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AN OPEN LABELED CLINICAL STUDY ON EVALUATING THE DE-ADDICTION EFFICACY SIDDHA DRUG KOTHTHAMALLI VITHAI CHOORANAM IN TREATING ALCOHOLISM (KUDIVERI NOI)

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ABSTRACT
Alcoholism commonly called by its name Kudiveri noi in siddha system of traditional medicines is considerably has created huge socio economic impact in both developing and developed countries. WHO estimates that about 76 million individuals worldwide are diagnosable alcohol use disorder (AUD) either with alcohol misuse or alcohol dependence. These numbers are anticipated that would be increment every year as it happen to the worldwide danger. Liver is the primary metabolic organ which were been affected with continuous and uncontrolled consumption of alcohol in excess and thus it become a leading cause of cirrhosis, liver cancer, and acute and chronic liver failure and as such causes significant morbidity and mortality. Increase in liver function enzymes and audit score is considered to be the severity scale of the alcoholism index. By considering the complexity in treating the AUD researchers are at constant search of exploring a drug which could acts in multiple ways and offers physiological and psychological support to the affected individuals. Principal of siddha medicine is to make the body perfect, imperishable and to promote longevity. This is the first system to emphasis health as the perfect state of physical, mental, social, moral and spiritual component of human beings. Present study aimed at evaluating the de-addiction efficacy of siddha formulation Koththamalli vithai chooranum (KVC) in patients with alcoholism. A total of 30 patients who are presented with pathology of the alcoholism along with secondary complication have been selected for the trial and were treated with KVC for the period of 48 days. It was observed from the clinical outcome of the present study that patients treated with KVC has shown significant reduction in serum glutamic oxaloacetic transaminase (SGOT) and Serum glutamic pyruvic transaminase (SGPT) level including audit score. Hence it was concluded from the outcome of the present study that reduction in biologically significant enzymes may be taken as good indication of liver rejuvenation and further this action of dug could be due to bioactive components present in the formulation which has tendency to halt the progression of liver damage caused due to AUD.

KEYWORDS: Alcoholism, Siddha medicine, Koththamalli vithai Chooranum, AUD, SGOT, SGPT.

1. INTRODUCTION
By considering the complexity in treating the AUD researchers are at constant search of exploring a drug which could acts in multiple ways and offers physiological and psychological support to the affected individuals. Principal of siddha medicine is to make the body perfect, imperishable and to promote longevity.[1,2] This is the first system to emphasis health as the perfect state of physical, mental, social, moral and spiritual component of human beings. AUD is likewise turned into a significant factor of climbing the medicinal services cost around 30 billion dollars every year, and the aggregate financial expense to society is a stunning 235 billion dollars every year. Thus the growing financial concern make this problem to become a global economical burden and that grabs the attention of the researcher to find out the proper therapeutic strategy that improves the quality of life of the individuals with AUD.[3,4] It's really a very challenging task for the scientist to discover the compounds that's acts centrally because of the stringent regulations and also complex in executing such trials clinically. It takes around 18 years to move a compound in this class from disclosure to showcase, 4.5 years longer than the normal restorative

compound Furthermore, just 8 percent of new CNS lead molecules entering Phase 1 that will achieve the commercial center.[5] Only 46 percent of CNS candidates prevailing in critical Phase 3 preliminaries contrasted and 66 percent, by and large, for all lead compounds. It is hard to assess the medication advancement procedure of alcohol medication since most of such drugs meant for alcohol treatment have been produced initially for other clinical indications.[6]

The World Health Organization advices that alcohol dependence is the third leading cause for illness load in creating nations around the world. In the United States alone the estimated healthcare cost of AUD is about $185 billion .It is assessed that 20 to 36% of patients in ambulatory care seems excessive drinkers. Further 40 % of all cases in trauma care unit also reported to be excessive alcohol users. In spite of these insights, even among patients who drink unreasonably and meet the criteria for an alcohol utilize clutter, the issue regularly goes undetected and untreated.[7-12]

Alcohol is a leading cause of liver disease and is associated with significant morbidity and mortality. Several factors, including the amount and duration of alcohol consumption, affect the development and progression of alcoholic liver disease (ALD). ALD represents a spectrum of liver pathology ranging from fatty change to fibrosis to cirrhosis. Early diagnosis of ALD is important to encourage alcohol abstinence, minimize the progression of liver fibrosis, and manage cirrhosis-related complications including hepatocellular carcinoma.[13]

AUD is a constant and leading heritable issue with a variable clinical representation. This inconstancy, or heterogeneity, in clinical introduction recommends complex collaborations among environmental and natural variables, bringing about a few fundamental pathophysiological systems in the improvement and movement of AUD. Classifying AUD into subgroups of normal clinical or pathological attributes would facilitate the unpredictability of prodding separated basic sub-atomic systems. Hereditary affiliation investigations have uncovered a few polymorphisms—little contrasts in DNA—that expansion a man's powerlessness to create AUD and other alcohol related transitional qualities, for example, seriousness of drinking, time of AUD beginning, or proportions of needing.[14]

Siddha medicine has unique advantage of treating AUD as it contains several indigenous preparation from herbal origin which rejuvenate the mind and body. Several siddha drug has a tendency to complete reverse the altered physiology that grabs the people to use the siddha formulation which offers greater therapeutic efficacy and with no side effects. This tendency makes the traditional siddha medicine pioneering the de-addiction remedy for treating AUD. The main aim of the present investigation is to evaluate the de-addiction efficacy of siddha formulation Koththamalli vithai chooranum (KVC) in patients with alcoholism.

2. MATERIALS AND METHODS

2.1. Source of raw drugs

The herb *Coriandrum sativum* seeds (Koththamalli vithai) with good oil content were purchased from a well reputed country shop and the drug will be authenticated by the competent authority (Medicinal botany dept.NIS). After that the raw drug will be cleaned and then the trial drug will be prepared in Gunapadam Laboratory of National Institute of Siddha.

2.2. Ingredient

Koththamalli vithai (Coriandrum sativum)

2.3. Preparation[15]

The Seed of *Coriandrum sativum* were powdered well and filtered through a cotton cloth (vasthrakayam).
Dosage : 1 gm twice a day
Adjuvant : Kaadi neer
Duration: 48 Days

2.4. Study design

An open-labeled observational study comprises of 30 subjects presenting the symptoms and habituation of alcoholism was chosen for the individualized in-depth evaluation. Protocol was approved by National institute of siddha, Chennai, Tamil Nadu 600047 with referral approval number IEC no NIS/IEC/10/2016-17/45 dated 20-05-2016.

2.5. Selection criteria

Patients visiting the out-patient department of Ayothidoss Pandithar Hospital of National Institute of Siddha, Chennai-47. The detailed study on Kudiveri noi with reference to its aetiology, pathogenesis, investigations, clinical features, diagnosis and treatment with trial drugs was done.

2.5.1. Inclusion criteria

- Age: 18 -60.
- Sex: Both Male and Female.
- Patients having
  - Physical symptoms like loss of appetite, nausea, vomiting, tremor.
  - Psycological symptoms like intoxication, craving/urge of alcohol, negligence of activity.
- Patients who are will to undergo hematological investigation & other lab investigation.
- Patient willing to sign the informed consent stating that he/she will consciously stick to the treatment during 48 days.

2.5.2. Exclusion Criteria

- Chronic diseases like cardiac disease, hormone imbalance
- Other psychiatric problem
- Pregnancy and lactation
- Withdrawal symptoms like seizure, delirium.

- Any other serious illness

2.5.3. Withdrawal Criteria

- Intolerance to the drug and development of adverse reactions during drug trial.
- Poor patient compliance & defaulters.
- Patient turned unwilling to continue in the course of clinical trial.
- Any drastic changes occurring in hematological finding during treatment period.
- Increase in severity of symptoms

2.5.4. Tests and Assessments

A. Clinical assessment
B. Siddha assessment
C. Laboratory investigations

2.6. Data collection

Required information will be collected from each patient by using the following forms

- FORM l Screening and selection Proforma.
- FORM lI Clinical assessment Proforma.
- FORM llI Laboratory investigation Proforma.
- FORM IV Drug compliance form.
- FORM V Patient information sheet.
- FORM VI Consent form.
- FORM VII Withdrawal form
- FORM VIII Dietary Advice form.
- FORM IX Adverse reaction form

2.7. Alcohol use disorder identification test (AUDIT)

The Alcohol Use Disorders Identification Test (AUDIT), developed in 1982 by the World Health Organization, is a simple way to screen and identify people at risk of alcohol problems.

2.8. Drug Administration

Each subject was provided with 1 gm of trial drug *KVC* for the period of 48 days further they were monitored for clinical improvement and other Compliance

2.9. Clinical Study Assessment[16-19]

Each patient was subjected to the clinical investigation for evaluating the improvement in their disease condition through regular serum Investigation such as SGOT and SGPT level. Further the patient clinical improvement were subjectively analyzed using AUDIT score

3. RESULTS

3.1.Result analysis on Prevalence of alcohol with respect to the age group

Result analysis of the present study has revealed that out of 30 cases included for analysis, between 18 to 60 years. The prevalence of alcohol consumption showed a peak near age 40. They found that 58.3% individuals in age group between 45 – 54 years old.

3.2. Result analysis on Evaluation of Serum SGOT level before and after administration of trial drug KVC in patients with Alcoholism

Abnormal increase in liver enzyme levels were seems to be the alarming signal for the patient with alcoholism. Liver enzyme alteration may be either the accompanying biochemical picture in a patient with symptoms or signs suggestive of liver disease. Results of the present clinical study has proved that there was a significant decrease in the SGOT level of the patient treated with KVC.

Table 1: Serum SGOT level before and after administration of trial drug KVC.

Patient Id	Age	Before Treatment SGOT Level Mg/dl	After Treatment SGOT Level Mg/dl
1.	58	24	22
2.	35	61	50
3.	56	140	22
4.	55	21	20
5.	32	37	30
6.	32	197	150
7.	32	42	40
8.	32	12	12
9.	38	34	30
10.	33	53	41
11.	32	109	88
12.	27	27	26
13.	42	52	40
14.	38	57	52
15.	33	76	60
16.	56	147	79
17.	45	21	25
18.	27	31	35
19.	47	44	42
20.	40	79	34

21.	54	62	52
22.	34	34	33
23.	48	69	79
24.	38	72	53
25.	33	29	61
26.	39	46	31
27.	49	33	12
28.	25	39	35
29.	26	17	31
30.	56	37	36

3.3. Result analysis on Evaluation of Serum SGPT level before and after administration of trial drug KVC in patients with Alcoholism

Elevated SGPT level frequently observed in the condition of extensive tissue necrosis and also in chronic liver diseases like liver tissue degeneration and necrosis which was pathological in the condition of alcohol addiction. Results of the present clinical study has revealed that there was a significant decrease in the SGPT level after treatment with the siddha drug KVC.

Table 2: Serum SGPT level before and after administration of trial drug KVC

Patient Id	Age	Before Treatment SGPT Level Mg/dl	After Treatment SGPT Level Mg/dl
1.	58	23	26
2.	35	45	25
3.	56	85	25
4.	55	28	25
5.	32	70	50
6.	32	62	30
7.	32	62	51
8.	32	12	13
9.	38	38	34
10.	33	47	45
11.	32	41	30
12.	27	40	40
13.	42	48	32
14.	38	38	35
15.	33	59	42
16.	56	69	79
17.	45	11	18
18.	27	32	33
19.	47	74	66
20.	40	60	18
21.	54	58	41
22.	34	28	32
23.	48	44	40
24.	38	67	42
25.	33	25	61
26.	39	53	37
27.	49	52	16
28.	25	67	42
29.	26	28	28
30.	56	28	18

3.4. Result analysis on Evaluation of Audit score before and after administration of trial drug KVC in patients with Alcoholism

The outcome of the AUDIT score, which has been validated and widely used in India. Which shows encouraging results of good improvement in 22 patients, moderate improvement in 4 patients, mild improvement in 4 patient .Good Improvement was observed in voluntary cases and person who were strong desired to stop alcohol intake. Further none of the patients have been observed with any adverse event or clinical abnormalities during entire treatment period.

Table 3: Audit score on patient with alcoholism before and after administration of trial drug KVC.

Patient Id	Age	Audit Score Before Treatment	Audit Score After Treatment
1.	58	24	3
2.	35	20	2
3.	56	18	2
4.	55	18	9
5.	32	14	1
6.	32	13	16
7.	32	16	0
8.	32	17	1
9.	38	18	0
10.	33	18	1
11.	32	19	2
12.	27	17	10
13.	42	17	2
14.	38	16	17
15.	33	15	0
16.	56	20	2
17.	45	17	8
18.	27	18	1
19.	47	20	19
20.	40	20	3
21.	54	17	1
22.	34	20	2
23.	48	15	0
24.	38	21	3
25.	33	17	8
26.	39	19	1
27.	49	17	18
28.	25	16	1
29.	26	16	0
30.	56	20	1

4. DISCUSSION

Alcoholism remains a leading cause of mortality, regardless of advancement through neurobiological research in recognizing new pharmacological techniques for its treatment. Medications that influence neural pathways that regulate the action of the cortico-mesolimbic dopamine framework have been appeared to change drinking conduct, apparently on the grounds that this dopaminergic framework is nearly connected with remunerating conduct. Ondansetron, naltrexone, topiramate, and baclofen are models. Subtyping alcohol abuse in grown-ups into an early-beginning compose, with incessant side effects and a solid natural inclination to the malady, and a late-beginning compose, regularly expedited by psychosocial triggers and connected with state of mind indications, may help in the determination of ideal treatment.[20]

Alcohol dependence frequently pursues a perpetual backsliding course like other restorative issue, for example, diabetes. In spite of its mental and social sequelae, when set up, alcohol dependence is basically a cerebrum issue. Without a pharmacological extra to psychosocial treatment, the clinical result is poor, with up to 70% of patients continuing drinking inside 1 year. In this way, psychosocial mediation alone isn't ideal treatment for alcohol dependence.[21-23] In the present study withdrawal symptoms like sleep disturbance, tremor, alcoholic hallucination and palpitation were reduced within 3-5 days. None of patients reported in severe withdrawal symptoms like seizure and delirium. In this study no adverse events were observed during the course of the treatment.

The primary goal of the treating AUD is to develop a pharmaceutical ailment that has multiple mechanism which either be a single moiety or in combination has successful history of pre-clinical and also has minimum adverse event. However, the U.S. Food and Drug Administration (FDA) have only approved three specifically for treating AUD oral and long-acting injectable naltrexone, acamprosate, and disulfiram.

Disulfiram has been utilized in the treatment of AUD with reliably victories in people with high consistence or when prescription admission has been specifically managed.[24-26] Its instrument of activity for keeping up alcohol forbearance is believed to be basically mental.[27-29] and dependent on an exceedingly repulsive pharmacological impact if alcohol is devoured.

Disulfiram hinders the catalyst aldehyde dehydrogenase (ALDH). On the off chance that alcohol is available, acetaldehyde amasses more often than not bringing about a repulsive response, the disulfiram-ethanol response (DER), comprising principally of tachycardia, flushing, sickness, and regurgitating.[30] To keep the primary beverage, in any case, the mental or psychological risk is believed to be prevailing and dynamic and in this manner prevent utilize.[31,32] The danger of a DER, in reality the anticipation of negative outcomes if alcohol somehow managed to be assimilated and resulting musings about maintaining a strategic distance from torment and infection represent the medication's viability.

Coriandrum sativum is widely consumed herb pertains to the family Apiceae, is valued for its traditional and medicinal uses. The plant is a potential wellspring of lipids (wealthy in petroselinic corrosive) and a basic oil (high in linalool) segregated from the seeds and the flying parts. Because of the nearness of a large number of bioactives, a wide cluster of pharmacological exercises have been credited to various parts of this herb. Due to the presence of a multitude of bioactives, a wide array of pharmacological activities have been ascribed to different parts of this herb, which include anti-microbial, anti-oxidant, anti-diabetic, anxiolytic, anti-epileptic, anti-depressant, anti-mutagenic, anti-inflammatory, anti-dyslipidemic, anti-hypertensive, neuro-protective and diuretic. Interestingly, coriander also possessed lead-detoxifying potential.[33]

Liver enzymes are the core indicators for enumerating the effectiveness of the de-addiction therapy of the siddha drug KVC in treating Alcoholism (Kudiveri noi). Several researches have clearly evident there was an abnormal increase in the SGPT and SGOT level in individuals with chronic alcohol addiction. Henceforth the liver function test was considered to be the scale of measuring the treatment potency. Results of the present clinical study has revealed that there was a significant decrease in the SGPT and SGOT level after treatment with the siddha drug KVC.

5.CONCLUSION

In recent time alcoholism considered to be one of the leading cause of death and debilities in people of developing countries. Conventional medicines used for treating alcoholism liberates potential life threatening adverse effects in the patients upon chronic usage. Hence exploration of alternate medicine from herbal origin become essential and need of the hour for managing AUD. Among different medication based prescriptions (over 80%) usually rehearsed are from herbal source. From the data's obtained from the present investigation it was evident that treatment with siddha drug KVC has an tendency to reverse the liver inflammation caused to ingested alcohol and was well justified by significant decrease in SGOT and SGPT level. Further there is a significant decrease in AUDIT score of the treated cases. Hence it was concluded from the results of the present clinical investigation that the siddha drug KVC has de-addiction property and shall be used for treating patient with AUD.