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# **Review Article**

# ALCOHOLISM: AN UNDERSTANDING OF THE NEUROSYSTEMIC APPROACH INVOLVEMENT WITH AYURVEDA

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#### ABSTRACT

Alcohol consumption is an integral part of daily life in many societies. In general it is related to lower health status, more health problems and a shorter life expectancy. being a social stigma, it ranks among the top 5 risk factor of diseases. Ayurveda considers addiction under the topic of *Madatya*, which means intoxication. *Madatya* is the state or symptoms that arise due to continuous use or a high dose of substances that are intoxicating. According to Ayurveda, *Madya* (alcohol/drug) is the complete opposite of *Ojas* (source of energy) which is a prerequisite for good health and wellness. *Madya* finishes *Oja* in the body and when a person reaches that stage, he experiences the symptoms of *Madya*. According to modern medicine there are four stages of addiction – Acute intoxication, withdrawal symptoms, drug dependence and finally drug abuse. The stage of *Madatya* can be compared to the 3<sup>rd</sup> and 4<sup>th</sup> stage. In *Charak Siddhisthana* it says that the *Hridaya* present in *Shira* effects the *Gyanendriya* and *Karmendriya*. and this *Shira* is effected by the *Madya* which disrupts the *Ojha*. Going through various research study it has been proved that alcohol leads to Neurodegeneration, which changes in the neuronal function viz. reward circuits and neurotransmitter system particularly dopamine system, opiod system, gamma-aminobutyric acid system acid system, glutamate system etc. Thus an humble attempt has been made to understand the neurosystem involvement and degeneration caused by alcohol (*Madya*) by both Ayurveda and modern science.

**KEYWORDS:** Alcohol, Madya, Neurodegeneration, Ojha.

#### INTRODUCTION

Alcoholism is a social stigma. It is a debilitating disease and has a negative impact on the sociopshychology of a person. It has been very rightly quoted that "the disease that makes you too selfish to see the havoc you created and care about the people you shattered". when the amount is directly related to create serious condition then that state is alcoholism. Alcohol is a psychoactive substance with dependence producing properties that has been widely used in many cultures for centuries (WHO). The harmful use of alcohol causes a large disease, social and economic burden in societies.

The harmful use of alcohol ranks among the top five risk factors of disease, disability and death throughout the world (WHO, 2011 a; Lim et al, 2012) 25. The development of alcoholism is characterised by frequent episodes of intoxication, preoccupation with alcohol, use of alcohol despite adverse consequences, compulsion to seek and consume alcohol, loss of control in limiting alcohol intake, and emergence of a negative emotional state in the absence of the drug (American Pshychiatric association, 1994). More than 17 million people in the united states either abuse or are dependent on alcohol (NIAAA)<sup>3</sup> with a cost to US society of over \$180 billion annually (NIAAA)<sup>3</sup>. The UN political declaration on NCDs endorsed by head of state and government in September 2011, acknowledged that the global burden and threat of NCDs constitute one of the major challenges for the development in the 21st century. the declaration, recognises that the most prominent NCDs are linked to common risk factor namely tobacco use, harmful use of alcohol. An unhealthy diet and

lack of physical activity and underlines the critical importance of reducing the level of exposure of individuals and population to these risk factors while strengthening the capacity of individual and population to make healthier choices to follow lifestyle patterns that foster good health.

## MATERIAL AND METHODS

Ayurvedic textual materials were referred mainly Charak Samhita, Astanga Hridaya, Bhavaprakash and Harita Samhita with available commentaries of these Samhitas for the study. Some modern books of medicine, pharmacology, journals etc have also been over. From these books references have been collected and studied systemically.

#### **AIMS AND OBJECTIVE**

- 1. Understanding the effect of alcohol from observance in the neuropshychological line.
- 2. The view of Madatya in Ayurveda
- 3. Bringing an relation between *Ojha* disrupted by *Madya* and alcohol on the nervous degeneration.

#### DISCUSSION

Alcohol abuse is defined as repetitive problems with alcohol in any four life areas social, interpersonal, legal and occupational or in hazardous situation such as driving while intoxicated. if an individual is not alcohol dependant, he or she still may be given a diagnosis of alcohol abuse.

# Epidemiology

The lifetime risk for alcohol dependence in most western countries is about 10-15% for men and 5-8% women. rates are generally similar in US, Canada,

Germany, Australia and England. The rate difference both cultural and genetic influences (Harrison)<sup>1</sup> Thus, the global information system on alcohol and health (GIASH) is further development of the WHO global alcohol database, providing easy and rapid access to a wide range of alcohol related health indicators (WHO).

In alcohol epidemiology is defined as the study of<sup>2</sup>

A: Patterns of alcohol use, abuse and dependence.

B: The developmental course of alcohol problems within a community or population.

C: Factors that are associated with an increase risk or susceptibility in a population for developing alcohol related problems, alcohol abuse or dependence.

#### What is alcoholism

When repeated problems in multiple life area develops, the individual is likely to meet criteria for alcohol abuse or dependence.<sup>3</sup>

**Alcohol dependence:** is defined as DSM -4, as repeated alcohol related difficulties in atleast 3 of seven areas of functioning that cluster together over a 12 month period. the diagnosis of alcohol dependence predicts a course of recurrent problems with the use of alcohol and consequent shortening of lifespan by a decade on average.

#### Genetics of alcoholism<sup>3</sup>

Different distinct characteristics appear to contribute to the risk. for e.g.,

- 1. Some families carry a risk for both alcoholism and drug dependency, as seen in antisocial personality disorder.
- 2. The risk for alcohol dependency, relate to a genetic vulnerability.
- 3. A different mechanism increases, only the alcoholism risk, through a low response to alcohol and subsequent drinking higher doses to achieve the desired effects.

#### When to intervene

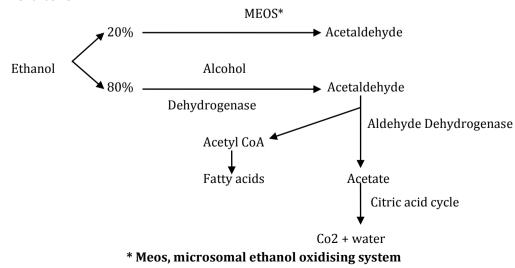
It is important to pay attention to the alcohol related symptoms and signs as well as laboratory test that are likely to be abnormal in the context of regular consumptions of drink per day. The blood test with >70% sensitivity and specificity for heavy alcohol consumption **The metabolism of alcohol** 

are gamma glutamyl transferase (GGT) (>35U) and carbohydrate deficient transferring (CDT)(>20U/L). Other blood test that can be useful in identifying individuals are high normal MCVs ( $\geq$ 91µm<sup>3</sup>) and serum uric acid (>416 mol/L). for, screening of a person, an AUDIT (Alcohol use disorder screening test) is developed.

#### Pharmacology and nutritional impact of ethanol:

Ethanol is a weekly charged molecule that moves easily through cell membrane, rapidly equilibrating between blood and tissues. The level of alcohol in the blood is expressed as milligrams or grams of ethanol per decilitre (eg 100mg/dl or 0.10g/dl) with blood values of about 0.02g/dl resulting from the ingestion of one particular drink. These beverages have additional components called congeners, that affect the taste and effect, congeners include low molecular weight alcohols (e.g., methanol and butanol), aldehydes, esters, histamines, phenols, tannins, iron, lead and cobalt. Such congeners might also contribute to the adverse health consequences associated with heavy drinking.

Ethanol is a CNS depressant that decreases neuronal activity, although some behavioural stimulation is observed at low blood levels. This drug has cross tolerance with other depressants, including benzodiazepenes and barbiturates. Alcohol is absorbed from mucous membrane of mouth and oesophagus (small amounts), from stomach and large bowel (in modest amount) and from the proximal site of small intestine (major site). The rate of absorption is increased by rapid gastric emptying, by absence of protein, fat and carbohydrate, by absence of congeners and by dilution to a modest percentage of ethanol. Between 2% (low concentration) to 10% (high concentration) of ethanol is excreted directly through the lungs, urine or sweat but the greater part is metabolized to acetaldehyde, primarily in the liver. The most important pathway occurs in the cell cytosol where alcohol dehydrogenase (ADH) produces acetaldehyde, which is rapidly destroyed by aldehyde dehydrogenase in cytosol and mitochondria. the second pathway in the microsomes of the stomach endoplasmic reticulum is responsible for 10% of ethanol oxidation at high blood alcohol concentrations.



# The effects of ethanol on organ system

# 1. Nervous system<sup>4</sup>

Neuroimaging studies, neuropathological observations and experiments in animals and cultured cells provides evidence that ethanol is neurotoxic.

- a) The ventricles and sulci become significantly smaller within about one month of abstinence (Carten et al 1988,1984; scroth et al 1988) or chemical analysis (Harper et al 1988) does not change consistently. It has been hypothesized that changes in brain parenchyma, but not brain water, may account for cognitive abnormalities of the alcoholics.
- b) Pathologic study have provided mixed evidence for ethanol induced cerebral atrophy (victor et al 1989).
- c) The identification of selectively affected neurotransmitter pathways could have important implication for management of dementia in Alcoholics (Arendt et al 1983, Antuono et al 1980, Nordberg et al 1980).
- d) Long term administration of ethanol to well nourished rats causes memory deficits, reduction in CAT levels and choline uptake and a slight (17%) loss of neuron in the nucleus basalis (Arendt et al 1988a 1988b).

# 2. The GI system

- Esophagus and stomach
  - ✤ Epigastric distress
  - ✤ GI bleeding
- Liver
  - \* Alcohol induced hepatitis
  - ✤ Perivenular sceloris
  - ✤ Cirrhosis
- Pancreas
  - \* Acute pancreatitis three times more
    - \* Impairs gluconeogenesis in liver
- **3. Cancer** 1.5 drinks per day increase risk of breast cancer 1.4 fold for both the gender 4 drinks per day increase the risk for oral and oesophageal cancers 3 fold and rectal cancer by a factor of 1.5, 7 -8 drinks per day enhances approx fivefold the risk for many cancer

# 4. Haemopoetic System: Ethanol causes an

- Increase in RBC size (mcv) which reflects its action in the stem cells.
- Heavy drinking with folic acid deficiency can also be hypersegmented neutrophils, reticulocytopenia.
- \* If malnutrition present, sideroblastic changes .
- Chronic heavy drinking can decrease production of WBC, decrease granulocyte mobility and adherence and impair delayed hypersensitivity response to novel antigens.

## 5. CVS

- Ethanol decrease myocardial contractibility and causes peripheral vasodilation.
- ¾ drinks per day dose dependence increase in blood pressure which returns to normal within weeks of abstinence.

- Chronic drinkers have 6 fold high chance of CAD and cardiomegaly.
- Atrial or ventricular arrhythmias, paroxysmal tachycardia.

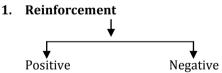
# 6. Genito Urinary System, Sexual Function

- Men = modest ethanol doses, increases sexual drive, but also decrease erectile capacity in men. even in the absence of liver impairment, a chronic alcoholic men causes irreversible testicular atrophy with shrinkage in seminiferous tubules, decrease in ejaculate volume and lower sperm count.
- Female = amenorrhea, decrease in ovarian size, infertility and increase risk of spontaneous abortion.

## The concept of alcoholism

Consuming chemical substances produce feelings of euphoria or pleasure and the development of dependence on those substances by a subset of individuals is as old as human race itself. The challenges of present and future studies is to understand how alcohol alter the brain systems to influence tolerance and to lead to the addicted state with the overarching goal of indentifying vulnerable populations and improving on current treatment strategies. Drug addiction is defined as a chronic relapsing disorder and the pattern of addiction depends on different components of the addiction cycle, depending on the dose and length of use. The cycle from being a user to abuser and then addiction is a negative one. The progression of drug addiction involves alteration in normal brain circuitry that results in long lasting drug induced neuroplastic changes (Koob and volkow, 2010)<sup>5</sup>. A better understanding of the main cellular mechanism and circuits affected by chronic drug use and the influence of environmental stressors, developmental trajectories and genetic factors on these mechanism will lead to a better understanding of the addictive process.

## The various concept behind these are



Reinforcement is a process, in which a response or behaviour is strengthened based on previous experience.

Positive reinforcement describes a situation in which a presumably rewarding stimulus or experience (eg. alcohol induced euphoria) increases the probability that the individual exhibits a certain response (alcohol seeking behaviour). Negative reinforcement occurs when the probability of an instrumental response increases if this response allows the individual to circumvent or alleviate an adverse stimulus. In alcohol dependence, the adverse stimulus often is composed of motivational/affective symptoms that manifest in the absence of alcohol (i.e during withdrawal) and which result from prior discontinuation of alcohol consumption. Sikha Lekharu, Khagen Basumatary. Alcoholism: An Understanding of the Neurosystemic Approach Involvement with Ayurveda

# 2. Neuroadaption

Changes in the reinforcing value of alcohol during the transition from alcohol use and abuse to dependence reflect adaptive neural changes resulting from chronic exposure to high alcohol doses. Multiple processes contribute to the increased motivation to seek drugs during the development of dependence.

- ✤ Sensitisation
- ✤ Tolerance
- ✤ Withdrawal

## Sensitisation

The incentive sensitisation theory of addiction points that addictive drugs activate a common neural system responsible for attributing incentive salience to events and stimuli associayed with the activation of that system (robinson & berridge, 1993)<sup>6</sup>. As a result, the liking of alcohol effects become closely associated incentive stimuli. Following repeated drug exposure, the wanting

**Brain Circuits Mediating Alcohol Reinforcement:-**

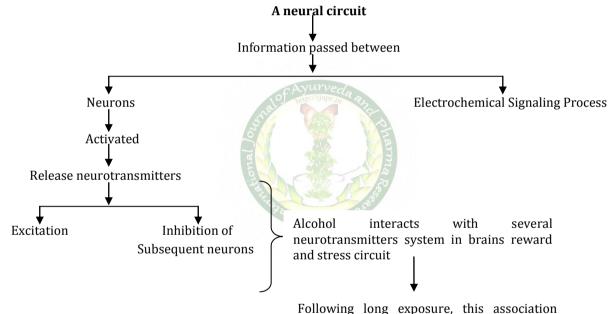
becomes stronger and transform into pathological craving for the drug

#### Tolerance

An organism that is chronically exposed to alcohol develops tolerance to its functional effects (Leblanc etal 1975)<sup>7</sup>, metabolic effects (wood & Laverty 1979)<sup>8</sup> and reinforcing properties (walker and koob 2007)<sup>9</sup>. once tolerance to the pleasurable effects of alcohol develops, the individual requires gradually higher doses of alcohol to produce the same effect previously experienced at lower doses.

## Withdrawal

Following chronic alcohol exposure, the removal of alcohol reliably produces a constellation of withdrawal symptoms, which may vary in severity according to the history of the individual. The physiological aspects of withdrawal in human last upto 48 hrs following termination of alcohol exposure and include convulsions, motor abnormalities and autonomic disturbances.



## A) Reward circuits and neurotransmitter system

Dopamine system: A neurotransmitter involved in a circuit called the mesolimbic system. this influences how an organism react towards incentive changes in environment. Study suggest that dopamine also has a role in the incentive motivation associated with acute alcohol intoxication. Alcohol ingestion and even the anticipation that alcohol will be available produce dopamine release in the nucleus accumbens as determined by increased dopamine levels in the fluid outside neurons (weiss et al 1993)<sup>10</sup>. Also alcohol withdrawal produces decreases in dopamine function in dependent individuals and this decreased dopamine function may contribute to withdrawal symptoms and alcohol relapse (Melis et al 2005, volkow et al 2007).<sup>11</sup>

Opiod system - opiod systems influence alcohol drinking behaviour both via interaction with the mesolimbic dopamine system, as demonstrated by alcohol induced increases in extracellular endorphin content in

results in changes in neuronal function

nucleus accumbens. Researchers have hypothesized that positive alcohol reinforcement is mediated at least in part by the release of endogenous opiods in the brain.

# γ – aminobutyric acid system

Gaba is the major inhibitory neurotransmitter in the brain. it acts via 2 receptor subtypes gaba a and gaba b. Alcohol can increase gaba activity in the brain through 2 general mechanism.

- It can act on the gaba releasing (i.e. presynaptic) neuron, increase gaba release.
- It can act on the signal receiving (i.e postsynaptic) neuron, facilitating the activity of the gaba a receptor.
- Alcohol drinking is suppressed by compounds that interfere with the actions of the *gaba* a receptors as well as compounds that stimulate the *gaba* b receptors.

#### **Glutamate System**

It is the major excitatory neurotransmitter in the brain, it exerts its effects via several receptor subtypes, including one called the N-methylD-asparate (NMDA) receptor. In contrast to its effect on gaba, alcohol inhibits glutamate activity in the brain. The involvement of NMDA receptor in alcoholism is specially interesting because they also play a role in neuroplasticity, a process characterized by neural re-organisation that likely contributes to hyperexcitability and craving during alcohol withdrawal (pulvirenti and Diana 2011).<sup>12</sup>

#### Late Stages Of Alcohol Dependence

#### Neurodegeneration

Chronic exposure to high doses of alcohol can result in profound changes in the morphology, proliferation and survival of neurons. in alcohol binge drinking rats, however both the proliferation of neural stem cells and the survival of neurons produced from the stem cells during alcohol exposure are decreased (Nixon & crews, 2002).<sup>13</sup>

#### **AYURVEDIC VIEW**

Ayurveda considers addiction under the toxic of *Madatya*, which means "intoxication". *Madatya* is the state or symptoms that arises due to continuous use or a high dose of substances that are intoxicating. The word *Madya* 

is derived from root word "mad" with suffix "*Yat*" which defines "*Madhyati janonema iti*" which means after consumption which makes the person to lose his senses.

# The relation with the Vedas

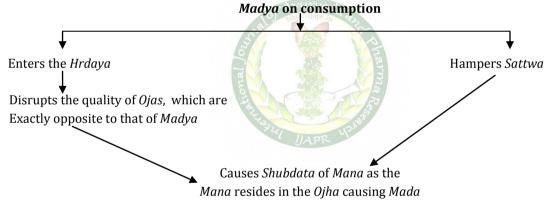
The role of *Madya* is relevant since time immemorial. in the *Yagnas* performed by the *Rishis*, *Madya* was used for proper functioning or completion of it. It was said to be "*Mohajanakatwa*" and having properties similar to *Vishas* (poison). The *Acharyas* are very clear that drinking *Madya* judiciously has a medicinal value in a person, but they have condemned the drinking of alcohol non judiciously

#### What is Madatya?<sup>14</sup>

Acharya Charaka has defined "Madatya" or "Mada" that state when excessive indulgence in alcohol, the properties (Gunas) of alcohol enters into the Hrdaya, causing Harsha, Tarsha, Rati, Sukha, Moha, Nidra etc based on the Rajasik or Tamasik nature of the individual. this disrupt nature of the mind which develops, is "Mada" or "Madatya".

#### Understanding the pathology

Acharya Charaka, has said likewise strong wind destroys the tree situated near the riverside, similarly "Madya" causes excessive "Shubdata" (injury) to the Mana i.e. mind. but how does this occur

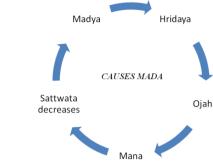


- a) The Marga or Srotas for the Rasadi Dhatus and Vatadi Tridoshas, Sattwa (Mana), Buddhi, Indriya, Atma and Ojha (Para Ojha)resides in the Hrdaya. So excessive intake of Mada, will destroy the Ojha, which will effect Hrdaya (Ashraya Ashrayi Bhava), leading to destruction of its components.
- b) The qualities of *Madya* are totally opposite to that of *Ojha*

Madya	Ojha
Laghuta	Gurutwa
Ushna	Shita
Amla	Madhur
Tikshna	Mridu
Ashu	Prasada
Ruksha	Snigdha
Vyavayi	Sthira
Vikasi	Sklakshna
Visada	Picchila
Sukshma	Bahala guna

- c) The *Ojha* is said to be the essence of all the *Dhatus*. The Para *Ojha* resides in the *Hridaya* and the *Apara Ojha* is circulated through the *Srotamsi* of the *Hrdaya*, all over the body. The long standing condition of alcohol abuse, will lead to conditions which arise as a result of metabolic abnormalities, leading to diminished production of *Ojha*.
- d) Evaluating the *Dosha* that are involved (*Rajasik* and *Tamasik*) effecting the *Satwata*, by the *Ojha* destroyed by the *Madya*, which resides in the *Hridaya*, the *Mana* gets effected.

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e) The stages and accordingly symptoms varies from the effect of *Ojha* 

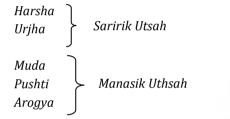
No Ojah Vikriti – Prathama Mada Avastha

Alpa Ojah Vikriti – Dwitiya Mada Avastha Uttam Ojah Vikriti – Tritiya Mada Avastha

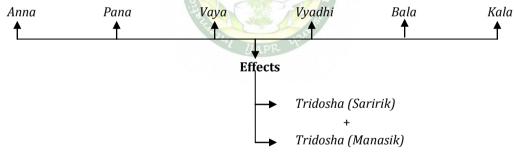
# Importance of proper way of drinking according to various texts

Ayurveda has given much interest on the drinking of alcohol. In *Charaka sutrasthana*, 5<sup>th</sup> chapter "*Matrashitiya aharamatra punaragnibalaapkekshini*" i.e., the food one takes depend on the quantity, which further depends on the *Agni* and *Bala* of an individual. likewise the amount of alcohol is choose based on this characters and is used judiciously is compared to nectar.

The benefits of drinking alcohol properly are



Thus the somatic and physhic development of a person takes place and factors which are involved in proper amount of intake are



# Some of the highlighting points are

- 1) The person who are *Prakrst* consumes alcohol at proper time, probably for him *Madya* is equivalent to amrita.<sup>14</sup>
- Madya is considered as Visha, but Visha if taken in proper amount acts as rasayana.<sup>14</sup>
- 3) In *Harita Samhita*, it has been said that as improper dose of alcohol acts as *Visha* (poison) similarly proper dose is beneficial and *Ayoga* leads to excessive problem.<sup>15</sup>
- Bhavaprakash has said that "Ayuktiyuktaya" leads to disease and "Yuktiyukta" of Madya acts as Rasayana.<sup>16</sup>
- 5) The qualities which are present in *Visha*, increasing the *Tridosha* are also present in *Madya*. The power of *Visha* is more powerful as compared to that of *Madya*.
- 6) In Astanga Hrdaya, Sutrasthana, "Dravadraviya Adhyaya", it is said that Madya acts as "Dipana" and "Rochana". The newly processed alcohol are guru

(digested lately) and is *Tridoshakarak*, while the old alcohol are *Laghu* (light to be digested) and is *Tridoshashamaka*.<sup>17</sup>

# CONCLUSION

- 1) *Madatya* causes psychosomatic disorder. *Manas* is *atindriya* and its action is either observable or inferable. Most of the pharmaceutical effects of alcohol are due to its accumulation in the brain. according to *Sarangadhar Samhita*, the drug possessing *Tamo Guna* predominantly causes derangement of mind called as *Madakari*.
- 2) Even though alcohol is widely used as a pshychosomatic drug, chronic alcohol consumption leads to permanent organ damage. alcohol abuse can result in brain damage and neurodegeration. Alcohol may also injure the brain by increasing the oxidative stress.

- 3) *Madya* on entering the heart counteracts the ten properties of *Ojas* with its corresponding ten properties and thus upsets the mind which ultimately give rise to mental disorders. *Oja* the essence in every *Dhatu* (tissue) is responsible for intelligence and memory. Apart from Longevity and better immunity Ayurveda believes that the body is made up of *Panchamahabhuta*, in the form of *Vata*, *Pitta*, *Kapha* at the physical level and *Sattwa raja Tamas* at the mental level. The imbalance in these body *humors* is the basic cause of any disease and in *Madatya* it is clearly indicative of *Madya* destroying the *Oja*.
- 4) *Oja* due to excess intake of *Madya* is destroyed. the Para *Oja* residing in the *Hridaya* is disrupted. In *Charak Samhita Siddhisthana*, it is said that *Urugata Hridaya* controls the activities of *Dasdhamani*, viz *Apana Vayu*, *Mana*, *Buddhi*, *Chetana* etc and the *Hridaya* present in *Shira* effects the *Gyanendriya* and *Karmendriya*.
- 5) The Gunas of Madya destroys the Gunas of Oja. The Gurutwa is destroyed by Laghutathus it does not remain in a place (Anaavastitawa), Ushnata causes Pitta prakopa, Tikshna being an attribute of Agnimahabhuta affects Marma (Shira, Hridaya), Ashu and Vyavayi as a drop of oil spreads over water as soon as it touches its surface, leads to quick dispersion of Visha (Madya) all over the body. Rukshata causes Vata to increase, Vikasi Guna breaks the bonding between various Dhatus and brings about Looseness in the Dhatus and resulting in improper function. Sukshma Guna of Madya helps in penetrating the Sukshma Srotas of the body.

## REFERENCE

- 1. Harrison's principles of internal medicine, 19<sup>th</sup> edition.
- 2. Baflour sclare, Epidemiology of Alcoholism, university of Glasgow.
- 3. NIAAA: Social work education for the prevention and treatment of alcohol use disorders; National institute on alcohol abuse and alcoholism, 2001a.
- 4. Richard A., Deitrich V gene Erwin, pharmacological effects of ethanol on the nervous system; pg no 375-376.
- 5. Koob & volkow; neurocircuitry of addiction, pubmed

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6. Robinson TE, Berridge KC. The neural basis of drug craving: An incentive sensitization theory of addiction. Brain Res Rev 1993; 18 (PubMed)

- Leblanc AE, Gibbins RJ, Kalant H. Generalization of behaviorally augmented tolerance to ethanol, and its relation to physical dependence. Psychopharmacologia. 1975;44(3):241–246. (PubMed)
- Wood JM, Laverty R. Metabolic and pharmacodynamic tolerance to ethanol in rats. Pharmacology, Biochemistry, and Behavior. 1979;10(6):871–874. (PubMed)
- 9. Walker BM, Koob GF. Pharmacological evidence for a motivational role of kappa opioid systems in Ethanol dependence; Neuropsychopharmacology, 2007, (PubMed)
- 10. Weiss F, Lorang MT, Bloom FE, Koob GF. Oral alcohol self-administration stimulates dopamine release in the rat nucleus accumbens: Genetic and motivational determinants. Journal of Pharmacology and Experimental Therapeutics. 1993;267(1):250–258. (PubMed)
- 11. Melis M, Spiga S, Diana M. The dopamine hypothesis of drug addiction: Hypodopaminergic state. International Review of Neurobiology. 2005; 63: 101–154. (PubMed)
- Pulvirenti L, Diana M. Drug dependence as a disorder of neural plasticity: Focus on dopamine and glutamate. Reviews in the Neurosciences. 2001; 12(2): 141–158. (PubMed)
- 13. Nixon K, Crew FT: Binge ethanol exposure decreases neurogenesis in adult rat Hippocampus. Journal of neurochemistry, 2002; 83 (5); 1087-1093 [PubMed].
- 14. Acharya Vidyadhar shukla, Prof Ravidatta tripathi; Chikitsasthana, Charak samhita; Choukhambha Sanskrit Pratisthana, Delhi.
- 15. Hariprasad Tripathi; Harit Samhita; Madatya Chikitsa chapter 16 pg 331 -332.
- 16. Sri Brahmashankarmisra Shastri, Bhavaprakash; Choukhambha Sanskrit Bhavan, Varanasi
- 17. Sri Vagbhatavirachitam; Hari Sadashiva Shastri Paradhara; Astanga Hridayam; Choukhambha Surabharati Prakasham, Varanasi.

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