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Pharmacological Screening of a Polyherbal Formulation - Ashwagandharishta

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Abstract

Ayurveda is one of the traditional medicinal systems of India. It is known as the "Mother of All Healing". World Health Organisation estimated that 80% of the world's inhabitants still rely mainly on traditional medicines for their health care. The titled study is to evaluate and confirm the CNS activities of experimental animal models. Aswhagandharishta (AA) is a herbo-mineral formulation consisting of 20 plants some of which are Medhyarasayanas. It has been claimed to be useful in treating central nervous system disorders. The animal models selected were tests for anti-convulsant activity, anti- inflammatory activity, anti-depressant activity, analgesic activity, anti-pyertic activity and learning and memory parameters. The study entails that polyhedral formulation of Ashwagandharishta has highly significant anti-inflammatory, anti-convulsant, anti-depressant activity, analgesic activity, anti-pyretic activity and learning and memory parameters. It was concluded that the Ashwagandharishta (AA) at a high dose (0.4 ml/Kg) have anticonvulsant, antidepressant activity, anti- inflammatory activity, anti-pyertic activity and analgesic activity whereas the low dose (0.2ml/Kg) have a sedative effect.

Keywords: Aswhagandharishta, Anti-convulsant, Anti-depressant, Analgesic,Anti-inflammatory, Anti-pyretic

Introduction:

Central Nervous System (CNS) controls important aspects of body function and maintains homeostasis. The human central nervous system is a network of more than 100 billion individual nerve cells that control our actions, sense our surroundings, and define who we are. Brain and mind disorders include a wide range of common neurological and psychiatric illnesses like Alzheimer's disease, Parkinson's disease, depressive disorders, epilepsy, insomnia, anxiety, dementia, mania etc. With the increasing number of cases in the world population, the need for drugs to treat CNS disorders, have acquired special urgency.[1,2] According to WHO by the year 2020, depression will be the second largest global burden of disease and other age related disorders like memory loss neurological or behavioral problems reflects the impact of CNS disorders. Around 10% people in North America, Western Europe, Australia, 8% in Middle East and 6% in Asia suffer from anxiety disorders. In India, 4.5-7.5% people suffering anxiety disorders[3]. Nearly 70 million people suffer from epilepsy and 80% reside in developing countries. In India about 10 million persons suffer from epilepsy[4]. In India more than 44 million people are living with dementia. Estimated 46.8 million people worldwide suffered from dementia in 2015 and this number is believed to be close to 50 million people in 2017. This number is reaching almost double in every 20 years, reaching 75 million in 2030 and 131.5 million in 2050[5].

Ayurvedic science is dynamic and progressive. It gives importance to therapeutic strategy. Ayurveda has been around for thousands of years, and was considered as one of the best ways to treat diseases and lead a healthy lifestyle in ancient India. In Ayurveda formulations containing multiple herbal and herbo-mineral ingredients are often used for many different conditions based on the concept that they provide synergistic therapeutic effect and help to minimize adverse effects of major drugs. One such multi ingredient plant based herbo-mineral formulation is Ashwagandharishta . The method of preparation of Arishta is known as "Sandhanakalpana". Arishtas are popular since Samhita period due to their better absorption in human body and thereby quick action. References of these preparations are available even during Vedic period. It is an "Nervine tonic" and has a special effect on Central nervous system. Also it is useful for all age groups. It is a liquid ayurvedic medicine whose chief ingredient is Brahmi (Bacopa monnieri). Saraswatarishta contains 5-10% of self generated alcohol in it. This self generated alcohol and the water present in the product acts as a media

to deviler water and alcohol soluble active herbal components to the body. Ashwagandharishta is claimed to be useful to treat acute anxiety, fatigue, insomnia, partial loss of memory, low grasping power, slurred speech etc.

Saraswatarishta is an decoction of Bicep Moniker , Asparagus racehorses , Pereira tuberose, Terminally chebula , Zinziber officinalis , Anethumsowa , Operculina ipomoea, Piperlongum, Syzygiumaromaticum, Acoruscalamus, Saussurealuppa, Withanias omnifera, Terminalia belerica, Tinosporacordifolia, Elettariacardmomum, Embeliaribes, Cinamomumzelonica, Mineral pure gold.

It is the most common ayurvedic medicine used for the treatment of neurological and psychological disorders. It is also used as a brain tonic, which helps to lower the risk of suffering from memory loss, dysfunction of the immune system, menstrual disorders, and semen problems. Saraswatarishta increases memory, attention span, concentration, intelligence, mental stamina and glow on the face. It decreases stress and mental fatigue. Ayurvedic medicinesare useful in treatment and management of depression, insomnia, anxiety, heart diseases, loss of desire to eat, restlessness, vertigo etc.

There is a lack of scientific data regarding the effect of Saraswatarihta (SA) on CNS activities. The present study is therefore, focused on the evaluation of the CNS activities of Saraswatarishta (SA) in experimental animals.

The genuine and authenticated raw materials of the test formulation were procured from Yucca Enterprises, Wadale (E), Mumbai. And other chemicals used were of analytical grade and procured locally.

Chemicals used:

Table no. 1 Chemicals used

Name & Concentration	Manufacturers
Diazepam (5mg tab)	Ranbaxy, India
Reserpine(0.25mg tab)	SG Pharma , India
Isoniazid (100mg tab)	Macleods, India
Imipramine (10mg tab)	Sun pharmaceuticals, India
Diclofenac sodium(50mg tab)	cipla Ltd,india
Pentazocine(30mg/ml inj)	Ranbaxy, India
Phenytoin (25mg tab)	Abbot, India
Dextropropoxyphene (65mg tab)	Jagsonpal Pharmaceuticals Ltd
Aspirin (150mg tab)	USV Ltd

Table 2 Muscle relaxant activity of AAPHF by using Tail immersion method

Groups	Treatment		Percentage inhibition
	Before treatment (sec)	After treatment (sec)	
Normal	5.53 ± 0.15	5.53 ± 0.15	0.00
LD (0.2ml/kg)	5.55.± 0.19	7.99± 0.19	20.21
HD (0.5ml/kg)	5.99 ±0.38	8.73 ±0.45	22.60
STD (Dextropropoxyphene)	5.58 ± 0.35	10.74 ± 0.52	48.04

Data was analysed by one-way ANOVA followed by Tukey-Karmer multiple comparison tests. Values are expressed as mean ± SEM (n=6) *p<0.05; ** p<0.01; *** p<0.001. #p<0.05; ##p<0.01; ###p<0.001

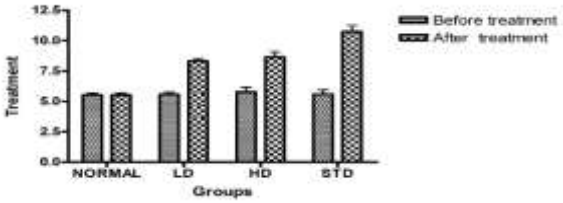

Fig1. Effect of AAPHF on Muscle relaxant activity using and tail immersion method in mice

Antipyretic:

Brewer's yeast pyrexia model:

The group received low dose of AAPHF(0.2ml/kg) shows significant decrease in rectal temperature from 38.46 ± 0.075 to 37.44 ± 0.0638 and the group received high dose of AAPHF(0.4ml/kg) shows significant decrease in rectal temperature from 38.99 ± 0.140 to 37.49 ± 0.038.

Table 3: Effect of AAPHF on Antipyretic activity by using brewer's yeast induced pyrexia model in rats

Group	Dose (mg/kg)	Rectal temp. before yeast injection	Rectal temp. after drug administration				
			0h	1h	2h	3h	4h
Control	-	37.14 ± 0.043	39.06 ± 0.041	39.58 ± 0.062	39.79 ± 0.035	39.60 ± 0.033	39.41 ± 0.045
Standard (aspirin)	150	37.91 ± 0.134	38.98 ± 0.195	38.38 ± 0.106	37.72 ± 0.141	37.33 ± 0.092	37.37 ± 0.058
LD(0.25 ml/kg)	100	37.64 ± 0.108	38.46 ± 0.075	38.04 ± 0.222	37.58 ± 0.114	37.34 ± 0.078	37.44 ± 0.0638
HD(0.5ml/kg)	200	37.78 ± 0.186	38.99 ± 0.140	37.90 ± 0.149	37.42 ± 0.057	37.26 ± 0.056	37.49 ± 0.038

Data was analysed by one-way ANOVA followed by Tukey-Karmer multiple comparison tests.

Values are expressed as mean ± SEM (n=6) *p<0.05; ** p<0.01; *** p<0.001. #p<0.05; ##p<0.01; ###p<0.001

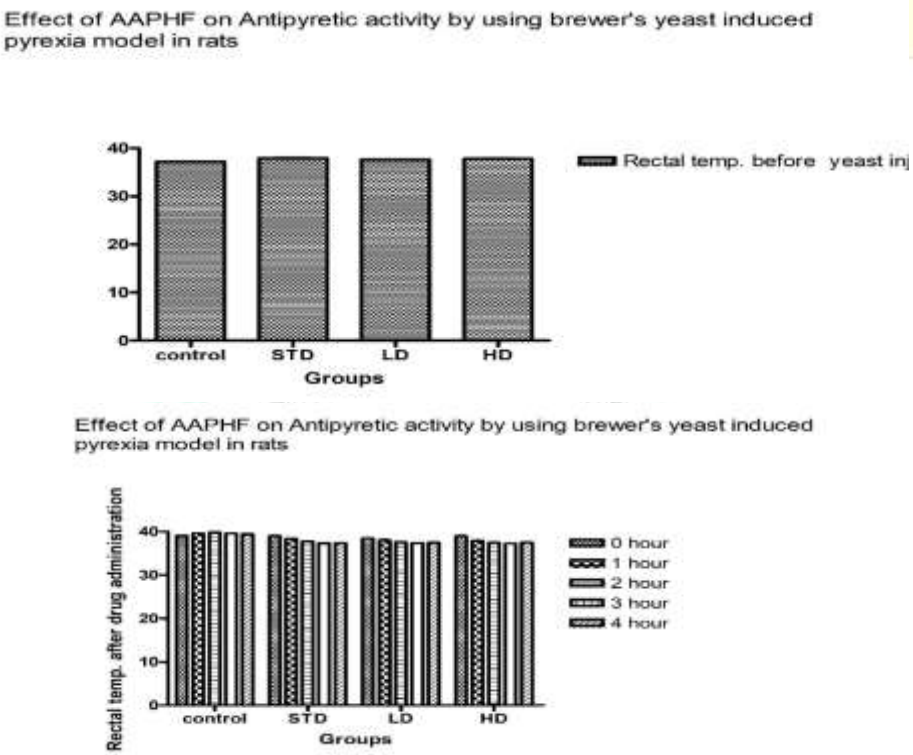

Fig.3 Effect of AAPHF on Antipyretic activity by using brewer's yeast induced pyrexia

Discussion

Ayurveda is one of the traditional medicinal systems with an established history of many centuries. Furthermore known as ayurvedic medicine, this ancient vedic knowledge is

considered to be one of the oldest healing sciences and has survived until the present generation over many centuries of tradition.

Psychoactive drugs interact at particular target sites or receptors found in the nervous system to induce widespread changes in physiological or psychological functions. Researchers are interested in any substance that crosses the blood-brain barrier, and thus has an effect on behavior, mood or cognition.

The present study was carried out to elucidate the CNS activity of polyherbal formulation Ashwagandharishta by using various experimental animal models. The studies reflected that Ashwagandharishta was effective in several models and showed anticonvulsant, antidepressant, analgesic, anti-pyretic and anti-inflammatory properties.

Antidepressant effect on tail suspension, forced swimming model and reserpine induced forced swimming model of depression provides a rapid and reliable behavior screening test for anti-depressants[53].The immobility has been expected to reflect a state of behavioral despair and failure to adapt to the stress. The results of the forced swimming and tail suspension tests showed a highly significant ($P<0.001$) decrease in the immobility time upon treatment with the Ashwagandharishta low dose and high dose.Imipramine acts by inhibiting NE (Nor Epinephrine) reuptake. The beneficial effect of imipramine in the FST model seems to be due to increased availability of these neurotransmitters nor epinephrine (NE) and serotonin (5HT) at the post synaptic site following reuptake inhibition. It has been established that the shortening of immobility time in the forced swimming and the tail suspension tests depends mainly on the enhancement of central 5-HT and catecholamine neurotransmission.[52] Thus, the overall results seem to be predictive for the anti-depressant action of AAPHF.

Ashwagandharishta at a dose (0.25ml/kg) have demonstrated a highly significant ($P<0.001$) anticonvulsant activity by suppressing extension, generalized tonic–clonic on MES induced convulsion and INH induced convulsion by increased onset time for clonic as well as tonic phases.

GABA is known to be an important inhibitory neurotransmitter in the brain, whereas glutamate is the excitatory neurotransmitter. GABA acts on the GABA receptors and glutamate acts through the N-methyl-D-aspartate (NMDA) and non-NMDA receptors. Activation of these receptors modifies various voltage-gated Na^+, K^+, Ca^{++} and Cl^- ion channels and excites or inhibits the neuron. Abnormalities in the GABA system have been found in neurological and psychiatric diseases. INH is regarded as a GABA-synthesis inhibitor. Clonic tonic seizures are elicited in mice which are antagonized by AED (Anti-Epileptic Drugs) that inhibit either voltage gated channels or by blocking glutamergic excitation mediated by the N-methyl-D-aspartame receptor.[51]

Ashwagandharishta treated groups were protected from seizures either by enhanced GABA synthesis by the stimulation of L-glutamate or by the prevention of GABA degradation by GABA transaminase. By the use of spectrophotometric methods, the rise in the amount of GABA in rat serum was detected. The results showed at high dose of Ashwagandharishta increased the serum GABA level extremely significant ($P<0.001$). The standard drug; gabapentin, is GABA analogoue which improve GABAregic transmission. The standard phenytoin and diazepam can prevent seizure induced by MES and INH. The brain and spinal cord play an important role in central pain mechanism. The dorsal part of the spinal cord is rich with endogenous opioids, somatostatine, and other inhibitory hormones which are the targets of pain and inflammation. It also established that tail clip and tail immersion model is well-established methods for measuring the central analgesic effects of drugs through opoid receptor . Our present study demonstrated that both low dose and high dose of AAPHF were effective which were comparable with standard drug dextropropoxyphene

Carrageenan induced hind paw edema is the standard experimental model of acute inflammation.Carrageenan induced paw edema is characterized by biphasic event with involvement of different inflammatory mediators.[112.113] Our results revealed that administration of AAPHF inhibit edema starting from the first hour and all phases of

inflammation, which is probably due to inhibition of release of different chemical mediators of inflammation. Based on the study the poly herbal formulation has signicant antiinflammatoty activityis also effective in inflammation associated pain.The phytoconstituents present in the AAPHF preclde inflammatory signaling which is learned from above anti-inflammatory

Anti-pyretic effect on Brewer's yeast pyrexia model is by inducing pyrexia with brewer's yeast.The doses of AAPHF shows some significant anti pyretic activity in rats dose-dependently and its effect is comparable to that of the standard(Aspirin) anti-pyretic drug which is used in this study.Aspirin have toxic effect to the various organs of the body,it is a result of secondary impact of infection,tuissue damage,inflammation etc.

In addition, administration of Ashwagandharishta on motor coordination shown some muscle-relaxant activity. Hot plate test and rota rod used to investigate both peripheral and central activity. Nociceptive reaction towards thermal stimuli in hot plate test. Hot water test using mice is a well-validated model for the detection of opiate analgesic as well as several types of analgesic drugs from spinal origin.[108]

Thus, the above observations indicate that Ashwagandharishta can overcome various CNS disorders like epilepsy, depression, pyretic etc… and it also have analgesic and anti-inflammatory property.The potential effect of Ashwagandharishta polyherbal formulation may be attributed to one or more bioactive principles present in these drugs such as steroidal saponins, flavonoids, alkaloids (mainly trigonelline), zingiberol, and free amino acids. There may be synergistic herb-herb interactions enhancing the total efficacy of the formulation. The exact mechanism of action of the drug needs to be evaluated by further extensive studies.

Summary:

In the preliminary pharmacological screening the main effects observed for polyherbal formulation Ashwagandharishta were**:**

Anti-convulsant activity
Anti-depressant activity
Analgesic activity
Anti-inflammatory activity
Anti-pyretic activity
Behavioural studies
Muscle relaxant activity

The High dose of AAPHF have demonstrated anticonvulsant activity on MES induced convulsion and INH induced convulsion by increased onset time for clonic as well as tonic phases and decreased mortality. The reason behind this was thought to be the enhanced GABA synthesis or prevention of GABA degradation by GABA transaminase. The increased GABA level in mice serum obtained by the spectrophotometric analysis was further evident for the anticonvulsant activity of higher dose of AAPHF.

The results provided by the higher doses of AAPHF in hot plate showed that the polyherbal has analgesic effect , a highly significant results were obtained at 90 minutes. Also, the drug shows satisfactory result in rota rod apparatus.

There was significant decrease in time of immobility in both tail suspension test and in reserpine induced test for antidepressant activity this may due the enhancement of central 5 HT and catecholamine neurotransmission which decreases immobility time in the reserpine and the tail suspension tests

The poly herbal formulation shows significant reduction in yeast induced pyrexia .most of the antipyretic drugs inhib COX-2 expression thus inhibiting PGE2 biosynthesisto reduce elevated body temperature.

Based on the study it can be concluded AAPHF has antinflammatory activity by blocking the the effect of COX enzymes.These enzymes forms other chemicals called prostaglandims,which causes of inflammation.By blocking the COX enzymes few prostaglandins are prodced which reduces the pain and inflammations

From the observations of the present study, as an overview, we can say that the AAPHF has sedative effect at lower doses whereas antidepressant, analgesic, anticonvulsant activity,anti-pyretic and antiinflammatory at higher doses. However further studies and researches are needed and advised for these interested activities in order to commercialize Ashwagandharishta as beneficent therapeutic product for various CNS disorders.

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