversely affect the physical as well as psychological functioning of the body\textsuperscript{162,163}.

**Impact of stressful life event on depression**

In the present study, an attempt was made to identify the core of stress, to detect the prevalence level of stressors. Assessment of stress through Holmes & Rahe’s Life Stress Inventory revealed that in 95.48\% of patients, the life events causing stress were positive. Among them, 4.61\% of the patients scored $\geq$250 whereas 22.31\% of the patients scored between 150-250 and 68.46\% of the patients scored <150. Stressful events traced out through this scale are: sleep less than 8 hours per night (67.69\%), change in financial state (64.62\%), work more than 40 hours per week (55.38\%), serious personal injury or illness (32.11\%) etc.

The influence of chronic stress and adverse life events on the development of depression has been subject of numerous investigations and the work has been influenced by studies of the somatic and endocrine consequences of stress in animals. Most findings show an excess of severely threatening events prior to onset, particularly for events categorized as exit events or undesirable events. Life events preceding depression are variable and are probably unrelated to the symptom pattern, which means that there is no clear cut difference in the presence of events provoking the onset of endogenous or non-endogenous depression. There is ongoing discussion on the impact of events on
A long standing clinical observation that has been replicated is that stressful life event more often precede first rather than subsequent episode of mood disorders. Some clinicians believe that life events play a primary role or principal role in depression whereas other suggest that life events have only limited role in the onset and timing of depression. The most compelling data indicate that the life event most often associated with a person later developing of depression is losing a parent before age 11 or loss of a spouse. The association between stressful life events and the onset of major depression decreases as the number of previous depressive episodes increases. The decline in the association between stressful life events and risk for major depression as the number of previous depressive episodes increased was strongest in those at low genetic risk and was weak to absent in those at high genetic risk. In the absence of previous depressive episodes, those at high genetic risk frequently experiences depressive episodes without major environmental stressors.

A number of studies have examined the hypothesis that exposure to stressful life events causes impairment in various aspects of cellular immune function, such as lymphocyte and natural killer (NK) cell activity\textsuperscript{164}. Concerning the underlying mechanism of this interaction, it is now well established that the immune system is a key mediator of brain–body interactions. Cytokines influence various CNS functions that are dysregulated in major depression, such as sleep, food intake, cognition, temperature, and neuroendocrine regulation\textsuperscript{165,166}. So along with the HPA axis dysregulation role of cytokines may explain the role of stress in depression.

Stress is the origin for all mental and physical disorders. Knowing this horrible factor, Charaka quoted\textsuperscript{167} “Aayasah Sarva Apathyanam Agyah” (Cha. Su. 25/40) which means stress is the foremost factor which is not to be followed. An earlier study reported positive history of psychological stress in 80.95\% of patients diagnosed with depression\textsuperscript{168}. This indicates the hazardous nature of stress in causing depression. Modern psychiatric research also shows the relation between stress and depression through disturbance of Hypothalamo-
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Pituitary-Adrenal (HPA) axis releasing more amount of cortisol- stress hormone in the blood. Enlightening the candle of happiness to overcome the darkness of depression is only possible after removing the underlying stress in the subconscious. Therefore the present investigation can be useful in determining influence of endogenous and exogenous stressors, response and adaptability of individual. This is important in preventing and treating stress related disease.

Childhood adversities & Depression

The 49.23% of the patients in the present study had complicated history of development and behavior in childhood. Many of them (18.46%) were not blessed with the love, care and affection of the parents due to parental conflicts and/or familial disruption, rather some of them (1.54%) had harassment from parents due to ill psychological health of the parents. Bereavement of either one or two parents was present in the childhood history of few patients (2.31%) and a very few patients (0.77%) had step mother. Prospective data from several cohort studies have also demonstrated a link between childhood adversity and depressive symptoms in adulthood. Early childhood adversity confers risk that persists beyond childhood. Research data shows that family disruption and low socioeconomic status in early childhood increase the long-term risk for major depression. Chronic adversity has been linked to disturbances in the hypothalamic- pituitary-adrenal (HPA) axis in children with depression; HPA abnormalities in major depression may also become more pronounced in adulthood\(^{169}\). Thus, reducing childhood disadvantages may be one avenue for prevention of depression.

Clinical features

The clinical picture of depressive syndrome is so varied that they cannot be described fully in a short space. Although severe depression is readily recognized it can be difficult to distinguish the milder forms of depression from the emotional changes that report of everyday life. Unlike most medical disorders, depression is not associated with any characteristic laboratory changes or microscopic tissue abnormalities that can be used to confirm a suspected diagnosis. The American psychiatric association has established diagnostic classification systems that allow consistent diagnosis of major depression.
Discussion

These criteria are contained in the revised fourth edition of a diagnostic and statistical manual of mental disorder (DSM - IV).

Various general symptoms of Diagnostic criteria for Major Depressive episode according to DSM-IV were affected to different extent in the patients registered in the present study. Among them Depressed mood and Anhedonia were present in maximum patients i.e., 98.46% and 97.69% of the patients respectively followed by Fatigue (93.85%), Inability to concentrate (90.77%), insomnia (72.31%), psychomotor agitation (56.15%), suicidal thoughts (56.15%), weight loss (26.15%), weight gain (22.31%), inappropriate guilt (26.92%), hypersomnia (16.15%) and these symptoms had produced clinically significant distress or impairment in social, occupational or other important area of functioning in 26.15% of the patients.

Mood disturbance:
Depressed mood: It always present in a mild or severe form. In its mildest form, the patient experiences a flattening of affect and as the depression increases, the patient is more miserable and unhappy. He becomes preoccupies with gloomy thoughts and tends to look on the dark side of things. Some patients conceal this mood change from other people, at least for short periods. The patient may try to hide his low mood during clinical interview, making it more difficult for the clinician to detect depression.

Anhedonia (loss of interest)
Loss of interest and an inability to enjoy are frequent, though not always complained of spontaneously. The patient showed no enthusiasm for daily activities and hobbies, that he would normally enjoy otherwise.

Psychomotor disturbances
Psychomotor retardation: It is frequent. The retorted patient walks and acts slowly. There is a slowness or difficulty in thinking, accompanied by a poverty of ideas, this leads to lock of concentration and indecisiveness. In severe forms, the patient’s activity is diminished the voice fades, and the speech an indistinct mumble and finally ceases, leading to mutism.
Psychomotor agitation: It is a state of restlessness which is experienced by the patients as an inability to relax. The patient is results and anxious, when it is mild and seems to e plucking
Discussion

his fingers and making restless movement of his legs. When agitation is severe, he can not sit for any length of time, but paces up and down.

Anxiety
It is also frequent, though not invariable, in moderately severe depression. Patients feel these, unable to relax, with difficulty in concentration and lack of affection. The anxiety is usually accompanied by somatic symptoms like dryness of mouth, palpitation, sweating, headache and giddiness.

Insomnia or Hypersomnia
Sleep disturbance is depressive disorder is of several kinds, the most characteristic of which is early morning (Insomnia delayed) awakening. However, insomnia initial and middle also occur. It is this combination of early morning awakening with depressive thinking that is important in diagnosis. In some depressed patients, hypersomnia rather than early morning awakening may occur, but they still report that the sleep was not refreshing.

Depressive ideation
Sadness of mood usually is associated with pessimism which commonly results in 3 common depressive ideas i.e., hopelessness (there is no hope in future due to pessimism), helplessness (no help is possible), worthlessness (feeling of inadequacy and inferiority).

Suicide
Suicidal thoughts are commonly present in depressive patient and they vary from mild to severe in intensity. Usually this symptom develops slowly and the risk of suicide is greater in men, older women and those living alone.

Guilt
The guilt feeling in depression varies from culture to culture. The underlying guilt is basically a feeling of inadequacy.

Somatic symptoms
Some somatic symptoms are characteristics of depression and may even come to dominate the clinical picture. Multiple physical symptoms like wariness of head, vague body ache are common in elderly depressives and depressive patients from developing country. Hypochondriac features may be present in up to a quarter of depressives presenting for
Discussion

These somatic symptoms are almost always present in severe depressive disorders; common symptoms are decrease appetite, loss of interest in work, dryness of mouth, constipation, loss of energy, fatigue, headache, loss of libido, erectile dysfunction etc.

Diurnal variation of symptoms
A diurnal variation of symptoms has long been recognized as a typical symptom of depression and is often present in endogenous depression as an early morning worsening of mood.

Psychotic features
Depressed patients have delusions, hallucinations, grossly inappropriate behavior or stupor. Psychotic features can be mood congruent (e.g., nihilistic delusions, delusions of guilt, delusion of poverty, stupor) which are understandable in the light of depressed mood or can be incongruent (delusion of control) which are not directly related to depressive mood.

Psycho-pathogenesis of Manasa Vibhrama

All these factors are regulated by psycho-neuro-endocrinial axis playing the main role in all this psychopathological tragedy of stress.
On examination of perversion of eight mental faculties in depression, it is revealed that mana (mind) and bhakti (desire) were perverted in maximum number of patients i.e., 93.08% and 90% of patients respectively followed by Smriti (memory) (54.62%), Shila (manner) (50.77%) and Buddhi (intellect) Vibhrama (48.46%) patients respectively. Sandnya (consciousness) was observed in 42.31% while Cheshta (conduct) and Aachara (behavior) vibhrama in 24.62% patients each.

The incidence may be rooted to prajnaparadha, dietary and life style etiological factors. This is also indicative of psychopathology disturbed at physical and psychic level and treatment attention is needed in this direction. Going through the psycho-pathogenesis of these perversions, it reveals the involvement of chintya (thought process) which may be altered in negative way worsening the psychopathology disturbed in stress. Vicharya i.e., the discriminatory power of buddhi to decide the right and wrong things also goes down. It is a well-known fact that stress covers the intellect and blocks all the way of recalling in memory, therefore the results of memory impairment is observed. All these processes have a neuro-biological basis, being serotonin as a key player controlling the appetite, sex drive. Imbalance of these neurotransmitters may lead to Bhakti vibhrama. This leads to dissatisfaction, improper fulfilling the desires leads to irritability and anger leading the patients to shila vibhrama. All these factors are regulated by psycho-neuro-endocrinial axis playing the main role in all this psychopathological tragedy of stress. Furthermore, incapability of body and mind can add more fuel to this worsening the overall vibhrama status of the patients. This also suggested involvement of cognition, conation and affect along with memory in stress and depression.
Manasa bhava pariksha:

In examination of Manasa bahva, negative emotions like Chinta (98.46%), Krodha (89.23%), Shoka (88.46%), Bhaya (83.08%), Dwesha (81.54%), Raja (80%), Manasa (39.23%) were found in majority of the patients and positive emotions like Dhairyya (91.54%), Avasthana (89.23%), Virya (73.85%), Dhriti (66.92%), Harsha (66.92%), Priti (50%) were found hampered in good number of patients of depression. These are the indicators of disturbance at psychic level. In order to improve mental work, one has to enhance the positive factors and on the other hand restrain the negative factors which are also enlisted as dharaniya vega and enemies of mind\textsuperscript{173}. The prevalent data may be due to prjnaparadha as cause and sign as well. The background players of Manasa vibhrama mentioned earlier and hampered mental factors here are Rajas and Tamas manas dosha, which can cause this damage to psyche. As Bhagavadgeeta states that Tamas is responsible for Moha and Ajnana whereas Rajas is originator of Sanga, Krodha and Kama. Similarly Sattva has the quality to produce Priti, Harsha, Dhairyya and Shraddha\textsuperscript{174}. These may be taken as the alarming signs of disastrous mental condition of patient.
Effect of therapy

Ashwagandharishta (group A) exhibited extremely significant improvement (p<0.0001) in mitigating the symptoms like dukhatvam, asiddhi bhaya, atmana ashaktatva, avasthana, karmeshu apravritti, daurbalya, arochaka, mano vibhrama, anavasthita chittatvam, kshudhamandya, nidrabhramsha, very significant improvement in suicidal thoughts and vivikta priyata and significant improvement in kheda, alpahara, alpa cheshta, alpdaavakyata. In rest of the parameters results were not statistically significant. On Manasa vibhrama pariksha, extremely significant results (p<0.0001) are reported in improving mana vibhrama, bhakti vibhrama and shila vibhrama; very significant out come in sandnya vibhrama and significant out come in improving buddhi vibhrama and achara vibhrama.

The combined treatment constisting of Ashwagandharishta & Atasi taila (group B), showed extremely significant (p<0.0001) results in alleviating the symptoms like dukhatvam, asiddhi bhaya, atmana ashaktatva, avasthana, karmeshu apravritti, daurbalya, suicidal thoughts, arochaka, alpa cheshta, alpavakyata, vivikta priyata, mano vibhrama, anavasthita chittatvam, nidrabhramsha; very significant improvement in kheda and atinidrata and significant results in Kshudhamandya and nidradhikya. On Manasa vibhrama pariksha, extremely significant (p<0.0001) improvement is noted in mana vibhrama, bhakti vibhrama, buddhi vibhrama, smriti vibhrama, sandnya vibhrama; very significant improvement in cheshta vibhrama and significant improvement in achara vibhrama.

The administration of Atasi taila alone (group C) exerted extremely significant (p<0.0001) results in dukhatvam, avasthan, karmeshu apravritti, mano vibhrama, anavasthita chittatvam, nidrabhramsha; very significant results in atmana ashaktatvam, daurbalya and arochaka and significant improvement in asiddhi bhaya, sadana, kshudhamandya. On Manasa vibhrama pariksha, extremely significant results (p<0.0001) are observed in improving mana vibhrama and bhakti vibhrama whereas rests of the parameters were improved but not up to the statistical significance.
Highly encouraging results have been noted on Manasa Bhavas, Hamilton Anxiety & Depression Rating Scale, Montgomery Asberg Depression Rating Scale, Beck Depression Inventory, DASS-21 by all the three interventional groups but while comparing the overall effect of therapy of over chief complaints and Manasa Vibhrama Pariksha, intergroup comparison showed insignificant difference whereas on Manasa Bhava Pariksha, Hamilton Anxiety Rating Scale and on Beck Depression Inventory; highly significant difference was reflected between Group A & B and significant difference between Group A & C evidencing supremacy of both Group B & C over Group A. Significant difference was witnessed between Group A & B proving higher effectiveness of Group B over Group A while evaluating the overall effect of therapy over Hamilton Rating Scale for Depression. Group A presented extremely significant decrease in depression and stress and very significant decrease in anxiety whereas both group B & C showed extremely significant effect on depression, anxiety and stress.

To reverse the Samprapti of Chittavasada and to restore normal psyche the prime aim is to eliminate Tamas and upliftment of Sattva and co-ordination with Rajas at psychic level and restoration of kshina vata upto normal level and elimination of apparent vikrit sleshmavridh at physical level. According to Vagbhata, drug acts by its Rasa, Guna, Virya, Vipaka, and Prabhava. Normally effect of Rasa is less than that of Vipaka. Effect of Vipaka is less than that of Virya, which further is less than effect of Prabhava, provided all are present in equal proportions.

**Ayurvedic & Modern Pharmacodynamics of treatment modalities**

The cumulative properties of Ashwagandharishta demonstrated Tikta, Madhura rasa, Laghu, Ruksha guna, (Arishta kalpana: Sara, vyavayi, vikasi, aashukari), ushna veerya, katu Vipaka with kaphapittashamaka, kaphavatashamaka and tridoshashamaka effect whereas Atasi taila possesses Madhura, Tikta rasa, Guru, Snigdha guna, Ushna veerya and Katu Vipaka having vataharha and kaphapittakrit action.
Tikta rasa is stated to alleviate Kapha and pitta dosha. Tikta rasa itself is not delicious but it promotes deliciousness when added with other things. Thus it is Arochakaghna which is important property in creating interest to relieve stress. It is having deepana, pachana, shodhana, lekhana, shleshmopashoshana properties, which shows that it promotes proper digestion, purification of body\textsuperscript{177}. Further, it is composed of Akasha and Vayu mahabhuta\textsuperscript{178} due to which it can have the highest penetrating capacity and reach the subtlest level of cell and mind. Tikta can cause prahlad (delightfulness)\textsuperscript{179} and it is said to possess medhya property, which is useful in enhancing Sattva guna and decreasing Tama by relieving stress and preventing its ill effects on the body and mind.

Madhura rasa has been stated as Sharira satmya (compatible to body), saptadhatu and Ojo vivardhaka, aayushya (increases longevity), shad indriya prasadana (creates happiness in all sense organs including mind), bala-varna karah (improves strength and complexion), preenana (instantly nourishing), jeevana (improves quality of life), tarpana (nurtures). At psychic level, Madhura may have sattva enhancing activity due to its other qualities sthira, snigdha etc.\textsuperscript{180}. On the other hand it can reduce Rajas.

Laghu guna is known for its action of Laghavakara (lightness), Kaphaghna (alleviating Kapha), and Shighra pakitva (quickly digestible)\textsuperscript{181}. Thus, this property helps to reduce Gaurava (heaviness), alleviate the aggravated Kapha and may hasten the metabolism and absorption of the drug at cellular level. Moreover, ruksha guna increases vata and decreases kapha thus helping in disintegrating the Samprapti of Chittavasada at physical level.

Hemadri quotes ‘yasya prerane Shakti sa Sarah’\textsuperscript{182} means which has the power to mobilize or excite the process is sara. Bhavamishra states it is pravartaka (inspirer)\textsuperscript{183}. It is another important quality to alleviate symptoms of inertia, psychomotor retardation, depressed mood, Anhedonia, etc. Further, Sushruta states that Sara shows Anulomana karma\textsuperscript{184} which is helpful in normalizing gati of vata dosha. It is also one of the qualities of pitta and nearer to chala quality of vata\textsuperscript{185}, so by this guna Ashwagandharishta can normalize depleted functioning of vata and pitta in chittavasada.
Guru guna of Atasi taila is responsible for stability and greater adaptation capacity and thus might be more helpful in promoting good sleep. Moreover, snigdha guna of it contributes to vatashamana which is again responsible for relieving anxiety symptoms.

Many of the ingredients of Ashwagandharishta & Atasi taila are having ushna veerya which helps in counteracting the Samprapti at physical level by decreasing kapha and vata and thereby disintegrating the Samprapti of Chittavasada and helping in relieving from many of the symptoms of depression whereas some ingredients of Ashwagandharishta is having sheeta veerya. At psychic level, sheeta is known to produce lhadana (delighten of mind)\(^1\)\(^8\)\(^6\), while at physical level it can aggravate vata and kapha due to similarity in qualities\(^1\)\(^8\)\(^7\). It has soothing and calming effect which is necessary in depressed patients for relaxation. It sedative property may be helpful in agitated and anxious patients. Thus, though Ashwagandharishta showed its potential effect on both anxiety and depression rating scale but it is proved more effective than Atasi taila in mitigating anxiety symptoms (table 87).

Arishta is a madya kalpana. Madya is having pancharasa except lavana, tikshna, sara, vyavayi, vikasi guna, ushna veerya, amla vipaka and vatashleshmahara, Pittaraktakara properties. According to Charaka, madya is laghu, sukshma, amla, ashukari, vikasi, tikshna, ushna, vyavyi, ruksa, vishada (Ch. Chi. 24/30). It is hridya, dipana, rochana, svaravrm prasadana, brimhana, balya, bhaya shoka shramapaha, swapnakara (Ch.Chi 24.64). According to Sushruta Madya is hridya, dipana, rochana, pittakara, kaphavataghna, indriyashodhana (Su. Su. 45/170). Arishta is superior among the madya kalpanas as it possesses the properties of different ingredients in it. It alleviates many doshas. It is deepana, kaphavtahara, and does not vitiate pitta. It is easily palatable, effective, and quick acting. Arishta is vyavayi, vikasi and ushna so it removes srotorodha. Srotorodha is due to parthiva guna and in arishta by agni sankara parthiva guna will be less and agneya, vayaviya and akashiya guna will increase. So arishta is better digested and absorbed.

**Probable mode of action of Ashwagandharishta**
Depression is an imbalance of neuro-transmitters. Many ingredients of the Ashwagandharishta are proven antidepressant activity. Amongst them Ashwagandha, Vacha, Pippali, Maricha and Daruharidra being serotonergic might be showing encouraging results in sleep problems, irritability, loss of appetite and loss of libido. Due to serotonergic effect of these drugs and GABAergic activity of Vacha only Ashwagandharishta is proved significantly better than Atasi taila in decreasing symptoms of Hamilton Anxiety Rating Scale but combined group showed highly significantly better in decreasing anxiety level compared to only Ashwagandharishta treated group (table 87). Thus, the results are in accordance that the administration of Atasi taila increases anxiolytic activity ofAshwagandharishta. Ashwagandharishta due to noradrenergic effect of Daruharidra might be showing convincing results on depressed mood, fatigue, difficulty in concentration, lack of interest (anhedonia) and decreased motivation. Due to
dopaminergic effect of Vacha, Chitrak, and Daruharidra; Ashwagandharishta not only decreases the depressed mood but also increases pleasure and motivation. Shweta mushali being a vrishya drug might be working as mood elevator contributing in decreasing sadness and increasing enthusiasm. Moreover, Ashwagandharishta contains 7.20% of alcohol. Alcohol removes the feeling of anxiety and mental fatigue. In daily life it is useful as hypnotic and also useful in reviving appetite and fatigue. In small doses it causes euphoria and depresses the CNS in descending order.

The ingredients of Ashwagandharishta viz., Ashwagandha, Haridra, Daruharidra, Musta, Krishna sariva, Rakta Chandana, Vacha, Maricha, Nagakesara have proven CNS depressant activity. Moreover, Ashwagandha, Mushali, manjishtha, Yashtimadhu, Arjuna, Trivritta, Sweta Chandana, Vacha, Chitraka, Shunthi, Twaka, Ela, Tamalapatra are rich in antioxidants. Furthermore, Ashwagandha, Manjishtha, Haridra, Yashtimadhu, Rasna, Vidari, Arjuna, Trivritta, Sweta sariva, Sweta chandana, Chitraka, Priyangu,
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nagakesara have anti inflammatory properties. Ashwagandha, Yashtimadhu, Arjuna, Chitraka possess immunomodulatory properties. Ashwagandha, Haritaki, Yashthi, Musta, Rakta chandana, Maricha, Nagakesara have Anticonvulsant activity and Ashwagnadha, Haritaki have proven anti stress, anti anxiety activities. Ashwagandha, Haridra are neuroprotective and increase Adult Hippocampal Neurogenesis. Vacha is having neuromodulatory effect. Hence, these psycho-neuro-pharmacological actions of various ingredients of Ashwagandharishta help in disintegrating various pathophysiology of depression and alleviate the symptoms of disease at psycho-physical level, ultimately improving the mental health.

Probable mode of action of Atasi Taila
A number of investigators have examined the role of pro-inflammatory cytokines in the pathophysiology of depression. A growing body of research indicates that depression is associated with excessive production of cytokines. These cytokines, including interleukin-1 beta (IL-1β), -2, and -6, interferon-gamma, and tumor necrosis factor (TNF-α), can have direct or indirect effect on CNS. They may lower neurotransmitter precursor availability, activate hypothalamic-pituitary-axis and alter the metabolism of neurotransmitters and neurotransmitter transporter mRNA. Ashwagandharishta consist many ingredients like Ashwagandha, Manjishtha, Haridra, Yashtimadhu, Rasna, Vidari, Arjuna, Trivritta, Sweta sariva, Sweta chandana, Chitraka, Priyangu, nagakesara etc. which are having established anti inflammatory activity and Flax seed oil being a source of omega 3 fatty acids may play an influential role in treating depression via inhibition of these pro-inflammatory cytokines and thereby regulating all the neurotransmitter production, metabolism and transportation and regulates the HPA axis.
Omega 3 fatty acids are well documented inhibitors of pro-inflammatory cytokines, particularly TNF-α and IL-β, although the precise mechanism is unclear. It is possible that omega 3 induces suppression of prostaglandins E2 (PGE2), thromboxane A2 and histamine are involved in anti-inflammatory effects and therefore alleviation of depression symptoms. It has been shown that, in addition to elevated cytokines, patients with major depression are more likely to have high levels of plasma and salivary PGE2\textsuperscript{189,190,191} (PDE - phospholipidesterases). Recently it was shown that PGE2, histamine and IL-β might, under certain circumstances, up-regulate PDE4 activity\textsuperscript{192,193,194}. If this is the case in CNS, then omega 3 fatty acids may actually trigger the cAMP cascade, leading to expression of CREB (cAMP response element binding protein) and BDNF (brain derived neurotrophic factor)\textsuperscript{195}. BDNF encourages synaptic
plasticity, provides neuroprotection, enhances neurotransmission and has antidepressant effect. Flax seed oil being a source of omega 3 fatty acid might be modulating neurotrophic mechanism involved in pathophysiology of depression.

Evidences has accumulated that omega 3 fatty acids have an influence on hippocampal Neurogenesis by increasing BDNF. Adult hippocampal Neurogenesis has been linked directly to cognition and mood\textsuperscript{196}, therefore modulation of AHN by flax seed oil, a source of omega 3 fatty acids; might be a possible mechanism by which nutrition impacts on mental health.
Flax seed oil is rich source of alpha lenolenic acid which is rapidly diffuse from plasma to brain. Recent researches\textsuperscript{197} have proven that sub-chronic treatment with alpha lenolenic acid induces an increase in BDNF levels, improves Neurogenesis and synaptic plasticity in specific brain regions, properties well known for the efficiency of antidepressant drugs\textsuperscript{198}. Thus, Neurogenesis and synaptogenesis associated with subchronic ALA treatment are strong arguments in favor of such mechanism involved in the ALA-anti depressant effect, which can also be related to additive/or synergic interaction with serotonin, norepinephrine, or dopamine pathways\textsuperscript{199,200}. 
Flax seed oil is a rich source of Alpha lenolenic acid which is endogenously converted into DHA. Recent researches have proved conversion of ALA to DHA in the liver is up-regulated, if direct source of DHA is unavailable and thereby the normal level of DHA in the brain is maintained. DHA, by maintaining membrane fluidity (by displacing cholesterol from the membrane) corrects receptor functioning, regulates neurotransmitter levels, neurotransmission and signaling within the cells. It acts as a source for second messenger within the cells. It helps in metabolism of monoamines implicated in the etiopathogenesis of depression.

Thus, Anti depressant activity of Flax seed oil may be due to the physiologic roles of ω-3 PUFA in regulating cell membrane fluidity, dopaminergic and serotonergic transmission, membrane bound enzymes, and cellular signal transduction and also by increasing BDNF and thereby increasing neurogenesis and synaptic plasticity.
Comprehensive solutions are needed to manage the negative mental health. All the negative emotions take root from the matter present in the subconscious. The basic cause of this is attachment. We human beings develop attachment to persons, things or emotions. This attachment raises desires and expectations. These desires and expectations if are not fulfilled ultimately lead to tensions, frustrations and conflicts. This affects the ego, which feels insecure. As a defense mechanism, the ego represses such emotions into subconscious so that mind can be peaceful again. However, repressions are not dead. They are after all repressed feelings. They remain active in the subconscious resulting in the negative emotions and results into anxiety, depression, fear, restlessness, aggressions etc. Thus, the solution lies in preventing the build up of such repressions in the subconscious and then also addressing the existing repressed garbage to gradually take it out of the system. Here comes the role of trance.
Mode of action of Trance

How Trance can help?

Trance
mind is internalized
encouraged to play with its own contents
the deep repressed impressions come up to the conscious level
These are again witnessed without ego attachment
ego does not feel insecure
So instead of sending them back to subconscious for recycling
they are thrown out of the system
bringing back from anxiety and depression

Jnana

Indriya Sapeksha (relative to senses)
By PMR & Suggestion
Through Trance
Obstruction
↓ Intensity; ↓ activity
↓ Raja & Tama
Manifestation of Sattva
Improvement in psychological health

Indriya Nirapeksha (relative to mind)
By Visualization & suggestion

Mode of Action of Trance
Through the technique of trance, the mind is internalized and encouraged to play with its own contents. In this process the deep repressed feelings come up to conscious level and witnessed without ego attachment. As a result ego does not feel insecure and the need to repress these impressions does not remain. As a result they are not sent back for recycling at a later date. Instead they are thrown out of the system for good. As such impressions are progressively thrown out, the mind gradually becomes understandable and forms a clean ground for fresh positive thoughts which results in mental quietness and peace. Thus, it brings back person from anxiety and depression\textsuperscript{202}.

In the process of trance, all the indriyas sapeksha (relative to senses) knowledge is obstructed through progressive muscle relaxation and suggestion and indriyas nirapeksha (relative to mind) knowledge is obstructed by breath watch, visualization, imagination and suggestions. These help in decreasing the intensity of thoughts and activity of mind. Thus, Rajas and Tamas is decreased and sattva guna is manifested which helps in overall improvement in psychological health.

**Cost of the drug**

- Ashwagandharishta: Rs. 7.2/day
- Atasi Taila: Rs. 4.2/day
- Total cost: Rs. 11.4/day

**Pharmacovigilance**

One patient with history of peptic ulcer developed hyperacidity, one patient with history of Prostatitis developed burning micturition in Combined group may be due to ushna guna of Atasi taila and pittavardhaka properties of Ashwagandharishta. 3 patients in combined group and 7 patients in Atasi taila alone group developed Abdominal heaviness, bloating, decreased appetite which is due to Guru guna of Atasi taila. But these cannot be counted as adverse drug reaction because these are the known reactions attributed to their own properties so should be used cautiously according to the condition and constitution of the patient.
Short comings of the present study & Suggestion to future researchers

Deficiency of Omega 3 FA is very vital in depressive illness and linked with neuro-chemical and neuro histological changes in depression. It also increases the neuro transmission of monoamines like serotonin, Nor Adrenaline and Dopamine. Therefore, quantitative analysis of Omega 3 fatty acids is very useful to pin point the mechanism of anti depressant action of plant based Omega 3 rich sources, whether ALA is converted to EPA & DHA to produce the anti depressant effect?

Or

ALA directly produces anti depressant action? The duration of treatment should be extended; preferably 3 to 4 months for more convincing results or at least 6 months to meet the complete remission under long term project.
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