بسم الله الرحمن الرحيم

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بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

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Erythrocyte Antioxidant Defence Potential in Chronic Ethanol and Cannabis Intoxication

THESIS

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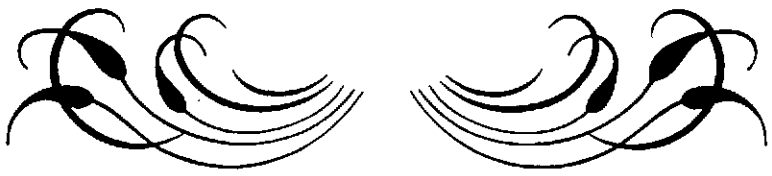

Dedicated To

My Mother

My Beloved Wife

My Children

CONTENT

INTRODUCTION

As far back as recorded history, every society has used drugs that produce effects on mood, thought, and feeling. Moreover, there were always a few individuals who digressed from custom with respect to the time, the amount, and the situation in which these drugs were to be used. Thus, both the nonmedical use of drugs and the problem of drug abuse are as old as civilization itself[1].

The term drug abuse refers to the inappropriate, and usually excessive, self-administration of a drug for nonmedical purposes[2]. The term "drug abuse" is unfortunate because it connotes social disapproval and may have different meanings to different people. One must also distinguish drug abuse from drug misuse. Abuse of a drug means any use of a drug for nonmedical purposes, usually for altering consciousness but also for body-building, etc. Drug misuse take a drug for the wrong indication, in the wrong dosage, or for too long a period[3,4]. The use of medically prescribed opioid analgesics for the relief of pain is quite proper; however, the self-administration of the same drugs, in the same dosages, for relief of depression or tension or to induce euphoria is considered flagrant abuse[1].

Drug abuse may lead to development of dependence[2]. Psychologic dependence is manifested by compulsive drug-seeking behavior in which the individual uses the drug repetitively for personal satisfaction, often in the face

of known risks to health. Cigarette smoking is an example[3]. Physiologic dependence is a condition in which the body needs the drug for physiological functions to remain normal. Alcohol drinking is an example[5].

Psychologic dependence almost always precedes physiologic dependence but doesn't inevitably lead to it. Addiction is usually taken to mean a state of physiologic and psychologic dependence, but the word is too imprecise to be useful. Tolerance signifies a decrease response to the effects of drug necessitating ever larger doses to achieve the same effect[6,7].

Ethyl Alcohol Dependence

Alcohol, primarily in the form of ethyl alcohol (ethanol), has occupied an important place in the history of human kind for at least 8000 years. Today, alcohol is widely consumed, and it is also the most commonly abused drug in the world[8]. People who continue to drink alcohol in spite of adverse medical or social consequences related directly to their alcohol consumption suffer from alcoholism, alcoholism remains a common chronic disease that is difficult to treat. Ethanol is also used in industry[9].

Absorption, Fate, and Excretion

Ethanol is a small water-soluble molecule that is absorbed rapidly from the gastrointestinal tract. After ingestion of alcohol in the fasting state, peak blood alcohol concentrations are reached within 30 minutes. The presence of food in the gut delays absorption by slowing gastric emptying[10].The distribution of ethanol is rapid and throughout the body fluids[9].

Over 90% of alcohol consumed is oxidized in the liver; the rest is excreted through the lungs and in the urine. The rate of oxidation follows zero-order kinetics, ie, it is independent of time and concentration of the alcohol. The amount of alcohol oxidized per unit time is approximately proportionate to body weight or liver weight, and the rate of disappearance of alcohol from the body is markedly reduced by liver damage[11].

Metabolism

Two pathways of alcohol metabolism to acetaldehyde have been identified (fig. 1). Acetaldehyde is then oxidized by a third metabolic process.

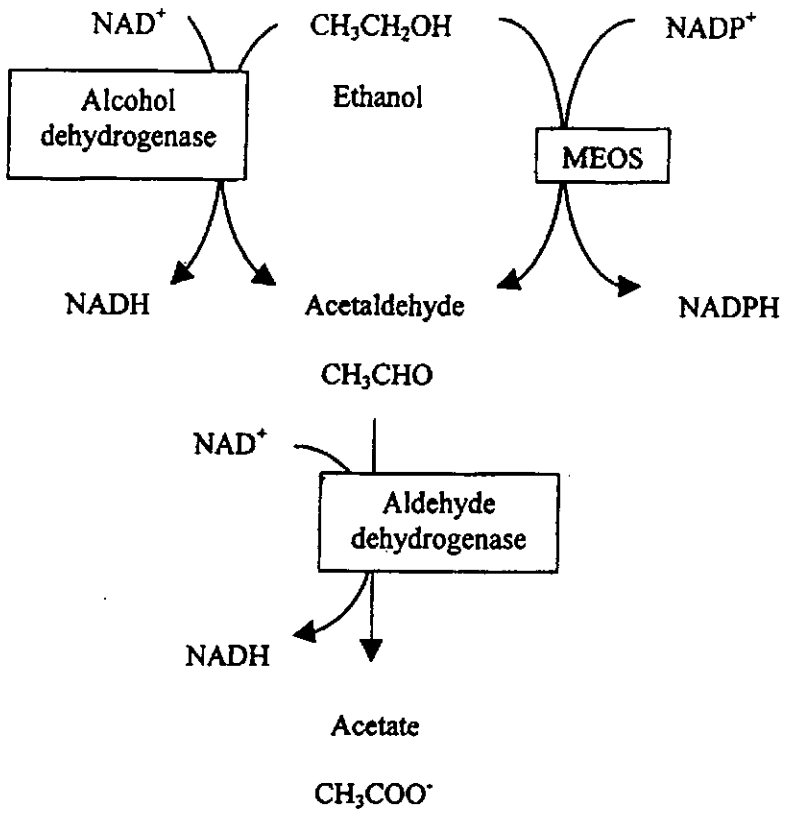

Figure (1): Metabolism of ethanol by alcohol dehydrogenase and the microsomal ethanol-oxidizing system (MEOS)[10]

A-1. Alcohol dehydrogenase pathway

The main pathway for alcohol metabolism involves alcohol dehydrogenase (ADH), a cytosolic enzyme that contains zinc and catalyzes the conversion of alcohol to acetaldehyde (fig. 1 left). This enzyme is located mainly in the liver, but it can also be found in other organs such as brain and stomach. During conversion of ethanol to acetaldehyde, hydrogen ion is transferred from alcohol to the cofactor nicotinamide adenine dinucleotide (NAD^+) to form NADH. As a net result, alcohol oxidation generates an excess of reducing equivalents in the liver, chiefly as NADH[10].

A-2. Microsomal ethanol oxidizing system (MEOS);

This enzyme system, also known as the mixed function oxidase system, uses $NADP^+$ instead of NAD^+ as a cofactor in the metabolism of ethanol (fig. 1 right). At blood concentrations below 100 mg/dL, the MEOS system contributes little to the metabolism of ethanol. However, when large amounts of ethanol are consumed, the alcohol dehydrogenase system becomes saturated owing to depletion of the required cofactor, NAD^+. As the concentration of ethanol increases above 100 mg/dL, there is increased contribution from the MEOS system, which doesn't rely upon NAD^+ as a cofactor[10].

During chronic alcohol consumption, MEOS activity increases. Chronic alcohol consumption can result in significant increases not only in ethanol metabolism but also in the clearance of other drugs that are eliminated by hepatic microsomal enzyme systems. Acute ethanol intake may inhibit drug metabolism while chronic ethanol intake may enhance the induction of drug metabolising enzymes in the liver[12].

B. Acetaldehyde Metabolism

Acetaldehyde is a highly reactive substance whose toxicity greatly exceeds that of ethanol, much of the acetaldehyde formed from alcohol appears to be oxidized in the liver[13]. Mitochondrial NAD^+-dependent aldehyde dehydrogenase is the main pathway for acetaldehyde oxidation. The product of this reaction is acetate (fig.1), which can be further metabolized to CO_2 and water. Chronic alcohol consumption results in a decreased rate of acetaldehyde oxidation in intact mitochondria[14,15].

Consequences of chronic alcohol consumption

Chronic alcohol consumption profoundly affects the function of several vital organs, particularly the liver, the nervous, gastrointestinal, and cardiovascular systems. Ethanol has direct toxicity[16,17].

Liver disease is the most common medical complication of alcohol abuse; it is estimated that about 15-30 % of chronic heavy drinkers eventually develop severe liver disease. Alcoholic fatty liver, a reversible condition, may progress to alcoholic hepatitis and finally to cirrhosis and liver failure[15,18].

The regular ingestion of more than moderate amounts of alcohol leads to increased accumulation of acetaldehyde, in part due to reduced activity of acetaldehyde dehydrogenase. The acetaldehyde is thought to cause a lot of deleterious effects, including enhanced lipid peroxidation[19].

Like other sedative-hypnotic drugs, alcohol is a central nervous system depressant. At high blood concentrations, it induces coma,

respiratory depression, and death[20]. The effects of ethanol on the CNS are proportional to its concentration in the blood[21]. Chronic excessive ingestion of ethanol is directly associated with serious neurological and mental disorders (e.g., brain damage, memory loss, sleep disturbances and psychoses)[22]. The most frequent neurologic abnormality in chronic alcoholism is a generalized symmetric peripheral nerve injury. Chronic alcoholic patients may also exhibit gait disturbances and ataxia that are due to degenerative changes in the central nervous system. Other neurologic disturbances associated with alcoholism include dementia and, rarely, demyelinating disease[23].

Alcohol alters the cardiovascular system in many ways. Heavy alcohol consumption of long duration is associated with a dilated cardiomyopathy with ventricular hypertrophy and fibrosis. In animals and humans, alcohol induces a number of changes in heart cells that may contribute to cardiomyopathy. Alcohol is estimated to be responsible for approximately 5% of cases of hypertension[24].

Ingestion of alcohol increases gastric and pancreatic secretion and alters mucosal barriers so that the risk of gastritis and pancreatitis is enhanced. Chronic consumption of large amounts of alcohol is associated with an increased risk of mortality[17].

The most common hematologic disorder seen in chronic drinkers is mild anemia resulting from alcohol-related folic acid deficiency. Alcohol has also been implicated as a cause of several hemolytic syndromes, some of which are associated with hyperlipidemia and severe liver diseases[25].

Ingestion of ethanol causes a feeling of warmth because alcohol enhances cutaneous and gastric blood flow. The consumption of ethanol in high doses over a long period results in tolerance and in physical and psychologic dependence[26].

Alcohol and cannabis have additive effect. Previous studies showed that the liver dysfunction was more pronounced in subjects associated cannabis smoking and drinking of alcohol[27,28].

Cannabis Dependence

Historically, cannabis [also known as marijuana (MJ) or marihuana] has been used, for thousands of years, for a variety of purposes. Extensive scientific efforts have been made to study its pattern of use vigorously, as well as its social and public health implications[29].

Cannabis has been regarded as useful medicinal drug by some, a sacred grass by others, a source of pleasure to many and a menace requiring dramatic public action by yet another group[30].

The chronicle of its 3000-year history shows that the oldest known therapeutic description was by the Emperor Shen-Nung in the twenty-eight century B.C. in china where the plant has been grown for fiber. He prescribed cannabis for the treatment of beriberi, constipation, gout, malaria, and absent-mindedness. He also considered cannabis as healthful and psychotic liberator substance. However, the Chinese were neither aware nor attracted by its euphoriant properties at that time[31]. The euphoriant properties of cannabis were mentioned by Herodotus, the greatest ancient Greek historian (484-404 B.C.), as a pleasure-inducing drug. In Egypt, in the twentieth century B.C., cannabis was used to treat sore eyes[32].

In India prior to the tenth century B.C. bhang, a cannabis preparation was used as an anaesthetic. The religious use of cannabis in India is thought to have preceded its medical use and is concerned with freeing the mind of the user from worldly distractions and concentrating on the Supreme Being. From the tenth century B.C. up to 1945 (or even later), cannabis has been used in India to treat a wide variety of diseases, as asthma and bronchitis[33].

The uses of cannabis gradually spread from India to the Middle and Near East during the next several centuries, then moved across North Africa to reach Latin America and the Caribbean, and finally appeared in the United States in the nineteenth century when french interest in cannabis was aroused by the returning soldiers and scientists of Napoleon's army shortly after invasion of Egypt, a source of cannabis. In the United States a similar interest occurred after the Korean war and has been intensified since Vietnam War[31].

According to modern Arabic historians, the herb came to be reintroduced (viz. planted and used) in Egypt around mid-twelfth century A.D. Its use became very common among members of the lower strata of the Egyptian society towards mid nineteenth century[34].

Chemistry of Cannabis

Over 60 naturally concurring cannabinoids have been characterized. Many of these compounds are present in low concentrations and play little or no part in the pharmacological profile of the plant[35,36]. Three major cannabinoids have been found in cannabis; cannabidiol