CHAPTER I
INTRODUCTION

I.1. Background

Curcuma longa turmeric is a spice derived from the rhizomes, which is a member of the ginger family (Zingiberaceae). Rhizomes are horizontal underground stems that send out shoots as well as roots. The bright yellow color of turmeric comes mainly from Fat-soluble, polyphenolic pigments known as curcuminoids. Curcumin, the principal curcuminoid found in turmeric, is generally considered its most active constituent Other curcuminoids found in turmeric include demethoxy curcumin and Bisdemethoxy curcumin. In addition to its use as a spice and pigment, turmeric has been used in India for medicinal purposes for centuries. More recently, evidence that curcumin may have anti-inflammatory and anticancer activities has renewed scientific interest in its potential to prevent and treat the disease.[1]

Curcuma longa (turmeric) is a small rhizomatous perennial herb of Zingiberaceae (Ginger family) originating from south eastern Asia, most probably from India. The plant produces fleshy rhizomes of bright yellow to orange color in its root system, which are the source of the commercially available spice turmeric. In the form of root powder, turmeric is used for its flavouring properties as a spice, food preservative, and food-colouring agent. Turmeric has a long history of therapeutic uses as it is credited with a variety of important beneficial properties such as its antioxidant, antibacterial, anti-inflammatory, analgesic, and digestive properties.[2]

Curcumin's cytoprotective, anti-inflammatory, antitumor, and antioxidant properties are based on several mechanisms. The reported ones are mainly based on the suppression of pro-inflammatory mediators like cyclooxygenase-2 (COX 2),lipooxygenase (LOX),IL1, inducible nitric oxide synthase (iNOS orNOS-2), nuclear factor kappa B (NF-κB) , tumor necrosis factor alpha (IL.1-α) and others . Another group of cellular constituents that can be affected by curcumin is the family of heat shock proteins(HSP). It was reported that induction of HSP 70 has cytoprotective effects, inhibition of HSP 90results in the enhancement of anti-proliferative and proapoptotic activities and induction of HSP (hemeoxygenase-1) is associated with protection against oxidative stress. [3]

Curcuma longa rhizome has hepato-protective effect is mainly a result of its antioxidant properties as curcumin suppresses lipid peroxidation.[4,5] Curcumin could also play an antioxidant role through its ability to bind iron, as well as its ability to decrease the formation of proinflammatory cytokines, especially curcumin downregulates the expression of various inflammatory cytokines including TNF, IL-1, IL-6, IL-8, and chemokines.[6,7]*Curcumin* has been shown to inhibit the action of IL-1 secretion.[8,9] Turmeric and *curcumin* also reversed biliary hyperplasia, fatty changes, and necrosis induced by toxin , Curcumin, the active ingredient found in turmeric, has a positive effect on the liver tissue. Even liver tissue that has been damaged by excessive exposure to alcohol or other damaging drugs can be positively affected by turmeric. Turmeric can be used in food and it is readily available in powdered form. Curcumin extracts in liquid form are also available. Turmeric powder can be

consumed with herb based teas, honey or hot water to treat gastric ailments. Dosage depends on whether turmeric is being consumed or its active ingredient, curcumin. Usually about a half to a quarter teaspoon of powdered turmeric should be consumed two to three times a day. Curcumin capsules with a dosage 250-500 mg can also be taken three times a day.[8,9]in this study was used the coarse powder of *Curcuma longa* to prepare extract as doses, which appropriate with the weight and age of experimental animals. Curcuma capsules are non-available in pharmacies and the get of very difficult.

Cigarette smoke has enormous negative health consequences worldwide, and the use of tobacco is still rising globally. Most people are well aware of effects of smoking on the heart and lungs. However, that smoking cigarettes can also severely affect the liver.The numerous toxins found in cigarette tobacco smoke lead to chronic inflammation and scarring in the liver, which in turn, increases the risk for liver damage including diseases such as Hepatitis B and C infections, liver cancer and liver fibrosis. Additionally, smoking affects the liver processes alcohol and medications, which can increase risk for alcoholism as well as overall drug and alcohol tolerance levels.[7]

Epidemiological studies show that non-smokers exposed to second-hand smoke are at risk for many of the health problems associated with direct smoking.2004 study by the International Agency for Research on Cancer of the World Health Organization concluded that non-smokers are exposed to the same carcinogens as active smokers.[66]

In a countries such as Libya the smokers people are increasing and in the same time there are no laws or rules to restrict or reduced the smokers specially in the public area so as a result of this habitat the non-smokers will affect directly by the passive smoke of the tobacco.There forby the result of the current study if the result will be good affective against the passive smoking may be *Curcuma longa* extract can be given to the people who are not smokers to reduce the affect of the passive smokers in the liver.

Science Daily (Sep. 10, 2009) A team of scientists at the University of California, found that second-hand tobacco smoke exposure can result in nonalcoholic fatty liver disease (NAFLD), a common disease and rising cause of chronic liver injury in which fat accumulates in the liver . The researchers found fat accumulated in liver cells of mice exposed to second-hand cigarette smoke for a year in the laboratory. Such fat buildup is a sign of NAFLD, leading eventually to liver dysfunction In their study, the researchers focused on two key regulators of lipid (fat) metabolism that are found in many human cells such as:sterol regulatory element-binding protein (SREBP) that stimulates synthesis of fatty acids in the liver, and adenosine monophosphate kinas (AMPK)that turns SREBP on and off. the second-hand smoke exposures inhibitadenosine monophosphate kinas(AMPK) activity, which, in turn lead to an increase in activity of sterol regulatory element-binding protein (SREBP).[9]

The liver is also partly responsible for nicotine addiction. When inhale smoke, the liver produces enzymes that help body clear out the toxins through urine. One

particular enzyme is specifically responsible for filtering out nicotine. Therefore, as liver produces more and more of this enzyme, the nicotine leaves body much faster, this means that, as smoke more cigarettes, more enzymes are created and nicotine leaves body more quickly. While this fact seems beneficial, it actually contributes to addiction because the nicotine is leaving so quickly, the body demands more, which leads to that overwhelming sensation to smoke.Though cigarette smoke does not directly come into contact with the liver, it does indirectly affect the liver.[10]the chemicals in cigarette smoke eventually make their way to the liver. These chemicals cause oxidative stress on the liver, which leads to damage to the liver cells and fibrosis.During exposure to cigarette smoke, large amounts of oxygen free radicals are generated; oxidative stress is involved in the aging of all the organs of the body. Oxidation produces free radicals that damage the cells of the body, these radicals could damage the lipid components of the cell membranes as well as the matrix components of the lung and liver by inducing vitamin A depletion. Fibrosis is the development of excess tissue during the body's attempt at repairing an organ or tissue. This is similar to scar tissue and it can adversely affect the liver.The chemicals that are present in cigarette smoke prevent the liver from performing its main function. Over time, the liver becomes less efficient at removing the toxins from body. This can also prevent the proper uptake of medications that may be taking for a particular illness. If body suffering from liver disease, smoking can hasten the further development of this disease.

The pro-inflammatory cytokines interleukin IL-1α, IL-1β, IL-6, interferon-γ and tumor necrosis factor-α have all been detected within the ocular fluids or tissues in the inflammation, IL-1 is expressed by many cells and has multiple functions including local inflammation. Cells known to express IL-1α include astrocytes, fibroblasts, hepatocytes, keratinocytes, brown fat adipocytes, dendritic cells, macrophages.IL-1α and IL-1β are produced by macrophages, monocytes, fibroblasts, and dendritic cells. They form an important part of the inflammatory response of the body against infection. These cytokines increase the expression of adhesion factors on endothelial cells to enable transmigration of leukocytes, the cells that fight pathogens, to sites of infection and re-set the hypothalamus thermoregulatory center, leading to an increased body temperature that expresses itself as fever.[10]IL-1αexpressionevidence that cigarette smoke may negatively impact the incidence, severity, and clinical course of many types of chronic liver diseases,Chronic liver diseases are commonly characterized by continuous inflammation and oxidative stress in the hepatic parenchyma, which are well-characterized systemic consequences of continuous exposure to cigarette smoking. It is then plausible that prolonged exposure to cigarette smoke negatively impacts key pathogenic events implicated in chronic liver injury.

I.2. Research Questions

Does *Curcuma longa* rhizome extract at a dose of 80 mg/kg b.whaspreventiveeffect to SpragueDawely rat's liver cell damage induced by cigarette smoke?

I.3. Objectives of the study

I.3.1. General Objectives

To explaine*the Curcuma longa rhizome* extract at dose of 80mg/kg b.w haspreventiveeffect to SpragueDawely rat's liver cell damage induced by cigarette smoke

I.3.2.Specific Objectives

1. To analyze the difference of liver nucleus changesk(aryopiknotic, karyorrhexisandkaryolysis)in*Curcuma longa*rhizome extractadministration among the treatment group at a dose of 80 mg/kg b.w and control group.
2. To analyze the difference of liver cell IL-1α expression score in*Curcuma longa* rhizome extractadministration among the treatment group at a dose (80 mg/kg of b.w) and control group.

I.4. Study Benefit

I.4.1. Benefit for Science

This study is providing scientific evidence the benefit of*CurcumaLonga*forpreventionof liver injury especially due to cigarette smoke exposure.

I.4.2. Benefit for Health Care Provider

The results of this study can be used as scientific information about the *Curcuma longa*when can it used as supplementary theory for liver disease caused by cigarette smoke or not.

I.4.3.Benefit for Research

The results of this study can be used for developing further research about the effectiveofcurcuma*Longa*astherapy for adverse effect of smoking.

I.5. Originality of the study

Based on searching on research publication onPubmed National Library of Medicine national Institute of Health USA and "Litbang Depkes" website, the study of reparative effect of *Curcuma longa* on liver nucleus change and IL-1α expression has notbeenconducted yet. There were several studies related to current studyas listed below:

Table 1. Originality of The Study

No	Title, Author,Journal	Method	Results
1	Al-Khawaja, et al. The effect of nicotine on the liver and kidney of prepubertal Sprague Dawley rats. FASEB J. 2008;22:1123.8.)[10]	Design: experimental Subjects:Prepubertal male Sprague Dawley rats(n=40), Treatment:Intraperitoneal injection ofnicotine 6.25 ng/g for 1 (G2) and 2 weeks (G4) Measured parameters: Liverhistopathology - ALT and AST - lipid profile,urea	Histological studies of the liver showed deleterious effects of nicotine on both liver and kidney in G4. ALT level showed a significant increase in G4, where a significant increase in AST was found in both G2 and G4. Urea showed a significant increase in G4. Lipids however, showed a significant decrease in cholesterol

No	Title, Author,Journal	Method	Results
		- IL-2, IL-6	and HDL-C (in both G2 and G4, while triglyceride level significantly increased in G4. A significant increase in IL-2 ($P<0.05$) in both G2 and G4 was detected. However, IL-6 showed a significant increase in G4. Nicotine exposure increases the risk of damage that occurs in the liver and kidney with increasing the period of exposure to nicotine.
2	Kalpana C, et al. Modulatory effects of curcumin and curcumin analog on circulatory lipid profiles during nicotine-induced toxicity in Wistar rats. J Med Food. 2005;8(2):246-50.[11]	Design: experimental Subjects: Wistar rats Treatment: subcutaneous injection of nicotine (2.5 mg/kg BB for 5 days a week, for 22 weeks), and curcumin (80 mg/kg) simultaneously along with nicotine by intragastric intubation for 22 weeks Study parameters: -AST,ALT,Lipidprofile - AP,LDH	In nicotine-treated rats, enhanced plasma marker enzymes and lipid profiles were observed. Administration of curcumin or curcumin analog to nicotine-treated rats significantly reduced the activity of marker enzymes and plasma lipid levels
3	Azzalini L, et al. Cigarette Smoking Exacerbates Nonalcoholic Fatty Liver Disease in Obese Rats.Hepatology. 2010 ;51(5):1567-76.[12]	Design: Experimental study,Research subjects: Normal and obese rats.Treatments: rats were exposedto 2cigarettes/day,5 days/week for 4 weeks. Variabels: - Insulin resistence (HOMA-IR) - Lipid profile Hepatic histological examination for assessing the degree of liver injury	Obese rats showed Hypercholesterolemia, insulin resistance, and histological features of NAFLD. Smoking increased alanine aminotransferase serum levels and the degree of liver injury in obese rats. Smoking increased the histological severity of NAFLD inobese rats. Smoking increased the degree of oxidative stress and hepatocellular apoptosis in obeserats. Smoking increased the hepatic expression of tissueinhibitor of metalloproteinase-1 and procollagen-alpha2 (I) in obese

No	Title, Author,Journal	Method	Results
			rats. Smoking causes oxidative stress and worsens the severity of NAFLD in obese rats
4	Valenca SS, et al. Effects of oral nicotine on rat liver stereology. *Int. J. Morphol.,2008 26(3)*:1013-1022[13]	Design: experimental study Study subjects: Male Wistar rats Treatment: oral nicotine (ON) diluted in drinking water during 32 days. Variabel: Liver tissue histopathology feature	Control group reserved hepatocyte with no presence of inflammatory cells. ON group showed varied size of hepatocytes with cloudy cellular limits and histoarchitecture loss. Capillaries were fully of red blood cells. observed also an increase of at globules with small size. Oral nicotine has harmful effects in liver induced by toxic mechanism with reduction of hepatocytes number and disturbance in lipid metabolism.

The current study is different with several previous studies that listed above. The differences are as follow:

- In current study, research subjects wereSD rats, previous studies used Wistar rats and genetically obese.
- In current study the SD rats were exposed to cigarette smoke through passive smokingof cigarette smoke from cigarette that commercially available in local vendor to mimic real condition of cigarette smoker.
- The length of exposure in current study was 13 weeks were the previous study rats were exposedto 2cigarettes/day, 5 days/week for 4 weeks.

- In current study *Curcuma longa extract*was given orally in the dose 80 mg/day by orogastric tube while the previous study curcumin (80 mg/kg) simultaneously along with nicotine by intragastric intubation.
- Outcome in this study were liver nuclouse change and IL-1α expression.

Based on these facts, current study will be different with several studies that have published previously.