REVIEW
OF
LITERATURE
Review of Literature

Cigarette smoking and alcohol are two independent risk factors responsible for a very large proportion of chronic diseases and several tumors. Much of the accumulated literature was on the effects, events, mechanisms and pathologies associated with chronic alcohol use or cigarette smoking separately. In reality many people both drink and smoke as 80% of alcoholics are confirmed smokers. Reports revealed that the neurochemical mechanisms of an action of nicotine and alcohol appear to be mutually reinforcing. Therefore, drinking and smoking together is strongly socially patterned. There is paucity of information concerning smokers who consume alcohol simultaneously.

Research for the past few decades on cigarette smoking or alcohol use separately revealed various facts related biochemical pathways, pathologies, etiology of diseases, nicotine dependence, the mechanisms associated with CVD, COPD, ARDS and their biochemical events, benefits as well as adverse effects of these psychoactive substances and also about ALD, CHD, Pancreatitis and their mechanisms. Limited studies are available on the combined use of alcohol and cigarettes. Those studies were also designed at scientists' discretion and reported conflicting and ambiguous results. Also several researchers emphasized to focus on comorbid effects of cigarette smoking and alcohol to understand the effect of one on the other. Available information related to the use of cigarette smoke, alcohol and combined exposure of cigarette smoke and alcohol is furnished below.

Cigarette smoke

Cigarette smoking is a reprehensible habit and the most preventable cause of death. Global estimates revealed that nearly 2.5 billion smokers exist in the world and also the number is on increase. Reports showed that 82% of total smokers were from low and middle income countries with 5-7 million deaths per year. Furthermore, by the end of the 21st century, 1 billion tobacco deaths are
projected and this could be avoided if people quit smoking. Studies revealed that quitting remains rare in low income and middle income countries.

**Prevalence, chemistry, biochemistry and toxicology:**

Prevalence of smoking is highest among people aged 30-49 years (37%) and lowest among youth 15-19 and is also relatively low among people aged 60 or older (24%). There is wide variation in smoking prevalence of males and females with higher in males in most countries about 60%. Among females the prevalence of smoking was highest in Europe and central Asia. Most smokers start before age 25, often in childhood and adolescent and most adult smokers' start their smoking when they are adolescent and parental separation increases the likelihood of commencement of adolescents smoking. Smoking habit is linked to several demographic variables (such as age, sex, socioeconomic level etc.,) with a number of general behavioral patterns (such as degree and kind of participation in a variety of social activities) with psychological characteristics (such as intelligence, school achievement etc) and with certain personality variables (such as intro and extroversion gregariousness, feeling of inferiority need for status etc).

Nicotine is the chief addictive compound of cigarette smoke that maintains cigarette smoking behavior. Nicotine activates the brains mesolymbic dopamanergic reward system and produces dependence resulting in physical and neurobiological withdrawal symptoms on abrupt cessation. Smoking intensity, smoking rate, or inhalation to maintain levels of nicotine is measured by plasma levels of nicotine in both adlibitum and laboratory smoking settings. The adverse effects of cigarette smoke are not due to nicotine but chiefly can be attributed to various other constituents of smoke. In fact, a single puff of cigarette smoke contains $1 \times 10^{15}$ reactive oxygen species, 500 ppm nitric oxide, and other reactive nitrogen oxides. Cigarette smoke has the capacity to damage the bronchi in a
number of ways, including direct toxicity to the bronchial epithelium, oxidative damage; recruitment of inflammatory cells, and increased epithelial permeability and smoking is associated with the development of airflow limitation in susceptible subjects.79

Nicotine interacting with nAChRs induces the release of various neurotransmitters, such as acetyl choline, growth hormone, adrenocorticotropic hormone (ACTH), noradrenalin, beta endorphin, glutamate, dopamine, serotonin and nitric oxide (NO).9 The released neurotransmitters exert numerous effects in the central nervous system and display a number of behavioral effects.9 As such nicotine exerts several beneficiary effects but cigarette smoke contains various other constituents which cause damage to all body organs. Hence the effects of nicotine can't be extrapolated to cigarette smoke. Cigarette smoke affects all body parts with no exception including the skin and integumentary system. Cigarette smoke, tobacco and its constituents affect the skin through external and internal exposure. Various skin cells express the nAChR of subtypes that affect cell survival and function. Heavy smokers can typically be identified by characteristic cutaneous and mucosal manifestations which include a yellow discoloration of right colored mustaches and finger nails that are stained by tobacco by products and also visible oral pigmentation, in particular Gingival pigmentation.3

Cigarette constitutes the major form of smoked tobacco.34 On an average smoker consumes 14-20 cigarettes each per day. Chinese records reveal that they cultivated and smoked it before the 1st millennium. Later it was spreaded to native populations of Americans and in Europe and subsequently brought to Africa and Asia.19 Now manufactured cigarettes are gradually replacing other forms of tobacco and tobacco products world wide. Various forms of tobacco pose greatest health risk since its combustion products are passed and absorbed through oral, pulmonary and vascular systems during puffs.34 Style of smoking and patterns of smoking
often differ. Cigarette smoking is often combined with the simultaneous use of other psychoactive drugs such as alcohol and other substances. Then interactions of smoke with other related constituents are common. However cigarettes are puffed repeatedly in order to keep them on and to make the smoker elite, and in doing so, they probably deliver relatively higher doses of constituents of smoke and tar.

The chemical composition of cigarette smoke is complex, with about 4000 known active chemicals and more than 1,00,000 unknown constituents (ocular, gas phase) of these more than 40 chemical are shown to be carcinogenic, and many others are deleterious to cardiovascular and pulmonary systems and other organs. Among these nicotine, tars, nitrosamines, polycyclic aromatic hydrocarbons, hydrogen cyanide formaldehyde and carbon monoxide are well known constituents of cigarette smoking. Besides many free radical species, aldehydes, peroxides, epoxides, nitrogen oxides, peroxyradicals and other prooxidants exist in gas phase.

Although nicotine is the addictive component of cigarette smoke, it should be recognized that effects of cigarette smoking are not equivalent to that of nicotine, as nicotine is one of the several thousand components of cigarette smoke. During the blending and processing of tobacco humectants such as glycerin and propylene glycol are added to increase the moisture holding capacity of tobacco to aid in processing while flavor in processing while flavor ingredients (nonvolatile aromatic materials like menthol and also foods such as chocolate, cocoa and spices such as vanilla nut mug ginger) are used to enhance flavor of tobacco smoke. Studies conducted by carmines et al., revealed the presence of various smoke constituents in different concentrations in normal cigarettes and cigarettes containing licorice extracts in TPM (total particulate matter). From earlier reports it is clear that cigarette smoke does contain numerous components. Cigarette smoke constituents can be categorized into two (i) The tar component of
cigarette smoke (ii) Gas components of cigarette smoke. Tar components of cigarette smoke contain an estimated $10^{18}$ spins/gram tar. The gas phase consists of as many as $10^{15}$ organic radical per puff.

**Risks from Smoking**

Smoking can damage every part of the body

- Cancers: Head or Neck, Lung, Leukemia, Stomach, Kidney, Pancreas, Colon, Bladder, Cervix
- Chronic Diseases: Stroke, Blindness, Gum infection, Aortic rupture, Heart disease, Pneumonia, Hardening of the arteries, Chronic lung disease & asthma, Reduced fertility, Hip fracture

Chronic cigarette smoking has been implicated in the pathogenesis of various pulmonary disorders, cardiovascular diseases and gastrointestinal disorders resulting in several cancers including lung, esophageal, pharynx.

**Pulmonary disorders:** Cigarette smoking is the major cause of chronic obstructive pulmonary disease (COPD) or chronic bronchitis and emphysema. In the epithelium of central airways, cigarettes smoke causes loss of cilia, mucus gland...
hyperplasia, and an increase in the number of goblet cells. Positive correlations between these pathological changes, as quantified by measurements of peripheral airway wall thickness and alveolar attachment, and bronchial hyper responsiveness have been documented, suggesting that exaggerated nonspecific airway narrowing in smokers with COPD and is secondary to structural changes caused by the disease.83,93

**Chronic Obstructive Pulmonary Disease:** Chronic obstructive pulmonary disease (COPD) is a long-term lung disease that causes shortness of breath, which initially occurs with exertion and becomes progressively worse over time. Limitation of the airways due to COPD is irreversible. Initially, shortness of breath may happen only when walking up hills or stairs. But with serious disease, even walking and normal activities will become difficult. People with these diseases often live for many years in varying degrees of discomfort and disability. Most people with COPD have smoked over 20 pack years of cigarettes (20 cigarettes per day for 20 years). Smoking contributes about 85% of the risk of developing COPD.48 The following three separate but often interconnected processes that occur in the lung lead to COPD. Inflammation of the bronchi, causing excessive amounts of mucus to be produced. This leads to coughing and phlegm production, and breathlessness. It may be associated with low-grade infection in the airways (chronic bronchitis). • The alveoli (air sacs) are gradually destroyed, so it becomes difficult to get enough oxygen (Emphysema).• Bronchi become narrow and floppy, making it difficult to breathe out. Chronic bronchitis and emphysema usually occur in current or former smokers. Current smokers are up to 10 times more likely to have the disease than non-smokers.27 Many people have a mixture of both diseases. While COPD is irreversible, quitting smoking has been shown to slow the progression of the disease. Other effects of COPD include a greater susceptibility to chest infections and pneumonia.
Lung cancer: The other major respiratory disease that smoking causes is lung cancer - the first major disease to be causally linked with smoking. Lung cancer mortality (death due to lung cancer) remains high once it has been diagnosed. Unlike many other cancers, there has been very little progress made in terms of early diagnosis and treatment.

New evidence has identified an important gene -p53, found in the nucleus of every cell. P53 is described as the 'guardian of the genome' and one of its main roles is to clean up any errors or changes that occur within copied cells. This means that any cell with damaged p53 is highly susceptible to cancer. Damaged DNA that replicates during cell division results in a modified cell population that may ultimately evolve into cancer. Men's lung cancer rates peaked in the early 1980's and are now in decline, reflecting declining smoking rates over the past three decades. Lung cancer in women is still increasing. In Australia in 2011, 90% of lung cancers in men and 65% in women were attributable to smoking. In smokers, the proportion of lung cancer attributable to smoking reaches 90% in both men and women. The risk of developing lung cancer is related to both extent and length of duration of smoking. For instance, a person who takes up smoking in their teens is five times more likely to die of lung cancer than someone who starts after their mid twenties. Smokers' risk of dying from Lung cancer is more than 10 times that of a non-smoker, and heavy smokers are between 15 and 25 times more at risk. Lung cancer usually takes at least 20 years to develop, and death rates today from lung cancer reflect increasing smoking rates beginning in 1910 -2011. Smoking is a major cause of cancers of the oral cavity, esophagus and larynx. The use of alcohol in combination with smoking greatly increases smokers' risk for these cancers.

Asthma: Asthma is a very common condition affecting the airways in the lungs. Exposure to cigarette smoke represents a major risk factor for the development of asthma. Tobacco smoke can affect the airway DC (Dendritic cells) network either directly or indirectly by causing the release of DC targeted mediator from the
pulmonary tissue environment resulting in the induction of a Th2-oriented pathological immune response. These become inflammation and irritable. When these irritable airways are exposed to certain 'triggers' the airways narrow, leading to difficulty in breathing. The result is a reduction of the flow of air in and out of the lungs. The most common symptoms of asthma are difficulty in breathing or shortness of breath, a feeling of tightness in the chest, wheezing and coughing (particularly at night). Asthma attacks can occur without warning, but are often related to poor control. The most common asthma trigger is viral infections (colds and flu). Others include house dust mite, pollens, moulds, animal dander (or hair), exercise (but this can be managed), tobacco smoke. Tobacco smoke is a powerful trigger for people with asthma, and one that all children should avoid. Exposure to cigarette smoke during pregnancy and early childhood significantly increases the risk of children developing asthma, and has also been shown to make asthma attacks more severe.

Cardiovascular risk: Heart damage is a consequence of harmful effects of smoking chemical components as well as metabolic changes of those parameters that cigarette smoking usually tends to alter. The two major mechanisms involved in coronary heart disease are atherosclerosis, which is a pathologic process that results in steanosis of the arteries, and thrombosis. Thrombosis, which causes the acute occlusion of the arteries usually at the site of a ruptured atherosclerotic plaque, is the final common precipitant of most acute coronary and other vascular events. Smoking impairs lipoprotein metabolism, reduces the distensibility of blood vessel walls, and induces a prothrombotic and proinflammatory state. Moreover, smoke exposure results in tissue damage by increasing the products of lipid peroxidation and of degradation of extracellular matrix protein, endothelial dysfunction, and by apoptosis. Among the parameters those are some related to atherogenic and thrombogenic risk such as increased cholesterol levels, triglycerides, total white, red and platelet blood cell count, hematocrit, prothrombin
time, partial thromboplastin time and fibrinogen, some related to ultrastructural changes of myocardial cell components such as mitochondria, enzyme chains, some intracellular bodies, and cellular receptors.\textsuperscript{13}

**Gastrointestinal disorders:** Cigarette smoking is responsible for the occurrence of cancer of mouth, pharynx, esophagus. The association of smoking with gastric duodenal ulcer disease is large. Smoking inhibits pancreatic bicarbonate secretion, decreases the pressure of esophageal and pyloric sphincters, impairs spontaneous and drug induced healing of peptic ulcer and increases the likelihood of duodenal ulcer recurrence.\textsuperscript{73} Due to the complexity of the pathogenesis of different GI disorders and the multiple actions of nicotine in the biological system, there is a long way to fully understand then involvement and therapeutic applicaation of nicotine in different kinds of diseases in the GI tract. Nicotine was found to boost up the mucin synthesis and thus provides a protective mucus layer in the colon.\textsuperscript{108} Nicotine also reduces circular muscle activity predominantly through the release of nitric oxide. It was found that nicotine reduced prostaglandin F1 alpha, F2 alpha and 15-hydroxyeicasatetraenoic acid levels in the rectal mucus of rabbits.\textsuperscript{113}

**Alcohol use**

Alcohol is a widely used and frequently abused psychoactive substance throughout world. Globally 2.5 billion people consume alcohol. Nearly 2 million deaths and many people are hospitalized every year are associated with alcohol.\textsuperscript{50} Besides, alcohol abuse and addiction are the leading causes of domestic violence and highway deaths. Alcohol is known to impair social, economic and sexual functioning as well as healthy life organization. However alcohol is consumed to excess by large population all over the world and the number of drinkers has been increasing alarmingly in the developing countries including India. Alcohol is often consumed by people for mood lifting and recreational purposes. Though moderate alcohol consumption has some benefits such as relaxation, protective effects on
Ethanol or ethyl alcohol (C₂H₅OH) is a transparent, colorless, volatile liquid having a characteristic spirituous odour with burning taste. Alcoholic beverages are a mixture of alcohol and water with small amounts of organic acids and esters. Alcohol (ethanol) content differs in different beverages as given below.⁴⁷

<table>
<thead>
<tr>
<th>Type</th>
<th>Alcohol content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rum, liquor</td>
<td>50 - 60%</td>
</tr>
<tr>
<td>Gin, arrack, whisky, brandy</td>
<td>40 - 45%</td>
</tr>
<tr>
<td>Port, sherry</td>
<td>20%</td>
</tr>
<tr>
<td>Wine</td>
<td>10 - 15%</td>
</tr>
<tr>
<td>Beers</td>
<td>4 - 8%</td>
</tr>
</tbody>
</table>

Arrack is the commonly used liquor by lower class Indian population. It is distilled from palm, rice, sugar or jaggery etc., and mixed with chloral hydrates and potassium bromide for getting greater kick.⁶⁶

Ethanol is responsible for characteristic effects of alcohol. While small amounts of alcohol acts as a drug producing euphoria for some people, it is addictive with the characteristics of tolerance, dependency, withdrawal symptoms and toxicity. Certainly alcohol is a substance available in the diet, but it does not meet the definition of a nutrient.⁴⁷ Ethanol is a central nervous system depressant that decreases the activity of neurons, although some behavioral stimulation is observed at low blood levels. 20 mM alcohol in plasma is an indicative of intoxication.⁴³ This drug has cross tolerance and shares a similar pattern of
behavioral problems with other brain depressants, including the benzodiazepines, barbiturates with other sedatives and hypnotics.  

Metabolism of alcohol:

In the digestive tract, mainly in the stomach alcohol diffuses into gut cells and travels via portal vein directly to the liver where most alcohol metabolism takes place. On the other hand, alcohol is subjected to renal clearance. The body works extra hard to get rid of it and quickly metabolizes and it removes from blood. If blood alcohol levels reach 0.04% (1 to 2 drinks) and cause mild, pleasant changes in mood and release of inhibitions. With more than 3 drinks, blood alcohol levels rise leading to impairment of coordination, judgment, reaction time and vision. People with blood alcohol levels 0.05-0.08% are not allowed to drive motor vehicles in United States of America and Canada. Consumed alcohol enters every organ system through the blood stream and affects all the tissues especially brain, heart, liver and gastrointestinal tract. As alcohol through circulation reaches the brain immediately after consumption, the alcohol concentration rises in different parts of the brain which are affected.

The liver selectively metabolizes alcohol and there exists alternative pathways to handle excess consumption. Mitochondrial alcohol dehydrogenase, a zinc containing enzyme converts alcohol to acetaldehyde and aldehyde dehydrogenase quickly and effectively converts acetaldehyde to acetate. When large amounts of alcohol prevail, the microsomal ethanol oxidizing system (MEOS) operates at a faster speed to process alcohol quickly and converts it to acetaldehyde. Hence this route is an overflow pathway. The peroxisomes contain the enzyme catalase which is capable of peroxidation of ethanol to acetaldehyde and water in presence of hydrogen peroxide. The hydrogen peroxide is generated in smooth endoplasmic reticulum by NADPH oxidase utilizing hydrogen equivalent and molecular O₂ for the formation of NADP⁺.
Acetaldehyde is then oxidized to acetate by a mitochondrial enzyme aldehyde dehydrogenase which is also NAD⁺ linked. Acetate formed from ethanol is activated to Acetyl CoA. The AcetylCoA formed is ultimately oxidized via citric acid cycle and yields 7.1 k.cal energy per gram. Much of the acetate formed from ethanol escapes from the liver and enters into blood. Virtually, every other cell with mitochondria can oxidize it to CO₂ by the way of TCA cycle. Acetaldehyde, the intermediate in the formation of acetate from ethanol, can also escape from the liver. Acetaldehyde forms covalent bonds with functional groups of biologically important compounds. Formation of acetaldehyde adducts with proteins in tissues and blood of animals and humans drinking alcohol has been demonstrated. Such adducts may provide a marker for past drinking activity of an individual. Recent studies suggested that acetaldehyde directly participates in the pathogenesis of alcoholism. Effects of chronic excessive alcohol consumption are well documented. Excessive alcohol intake adversely affects all the body parts and organs with no exception.
Alcohol Intake: Numerous gene-alcohol interactions influencing both intermediate (plasma lipid concentrations, glucose, anthropometric measures, inflammatory markers, etc.) and final disease phenotypes (cardiovascular diseases, cancer, neurodegenerative diseases, etc.) have been described.\textsuperscript{18,29,111}

Although there are differences among countries,\textsuperscript{23} the National institute on Alcohol Abuse and Alcoholism definition stipulates that a standard drink is 17.74 ml of pure alcohol. This amount is equivalent to 354.8ml of beer, 147.9 ml of wine, or 44.4ml of (40% alcohol by volume) hard liquor.\textsuperscript{68} Among the biomarkers most used in epidemiological studies as approximations to alcohol consumption are carbohydrate-deficient trasferrin (CDT) and gamma-glutamyltransferase (CGT) levels in plasma.\textsuperscript{70} In addition to CDT and CGT, commonly used biomarkers include mean corpuscular volume, aspartate aminotrasferase, alanine aminotrasferase, sialylation of apolipoprotein, ethyl glucuronide, and 5-hydroxytrytophol.\textsuperscript{33}

Alcohol liver disease (ALD): In many individuals, consistently high levels of alcohol intake leads to alcoholic liver disease (ALD), a major cause of morbidity and mortality worldwide and is responsible for about 3.8% of global mortality.\textsuperscript{97} Moreover, ALD remains one of the most important causes of liver-related deaths in the USA, with a mortality of 4.4 deaths per 100,000 of the population-even higher than that of hepatitis C (2.9 deaths per 100,000 people).\textsuperscript{74} ALD is, therefore, the second most common indication for liver transplantation in Europe and North America.\textsuperscript{12,101} Heavy alcohol drinking is also associated with disorders unrelated to the liver, such as infections, malignaneies, cardiovascular events and diseases of the nervous system, pancreas and kidneys.\textsuperscript{35} The spectrum of ALD encompasses fatty liver, hepatic inflammation and necrosis, progressive fibrosis and hepatocellular carcinoma.\textsuperscript{98} Furthermore, a sustained, excessive alcohol intake favors the
progression of other liver diseases, such as chronic viral hepatitis (hepatitis C and B) and other metabolic liver diseases, such as hemochromatosis, Wilson disease and fatty liver associated with the metabolic syndrome.16,37,38,40,92

Alcohol cardiovascular diseases: The American Heart Association estimates that more than 34 percent of the United States population has some form of cardiovascular disease. Tobacco use and alcohol consumption both are major risk factors for various forms of cardiovascular disease. However, little evidence exists to suggest that drinking and smoking together raise the risk more than the sum of their independent effects. Determining the risk factors for cardiovascular disease is difficult because the issues involved are extremely complex. First, cardiovascular disease encompasses a variety of conditions (such as heart attack, stroke, and hardening or narrowing of the arteries), which result from numerous factors. Second, although tobacco has been shown to raise the risk for cardiovascular disease in a dose-dependent manner. The more a person smokes, the more his or her risk of developing cardiovascular disease increases. Alcohol’s effect on cardiovascular disease depends on many factors, including gender, age, and drinking patterns. Epidemiological studies have suggested that moderate alcohol consumption reduces the risk of cardiovascular diseases.24 In the absence of large prospective clinical trials, dozens of studies, both ecological and case-control and cohort have shown an inverse relationship between moderate alcohol consumption and several outcomes related to cardiovascular diseases.24,65,85

A recent meta-analysis reviewed the results from interventional studies on the effects, of alcohol consumption on 21 biological markers associated with coronary heart disease risk in adults without known cardiovascular diseases.10 The markers studied were lipids (triglycerides, total cholesterol, HDL-C, low density lipoprotein cholesterol (LDL-C), lipoprotein (a), and apolipoprotein A-1), inflammatory markers (C-reactive protein, leukocytes, interleukin-6, and tumor necrosis factor-a), hemostatic factors (plasminogen activator inhibitor 1, von
Willebrand factor, tissue plasminogen activator, fibrinogen, and e-selectin), endothelial cell function markers (intracellular adhesion molecule 1 and vascular cell adhesion molecule), and hormones (leptin and adiponectin). Based on the pooled results, the authors found that alcohol consumption significantly increased HDL-C and apolipoprotein A-1 concentrations, with linear dose-response relationships. In contrast, alcohol didn't significantly change the levels of total cholesterol, LDL-C, triglycerides, or lipoprotein (a). Researchers also observed that a very high dose of alcohol (>60 g/day) caused an increase in plasma triglyceride concentrations. Apart from a favourable change in plasma lipid concentrations, recent studies have observed a favourable effect on other markers of inflammation and endothelial damage, as well as on hemostatic factors.

ARDS (Acute Respiratory Distress Syndrome): Alcohol abuse is a comorbid variable that independently increases by about 3-4 times the incidence and severity of acute respiratory distress syndrome (ARDS) in alcoholics. ARDS mortality was 65% in chronic alcoholics compared with 36% for non alcoholics. Chronic over consumption of alcohol causes oxidative stress in the lungs through its metabolism and diminishes the synthesis and utilization of glutathione (GSH), which is a major antioxidant, resulting in impairment of the antioxidant ability of cells. The clinical disorders commonly associated with ARDS can be divided into those leading to direct injury to the lung and those that cause indirect lung injury in the setting of a systemic process. The pathophysiology of ARDS involves multiple complex pathways and mechanisms, including the production of oxygen radicals by stimulated neutrophils and macrophages, resulting in oxidative stress. Alcohol metabolism in the lung through the cytochrome p450 leads to acetaldehyde production which in turn causes oxidative stress by oxygen radical generation, lipid peroxidation and decreased antioxidant activity.
**Alcohol consumption and cancer:** Studies of the associations between alcohol consumption and cancer have reported conflicting results. Currently, there is strong evidence that alcohol consumption increases the risks of cancers of the liver, oral cavity, pharynx, larynx, and esophagus.\(^{49,88,100,103}\)

**Cancers of the Mouth and Throat:** People who drink and smoke are at higher risk for certain types of cancer, particularly those of the mouth and throat. Alcohol and tobacco cause approximately 80 percent of cases of cancer of the mouth and throat in men and about 65 percent in women. For people who both smoke and drink, the danger of mouth and throat cancer increases dramatically. In fact, the combined risk is greater than or equal to the risk associated with alcohol multiplied by the risk associated with tobacco. Alcohol and tobacco co-use appears to substantially increase the risk of at least one type of cancer of the esophagus.\(^{100}\)

**Liver cancer:** Heavy, long-term alcohol use, together with hepatitis B or C virus infections, is the main risk factor for hepatocellular carcinoma.\(^{87}\) In around 80% of cases, hepatocellular carcinoma is associated with cirrhosis or advanced fibrosis, inflammation, and oxidative stress, and high alcohol consumption contributes to the development of these conditions. Alcohol consumption (former or current) was associated with a significant 17% (10-25%) increase in the rate of liver cancer. During the past decade, the incidence of liver cancer has increased dramatically in the United States. Although some studies have reported that alcohol and tobacco may work synergistically to increase the risk of liver cancers more research is needed to explore this issue.\(^{88}\)

**Gastric Cancer:** However, the suggestion that alcohol consumption might be associated with an increased risk of gastric cancer has become stronger, as there may have been confounding because of tobacco smoking and diet in the results of earlier studies.\(^{56}\) To explain this heterogeneity, the authors suggested the possible
role of ADH and ALDH polymorphisms, which have a different prevalence between Asian and non-Asian populations.30,60,75,76

Colorectal cancer: For many years, studies on the association between alcohol consumption and the risk of colorectal cancer have reported contradictory results, although many have concluded that there is a greater risk of colon cancer. They found a strong association between alcohol consumption and colorectal cancer, which followed a dose-response relationship. The greater the alcohol consumption, greater the risk of colorectal cancer.22 As with gastric cancer, the authors found heterogeneity depending on the geographical area. However, in contrast to gastric cancer, the colorectal cancer risk for heavy drinkers was greater in studies carried out in Asian populations.32

Breast Cancer: As with gastric cancer, there is great heterogeneity in the results published on the association between alcohol consumption and breast cancer. In the IARC study published in 2007,6 the breast was included as a cancer localization related to alcohol consumption. The authors hypothesized that increased alcohol consumption can lead to higher estrogen concentrations and that these estrogens contribute to an increased risk of cancer.27 Finally, the association between alcohol consumption and Lung cancer results from the frequent association between tobacco smoking and alcohol.

Outstanding among them is the work conducted by Hashibe et al., analyzing six ADH polymorphisms in over 3800 aero digestive cancer cases (and 5200 controls) from three individual studies.42 They found that polymorphisms in the ADH1 B (rs 1229984) and in the ADH 7 (rs 1573496) genes were significantly associated with a lower risk of cancer. The main metabolite of ethanol, namely, acetaldehyde, can induce DNA lesions, which if left unrepaired can initiate carcinogenesis.112 It would therefore be useful if the methodology for studying
gene-alcohol interactions was standardized in any new study undertaken in order to improve the consistency level among studies.27

Combined use of alcohol and cigarette smoke

Cigarette smoking is common among persons with alcohol dependence or abuse with as many as 85-95% of persons who are alcohol dependent also being smokers.6 This combined exposure to both tobacco smoke and alcohol results in major health consequences including additive risks for some diseases such as head and neck cancers, cardiovascular problems and many other problems. Vast literature is available separately on alcoholism as well on cigarette smoking. The precise mechanisms of action of alcohol and nicotine and several events related to these are not clear. Actual events and biochemical effects that occur in alcoholics who smoke cigarettes were not studied systematically so far.

Very limited literature explicitly explored the biochemical events and related mechanisms of exposure of cigarette smoking and alcohol consumption. A potential aspect in this regard is that several other unmeasured factors such as dietary intake and physical activity might act as confounding variable or interacts with alcohol consumption and cigarette smoking to influence biochemical events. Johnson et al. (1999) reported that cigarette smoking slows gastric emptying and as a consequence delays alcohol absorption.52 Most of the studies on cigarette smoking associated with alcohol consumption have been carried out in western societies with little published comparable data for Asian populations, in particular for Indian population. Several studies revealed association between blood lipids especially and the habits along with the joint use of alcohol and cigarette smoking which were reported to have strongly conditioned blood lipids, body weight and than non-smokers and non-alcoholics.
Nixon et al. (2007) observed cognitive enhancing effects of acute nicotine on attention processes and alcoholics who are regular smokers and more sensitive to the effects of nicotine on cognition. The combined ingestion of ethanol and cigarette smoke resulted in significant formation of smoke related DNA adducts in the esophagus and in their further dramatic increase in the heart. Moderate alcohol consumption among long term smokers may potentially decrease the risk of adenoma compared to abstainers. Human in vivo protein magnetic resonance spectroscopic imaging finding indicated that chronic cigarette smoking exacerbates chronic alcohol-induced neuronal viability and cell membranes in the midbrain and on cell membranes of the cerebellar vermis. Higher smoking levels are associated with metabolic concentrations in selected subcortical structures.

Though nicotine appears to be the chief constituent of cigarette smoke, many other known and unknown toxic components of the smoke interact directly and indirectly exert several effects. Ribeiro-Carvalho et al. (2009) demonstrated that the central cholinergic system in mice is a site at which nicotine and ethanol interact and this interaction was thought to be associated with tobacco and alcohol consumption. The combined use of alcohol and cigarettes smoke during pregnancy by women was reported to increase the risk of low birth weight in a South Africa. In view of this and adverse effects, pregnant women are advised to reduce or prevent the use of both substances during pregnancy as most of the women who drink during pregnancy also smoke cigarettes.

Reports also revealed that nicotine dependence as comorbidity of alcohol dependence and the possible biological causes for this high comorbidity are 1) an additive rewarding affect by combined consumption, 2) substance interaction with an impact on receptor activation and metabolism which results in reduction of adverse acute alcohol effects, and 3) a combined genetic disposition for both addictions. Abreu-Villaca et al. (2007) reported that the combined use of nicotine...
(cigarette smoking) and ethanol (use of alcoholic beverages) resulted in detrimental effects on memory and learning. On the other hand, the combined acute effects of red wine consumption and cigarette smoking post prandially indicated an additional favorable effect of red wine.\textsuperscript{109}

Antioxidant substances in red wine counteracted the smoking induced increase in peripheral systolic blood pressure. Serotonin (5-HT) is a biogenic amine synthesized in the central nervous system and modulates a variety of behavioral functions including the regulation of sleep, appetite, nociception, mood, stress and sexual behavior.\textsuperscript{102} Serotonergic dysfunction is implicated in various types of psychopathological conditions, such as antisocial personality disorder, alcoholism, depression with suicidality and antisocial behavior with aggression, obsessive-convulsive syndromes, psychosis, eating disorders, substance abuse and schizophrenia. Serotonin is also reported to be synthesized by intestinal enterochromaffin cells. Serotonin is actively incorporated into platelets and stored in platelet dense granules.\textsuperscript{107}

Both alcohol and smoking affect the physicochemical properties as well the functions of platelet membrane separately in alcoholics and smokers respectively. The combined use of alcohol and cigarette smoke has not been investigated thoroughly. Several biochemical components of platelet serve as biological markers in evaluating and confirming various health disorders including cardiovascular, neurodegenerative and psychiatric diseases. Both short and long term alcohol exposure affect the serotonin receptors that convert the chemical signal produced by serotonin into functional changes in the signal receiving cell. Drugs that act on these receptors alter alcohol consumption in both humans and animals. Serotonin, along with other neurotransmitters, also may contribute to alcohol intoxicating and rewarding effects, and abnormalities in the brains. Serotonin system appears to play an important role in the brain processes.
underlying alcohol abuse. Serotonin mediated neuronal responses to alcohol may arise from interactions between serotonin and other neurotransmitters such as GABA and dopamine.

Experiments of Wang et al. (2008) revealed that humans of different carriers of epsilon 3 and epsilon 4 and Avail (+) alleles would have higher risk of suffering from CHD if they drink alcohol or smoke heavily. Further, Ahmed et al. (1998) reported that cardiovascular abnormalities of long-term cigarette smokers predominantly depend on nicotine of cigarettes. Alcohol and cigarette smoking, together decrease serum or plasma beta-carotene levels and vitamin E indicated a protective effect of cigarette smoking and alcohol consumption in the occurrence of clinical benign prostatic.

Cooper and Magwere (2008) concluded that nicotine and alcohol consumption induced pathogenesis is mediated through nitric oxide. Several experiments reveal that chronic ethanol ingestion increases endothelial nitric oxide expression and nitric oxide production. Cigarette smoke induced oxidative damage is well documented. Several reports reveal a decrease in blood serotonin levels and also platelet MAO activity. Differential effects of nicotine on alcohol consumption in men and women were reported. Additive cardiovascular effects of ethanol and nicotine contributed to arrhythmias and sudden death in patients with coronary heart disease.

Ashakumary and Vijayammal (1996) reported that cigarette smoking and alcohol consumption had additive effect on lipid peroxidation, antioxidant defense mechanism in rats. Alcohol consumption induced changes in platelet properties and functions. Nicotine was reported to decrease blood alcohol concentrations in rats. Wu et al. (2001) reported that cigarette smoking and alcohol consumption were confirmed to have similar effects on lipid and lipoprotein levels in Caucasians. Furthermore, joint exposure to smoking and drinking would help in predicting lipid
and lipoprotein levels. Shrubsole et al. (2007) demonstrated that the effect of alcohol and tobacco is cumulative, with higher levels of alcohol and tobacco consumption being associated with higher levels of testosterone before and after alcohol withdrawal.

It is clear from literature that combined exposure to cigarette smoke and alcohol affects all body organs and tissues at a time with no exception leading to much oxidative damage resulting in several diseases. The therapy should be in such a way that multiple action of the therapeutic agents acting at several sites at a time. Hence treatment with phyto extracts containing compounds in multiple with multi model action along with free radical scavenging and antioxidants capacity is most warranted to reduce the burden of the combined use of alcohol and cigarettes.
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