CHAPTER II

LITERATUSE REVIEW

II.1 Cigarette smoking

A cigarette (French: "small cigar", from *cigare* + -ette) is a small roll of finely cut tobacco leaves wrapped in a cylinder of thin paper for smoking. The cigarette is ignited at one end and allowed to smoulder; its smoke is inhaled from the other end, which is held in or to the mouth and in some cases a cigarette holder may be used as well. Most modern manufactured cigarettes are filtered and include reconstituted tobacco and other additives.[14]

The term cigarette, as commonly used, refers to a tobacco cigarette but can apply to similar devices containing other herbs, such as cloves or cannabis. A cigarette is distinguished from a cigar by its smaller size, use of processed leaf, and paper wrapping, which is normally white, though other colors are occasionally available. Cigars are typically composed entirely of whole-leaf tobacco.[14,15]

Rates of cigarette smoking vary widely, and have changed considerably over the course of history – since cigarettes were first widely used in the mid-19th century. While rates of smoking have over time leveled off or declined in the developed world, they continue to rise in developing nations. Nicotine, the primary psychoactive chemical in tobacco and therefore cigarettes, is believed to be psychologically addictive, although it does not engender a physiological dependency (e.g.

discontinuation does not evoke somatic withdrawal syndromes as do drugs such as alcohol or opioids).[15] Cigarette use by pregnant women has also been shown to cause birth defects, including mental and physical disabilities.[16] Secondhand smoke from cigarettes has been shown to be injurious to bystanders, which has led to legislation that has banned their smoking in many workplaces and public areas.[14,15]

II.2 Smoking history .

Smoking's history dates back to as early as 5000–3000 BC when the agricultural product began to be cultivated in South America; consumption later evolved into burning the plant substance either by accident or with intent of exploring other means of consumption. The practice worked its way into shamanistic rituals. Many ancient civilizations, such as the Babylonians, Indians and Chinese, burnt incense as a part of religious rituals, as did the Israelites and the later Catholic and Orthodox Christian churches. Smoking in the Americas probably had its origins in the incense-burning ceremonies of shamans but was later adopted for pleasure or as a social tool. The smoking of tobacco and various hallucinogenic drugs was used to achieve trances and to come into contact with the spirit world. Maybe crops burned of a particular plant like cannabis or tobacco and then realizing the effects of the smoke, people harnessed it a more effective way.[17]

II.3 Demographics consumption of smoking

As of 2000, smoking is practiced by 1.22 billion people. Assuming no change in prevalence it is predicted that 1.45 billion people will smoke in 2010 and 1.5 to 1.9 billion in 2025. Assuming that prevalence will decrease at 1% a year and that there will be a modest increase of income of 2%, it is predicted the number of smokers will stand at 1.3 billion in 2010 and 2025. [18] Smoking is generally five times higher among men than women, however the gender gap declines with younger age.In developed countries smoking rates for men have peaked and have begun to decline, however for women they continue to climb. [11]

As of 2002, about twenty percent of young teens (13–15) smoke worldwide. From which 80,000 to 100,000 children begin smoking every day—roughly half of which live in Asia. Half of those who begin smoking in adolescent years are projected to go on to smoke for 15 to 20 years. The World Health Organization (WHO) states that "Much of the disease burden and premature mortality attributable to tobacco use disproportionately affect the poor". Of the 1.22 billion smokers, 1 billion of them live in developing or transitional economies. Rates of smoking have leveled off or declined in the developed world. In the developing world, however, tobacco consumption is rising by 3.4% per year as of 2002. The WHO in 2004 projected 58.8 million deaths to occur globally, from which 5.4 million are tobacco-attributed, and 4.9 million as of 2007. As of 2002, 70% of the deaths are in developing countries.[15]

II.2 Common constituents of cigarette smoking

The constituents of smoke are contained in either the particulate phase or gas phase.[14]

II.2.1 Particulate phase

Particulate phase components include tar, polynuclear hydrocarbons, phynol, cresol, catechol and trace elements (carcinogens), nicotine (ganglion stimulator and depressor), indole, carbazole (tumor accelerators) and 4-aminobiphenyl.[14]

II.2.2 Gas phase

Gas phase contains carbon monoxide (impairs oxygen transport and utilization), hydrocyanic acid, acetaldehyde, acrolein, ammonia, formaldehyde and oxides of nitrogen (cilitoxin and irritant) nitrosamines, hydrazine and vinyl chloride (carcinogens).[14]

II.2.3 Effect of smoking on the body

Smokers are at greater risk for cardiovascular diseases (ischaemic heart disease, hypertension), respiratory disorders (bronchitis, emphysema, chronic obstructive lung disease, asthma), cancer (lung, pancreas, breast, liver, bladder, oral,

larynx, oesophagus, stomach and kidney), peptic ulcers and gastroesophageal refl ux disease (GERD), male impotence and infertility, blindness, hearing loss, bone matrix loss, and hepatotoxicity.[19]

II.2.3.1 Effect of smoking on liver

The evidence that CS 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 two well-characterized systemic consequences of continuous exposure to CS. It is then plausible that prolonged exposure to cigarette smoke negatively impacts key pathogenic events implicated in chronic liver injury. In fact, epidemiologic studies suggest that CS could accelerate the progression of a variety of liver diseases such as hepatitis C [20] and primary biliary cirrhosis, and could represent a risk factor for hepatocellular carcinoma.[21,22]

II.2.3.2 Effect of smoking on lung

Smoke cigarettes, many chemicals enter your body through your lungs. Burning tobacco produces more than 4,000 chemicals. Nicotine, carbon monoxide and tars are some of these substances. Smoking greatly affects your lungs and

airways. Smokers get a variety of problems related to breathing. Problems range from an annoying cough to grave illness like emphysema and cancer.[23,24]

Smoking cigarettes causes many changes in lungs and airways. Some changes are sudden, last a short time, and then go away. These changes are acute. Colds and pneumonia are acute changes. Other changes happen slowly and last a long time. These are chronic changes. Some chronic changes may last the rest of your life. Emphysema is an example of a chronic change. Cigarette smoke also has been reported induces vitamin A depletion[25], which is associated with the development of emphysema.[23,24]

II.2.3.3 Effect of smoking on kidney

Increase the evidence that suggests that smoking adversely influences the prognosis of nephropathies.smoking increase the resk of microalbomenoria and accelerates the rat of progression from microalbuminoria to protienuria and subsequent renal failure in type 1 DM[26].

II2.3.4 Effect of smoking on heart

Cardiovascular disease (CVD) incorporates the disorders of the heart andcirculatory system, including coronary heart disease (angina and heart attacks), peripheral arterial disease, aneurysms and stroke. This factsheet examines the links

between smoking and CVD, smoking as a risk factor, the mechanisms by which smoking causes these diseases and how a person's risk may be reduced. Smoking is a leading cause of cardiovascular disease, causing around 25,000 deaths a year from heart and circulatory disease. Around one in five premature deaths from heart and circulatory disease are linked to smoking.[27,28]

II.3 Adverse effects of smoking on the liver

Smoking causes a variety of adverse effects on organs that have no direct contact with the smoke itself such as liver. The liver is an important organ that has many tasks. Among other things, the liver is responsible for processing drugs, alcohol and other toxins to remove them from the body. smoking yields toxins which induce necroinflammation and increase the severity of hepatic lesions (fi brosis and activity scores) when associated with hepatitis C virus (HCV) ,or hepatitis B virus (HBV) infection. Cigarette smoking increases the risk of developing HCC among chronic liver disease (CLD) patients independently of liver status. Association of smoking with hepatocellular carcinoma (HCC) irrespective of HBV status has been reported.[29]

II.3.1 Mechanism of hepatotoxicity of cigarette smoking

Smoking induces three major adverse effects on the liver: toxic effects either direct or indirect, immunological effects and oncogenic effects.

II.3.2 Direct toxic effect

Direct toxic effect: Smoking yields chemical substances with cytotoxic potentials. These chemicals created by smoking induce oxidative stress associated with lipid peroxidation,which leads to activation of stellate cells and development of fibrosis. In addition, smoking increases the production of pro-inflammatory cytokines (IL-1, IL-6 and TNF-α) involved in liver cell injury. It has been reported that smoking increases fibrosis score and histological activity index in chronic hepatitis C (CHC) patients and contributes to progression of HBV-related cirrhosis.[29,20]

II.3.3 Indirect toxic effect *(concomitant polycythemia)*

Smoking is associated with increased carboxyhaemoglobin and decreased oxygen carrying capacity of red blood cells (RBCs) leading to tissue hypoxia. Hypoxia stimulates erythropoetien production which induces hyperplasia of the bone marrow. The latter contributes to the development of secondary polycythemia and in turn to increased red cell mass and turnover. [29]This increases catabolic iron derived from both senescent red blood cells and iron derived from increased destruction of red cells associated with polycythemia. Furthermore, erythropoietin stimulates absorption of iron from the intestine. Both excess catabolic iron and increased iron absorption ultimately lead to its accumulation in macrophages and subsequently in hepatocytes over time, promoting oxidative stress of hepatocytes. Accordingly, smoking might be a contributing factor to secondary iron overload disease in addition

to other factors such as transfusional hemosiderosis, alcoholic cirrhosis, thalassemia, sideroplastic anemia and porphyria cutanea tarda. These effects are attributed to iron overload with consequent iron deposition in hepatocytes.Excess hepatic iron induces oxidative stress and lipid peroxidation[29,30].

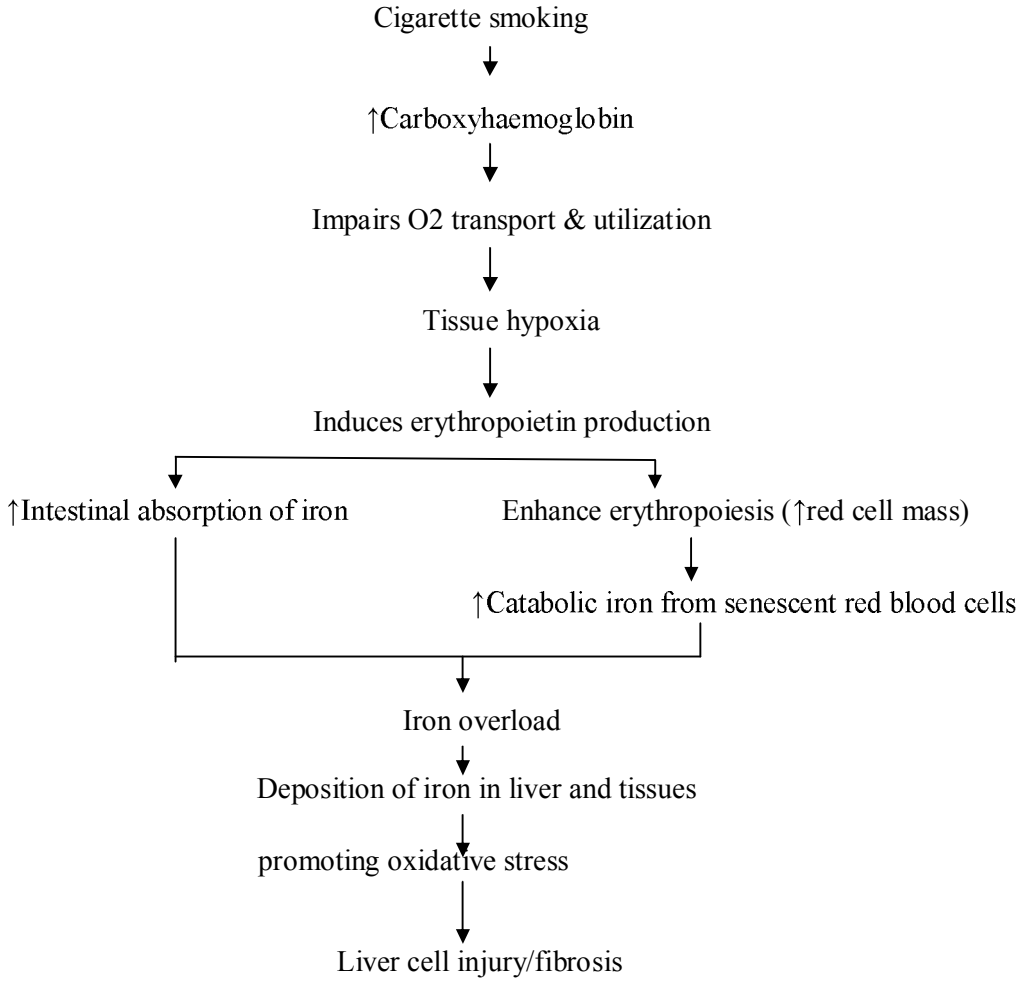

Fig 1. Indirect toxic effect of smoking on liver cell
Source: Gutteridge[30]

II.3.4 Immunological toxic effect of smoking

Smoking affects both cell-mediated and humoral immune responses. Nicotine blocks lymphocyte proliferation and differentiation including suppression of antibody-forming cells by inhibiting antigen-mediated signaling in T-cells and riboneucleotide reductase.Furthermore, smoking induces apoptosis of lymphocytes by enhancing expression of Fas (CD95) death receptor which allows them to be killed by other cells expressing a surface protein called Fas ligand (FasL). Smoking induces elevation of CD8+ T-cytotoxic lymphocytes, decreased CD4+ cells, impaired NK cell activity and increases the production of pro-inflammatory cytokines (IL-1, IL-6, TNF-α).[31]

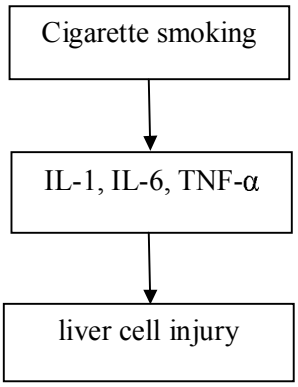

Fig 2. immunologic toxic effect of smoking on liver cell
Source: El-Zayadi[29]

II.3.5 Oncogenic toxic effect of smoking.

Smoking yields chemicals with oncogenic potentials such as hydrocarbons, nitrosamine, tar and vinyl chloride.[14] Cigarette smoking is a major source of 4-aminobiphenyl, a hepatic carcinogen which has been implicated as a causal risk factor for HCC. Smoking increases the risk of HCC in patients with viral hepatitis.[22] Furthermore, recent data from China and Taiwan have shown an association of smoking with liver cancer independent of HBV status.[32] Tobacco smoking is associated with reduction of p53, a tumour suppressor gene. which is considered “the genome guardian”. Suppression of T-cell responses by nicotine and tar is associated with decreased surveillance for tumour cells.[33]

II.3.6 Affect of smoking on cytochrome P450 enzyme .

During the phase 1 pathway, toxin chemicals and metals (from food, water, and air) are converted into less harmful chemicals through many chemicals reactions through the induction of P-450 enzymeand consists of oxidation and reduction reaction, Excessive amounts of toxic chemicals can disrupt the P-450 enzyme system by causing hyper activity or what is called 'induction' of this pathway. This will result in high levels of damaging free radicals being produced. Substances that may cause hyperactivity of the P- 450 enzymes like nicotine and arsenic compound in cigaratte smoking, A significant side-effect of phase I detoxification is the production of *free*

radicals as the toxins are transformed--for each molecule of toxin metabolized by phase I, one molecule of free radical is generated. Without adequate free radical defenses, every time the liver neutralizes a toxin exposure, a build up of reactive intermediate metabolites can occur which in turn can lead to tissue damage and disease 'Pathological Detoxifiers.[34]

II.4. *CURCUMA LONGA* RHIZOMA HERBAL .

Curcuma longa is an herbaceous perennial plant, It belonging to the family Zingiberaceae. It has a large oval rhizome with sessile cylindrical tubers, orange coloured inside. Its leaves start from the rhizome, are elliptical and can reach up to 1.2 m in length. Its flowers are yellow, between 10 to 15 cm in length and they group together in dense spikes, which appear from the end of spring until the middle of summer. No fruits are known for this plant. Curcuma longa grow in temperature between 20°c to 30°c.The Curcuma genus contains around known as "Haldi". Turmeric became known as Indian saffron In Indian state of Tamil Nadu is the world's largest producer it has been well studied in Malaysia, Indonesia and India due to its economic importance. The rhizomes of curcuma longa are commonly used as a flavoring, coloring agent and preservative. Commercially, it is traded as a dye, spice and source of industrial starch.[35] Its taxonomical classification is follow:

Class Liliopsida

Order Zinigiberales

Genus Curcuma

Family Zingiberaceae

Subclass Commelinids

Species *Curcuma longa*

Curcuma longa rhizoma is distributed throughout tropical and subtropical regions of

the world, being widely cultivated in Asiatic countries, mainly in India and China[36].

Figure 3. Curcuma longa
Source: Ma[37]

II.4.1 History and Folk Use.

Curcuma longa rhizome has a long tradition of use in both the Chinese and Ayurvedic systems of medicine.[36] The turmeric was isolated in the 19th century and its active constituents are Curcumin, which was extracted from the rhizomes of *Curcuma longa* with yellow color and which responsible for the anti-inflammatory effects. It is commonly used as a dietary spice and coloring agent. It has been in continuous use for its flavoring, as a spice in both vegetarian and non-vegetarian food preparations and it also has digestive properties . Curcumin produces different pharmacological effects including anti-inflammatory, anti-oxidant, anti-cancer, ant-diabetic, anti-rheumatic, angiogenic, anti-fertility, anti-viral and anti-infectious

activities and wound healing properties. Recently, it has attracted much attention due to its significant medicinal potential .The main active constituents of curcuma longa rhizome is curcumin, demethoxycurcumin, bisdemethoxycurcumin. They also possess anti-inflammatory, hepatoprotective, antitumor, anti-viral activities .and anti-cancer activity.[38]

II.4.2 Chemistry of curcuma longa rhizome

The major constituent, curcumin (diferuloylmethane) is in the most important fraction of *Curcuma longa*.and its chemical structure was determined. It melts at 176-177°C and forms red-brown salts with alkalis. Curcumin is soluble in ethanol, alkalis, ketone, acetic acid and chloroform; and is insoluble in water. In the molecule of curcumin, the main chain is aliphatic, unsaturated and the aryl group can be substituted or not. Curcuminoids are between 2 and 9%. Their main components are: curcumin (60%), desmethoxycurcumin, monodemethoxycurcumin, bisdemethoxycurcumin, dihydrocurcumin and cyclocurcumin. Curcumins oxidation yields vanillin. Its chemical study shows that it contains proteins, carbohydrates and fibre. Its mineral and vitamin contents are calcium, phosphorus, iron, carotene, thiamine and niacin. It contains 5% of volatile oil, resin, abundant Zingiberaceous starch grains and yellow coloring substances known as curcminoids. .Chemically, curcuma species contain volatile oil, starch and curcumin It can exist at least in two

tautomeric forms, keto and enol. The keto form is preferred in solid phase and the enol form in solution.[39]

II.4.3 pharmacokinetics *Curcuma longa(curcumin)*

Curcumin is poorly absorbed following oral administration. It has been found to be far more active with parenteral administration than with oral administration. This difference between enteral and parenteral activity may be due to several factors.[5,39]

II.4.5 Curcumin receptors

Cellular receptor are cellular protein to which molecule binds, lead to secondary cellular responses. Whether there are any authentic receptors for curcumin is unknow

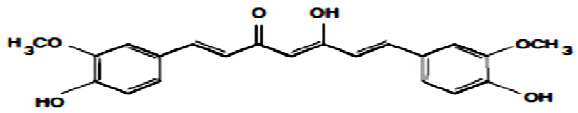

Figure 4. Chemical structure of curcumin.

Source: Menon VP.[59]

However, numerous molecules to which curcumin binds have been identified.These include serum albumin,5-LOX, xanthine oxidase,thioredoxin Receptors are cellular proteins to which a molecule binds, leading to reductase, iron, COX-2, IKK, *p*-glycoprotein, GST, PKA, PKC. cPK, PhK, autophosphorylation-activated protein kinase,pp60c-src tyrosine kinase, Ca2+-dependent protein kinase (CDPK), Ca2+-ATPase of sarcoplasmic reticulum, aryl hydrocarbon receptor, rat river cytochrome p450s, Topo II isomerase, inositol 1,4,5- triphosphate receptor, and glutathione.[3]

II.4.4 Metabolic pathways of curcumin

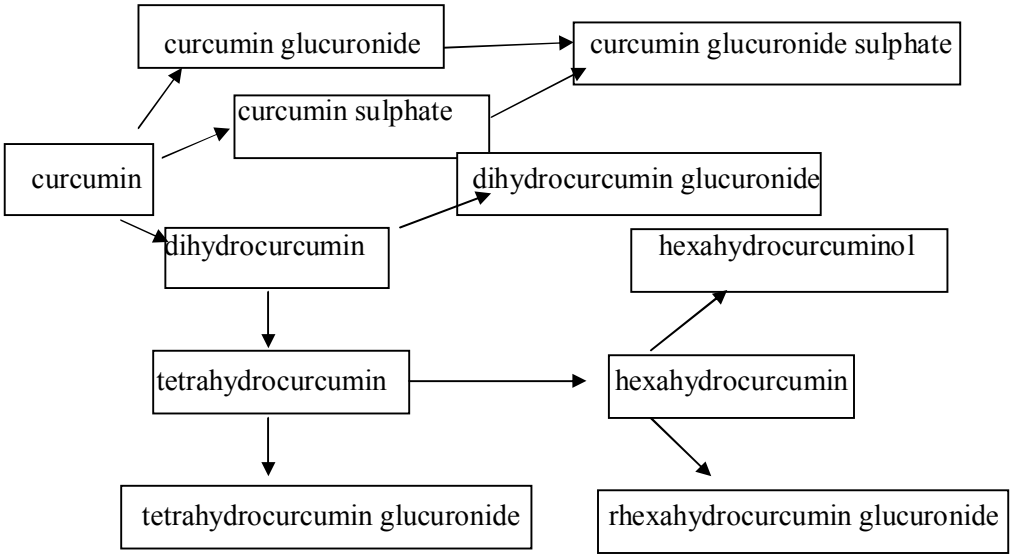

Figure 5. Metabolic pathway of curcumin
Source: Hassaninasab A.[63]

Curcumin is a bis-a,b-unsaturated b-diketone. As such, curcumin exists in equilibrium with its enol tautomer. The bis-keto form predominates in acidic and neutral aqueous solutions and in the cell membrane At pH 3–7, curcumin acts as an extraordinarily potent H-atom donor This is because, in the keto form of curcumin, the heptadienone linkage between the two methoxyphenol rings contains a highly activated carbon atom, and the C–H carbon bonds on this carbon are very weak due to delocalisation of the unpaired electron on the adjacent oxygens In contrast, above pH 8, the enolate form of the heptadienone chain predominates, and curcumin acts mainly as an electron donor, a mechanism more typical for the scavenging activity of phenolic antioxidants Curcumin is relatively insoluble in water, but dissolves in

acetone, dimethylsulphoxide and ethanol. Curcumin exhibits low oral bioavailability in rodents and may undergo intestinal metabolism; absorbed curcumin undergoes rapid first-pass metabolism and excretion in the bile.[5]

II.4.6 Hepatoprotective effect of *curcuma longa rhizome (curcumin).*

II.4.6.1 anti-inflammatory of *curcuma longa rhizome*

The curciumn is a potent anti-inflammatory agent ,First, curcumin suppresses the activation of the transcription factor NF–□B, which regulates the expression of pro-inflammatory gene products.[40,40,41] Second, curcumin downregulates the expression of COX-2, an enzyme linked with most types of inflammations.[42,43] Third, curcumin inhibits the expression of another pro-inflammatory enzyme: 5-LOX. Additionally, curcumin has been shown to bind to the active site of 5-LOX and inhibit its activity.[42] Fourth, curcumin downregulates the expression of various cell surface adhesion molecules that have been linked with inflammation.[44] Fifth, curcumin downregulates the expression of various inflammatory cytokines, including TNF, IL-1, IL-6, IL-8, and chemokines. [44,45]Sixth, curcumin has been shown to inhibit the action of TNF, one of the most pro-inflammatory of the cytokines.[44] Seventh, curcumin is a potent antioxidant, which might contribute to its anti-inflammatory action. All of this recent evidence confirms the anti-inflammatory action of curcumin, known for thousands of years. Its pharmacological safety combined with its anti-inflammatory action, makes it an ideal agent to explore for preventive and therapeutic situations.[46.]

II.4.6.2 Antioxidant of curcuma longa rhizome

Whereas pro-oxidants are considerd mediators of numerous diseases, antioxidants are generally believed to delay or halt the disease. However, this paradigm is not always valid, as most cytokines mediate their effects through pro-oxidant mechanisms. Reactive oxygen species (ROS) also play an important role in cell mediated cytotoxicity (CMC) of the immune system.[47,48] Numerous reports indicate that curcumin could mediate both pro-oxidant and antioxidant roles. First, curcumin could induce the expression of ROS, which plays an important role in the antiproliferative effects of this molecule. Second, curcumin bind thioredoxin reductase (TR) and converts this enzyme toNADPHoxidase, thus leading to the production ofROS. Because TR is overexpressed in tumor cells, curcumin kills tumor cells through this mechanism. Third, curcumin suppresses lipid peroxidation. Fourth, curcumin increases the expression of intracellular glutathione. Fifth, curcumin could also play an antioxidant role through its ability to bind iron[49].

Nitric oxide (NO) is a short-lived, lipophilic molecule generated from L-arginine by various NADPH-dependent enzymes called NO synthases (NOS) . NO is involved physiologically in vasorelaxation, neurotransmission, inhibition of platelet aggregation, immune defence and intracellular signalling. NO has an unpaired electron, and is therefore a free radical species; its bioactivity is related to production of many reactive intermediates, but many of these reactive nitrogen species are capable of damaging DNA or hindering DNA repair.Peak inducible NOS (iNOS)

activity may relate to the transition of colonic adenomas to carcinomas Upregulation of COX-2 via NF-□B or AP-1 pathways, or increasing intracellular concentrations of reduced glutathione, appears to confer resistance toNO-induced apoptosis in malignant cells.[50]

II.4.6.3 Antitumor of curcuma longa*(curcumin)*

To explain the anticarcinogenic effects of curcumin on different tumors, a wide variety of mechanisms have been implicated, including inhibition of ROI, suppression of inflammation, downregulation of ODC, inhibition of cell proliferation, inhibition of cytochrome P450 isoenzymes, induction of GSH, suppression of certain oncogenes (e.g., cHa-ras, c-jun, and c-fos), inhibition of transcription factors NF-κB and AP-1, suppression of COX2, inhibition of cell-cycle–related proteins (PCNA, cyclin E, p34 cdc2), inhibition of chromosomal damage, inhibition of oxidation of DNA bases, inhibition of malondialdehyde (MDA) DNA adduct formation, inhibition of tumor implantation, inhibition of protein tyrosine kinase and protein kinase C activity.[47]

Curcumin has been shown to suppress the proliferation of a wide variety of tumor cells through the downregulation of antiapoptotic gene products, activation of caspases, and induction of tumor suppressor genes such as *p*53. Second, curcumin has also been to shown to suppress the invasion of tumors through the downregulation of matrix metalloproteinases (MMPs) and cell surface dhesion molecules Third, curcumin suppresses the angiogenesis of tumors through the

suppression of angiogeneic cytokines. Fourth, the anti-inflammatory effects of curcumin contribute to its antitumor activity as well. [47]

II.4.6.4 Effects on phase I and II liver detoxification enzymes

The cytochromes P450 (CYP) enzyme system is important in the metabolic conversion and activation of many compounds, Inhibition of CYP isoenzymes by curcumin has been demonstrated in cells. Curcumin it inhibits phase I while stimulating phase II. This effect can be very useful in preventing certain types of cancer.[51] Curcumin has been found to inhibit carcinogens, It appears that the curcumin exerts its anti-carcinogenic activity by lowering the activation of carcinogens while increasing the detoxification of those that are activated. Curcumin has also been shown to directly inhibit the growth of cancer cells. As most of the cancer-inducing chemicals in cigarette smoke are only carcinogenic during the period between activation by phase I and final detoxification by phase II, curcumin in the turmeric can help prevent the cancer-causing effects of tobacco.[52]

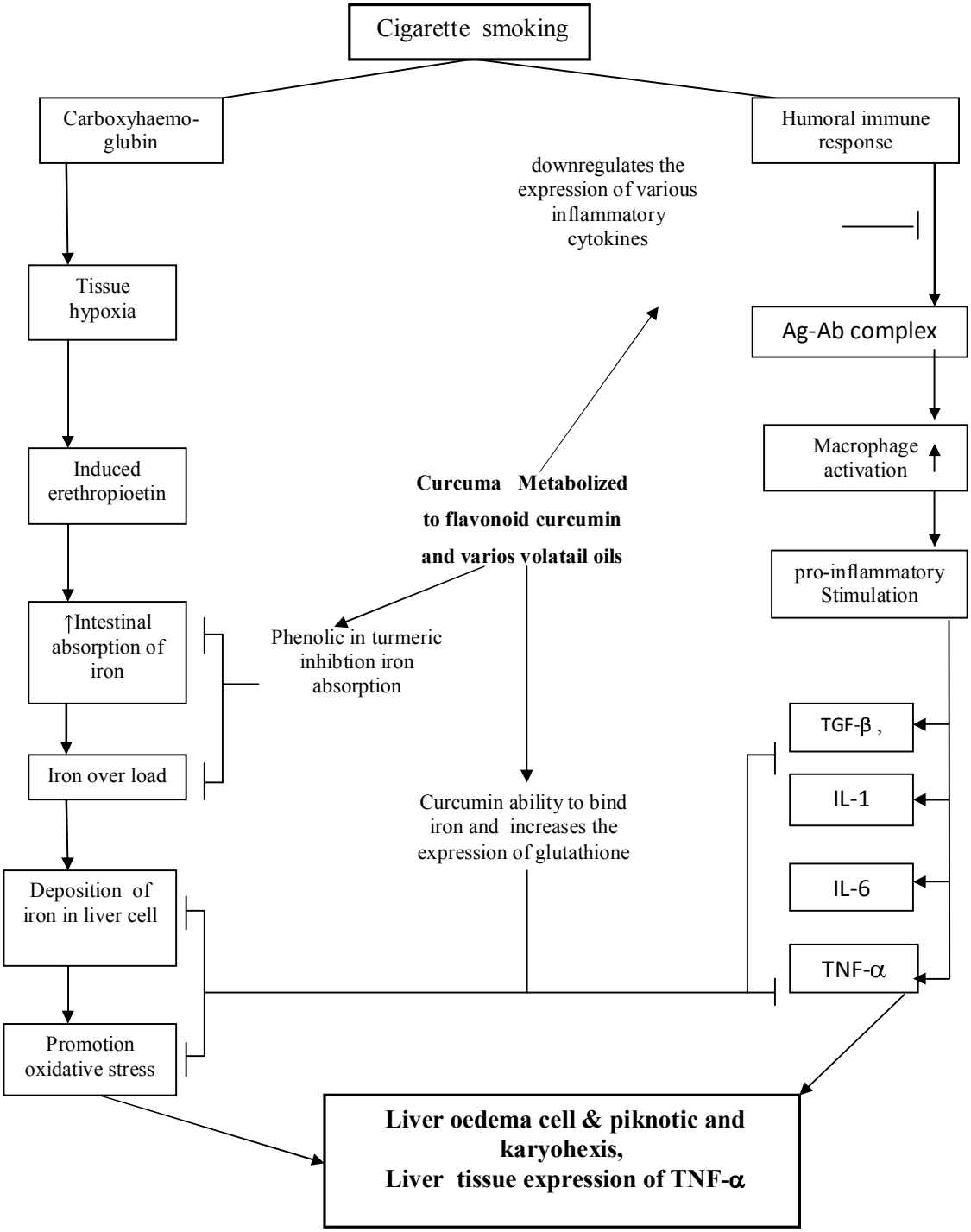

Fig 6. Physiology effect of *curcuma longa rhizoma* on liver cell affected by passive smoking

II.4.6.5 The Side Effects of curcuma longa rhizoma (curcumin)

turmeric is not free from side effects, especially when taken in excessive doses.

A.Digestive Effects

Practitioners of Ayurvedic and traditional Chinese herbal medicine use turmeric to treat digestive disorders. However, according to MedlinePlus, turmeric at high doses or after prolonged use can itself create digestive problems, including stomach irritation or upset, heartburn, nausea, diarrhea and even ulcers[52]

B. Gallbladder Effects

In animal tests during the 1990s, researchers M. S. Hussain and N. Chandrasekhara found that curcumin (turmeric's most biologically active component) inhibited the formation of gallstones (Ravindran et al., eds., 2007, pp. 326--327). According to MedlinePlus, turmeric induces gallbladder contractions. These findings suggest that turmeric could be beneficial for persons with healthy gallbladders. However, it could present problems for those with existing gallstones or bile duct obstructions. [52]

C. Uterine Effects

Turmeric is a mild uterine stimulant that aids menstrual flow. For this reason, women should avoid using turmeric for medicinal purposes during pregnancy. Turmeric in normal dietary quantities should not pose a problem.

(MedlinePlus reports that the Indian population's average dietary turmeric consumption ranges from 2 to 2.5 grams a day. [52]

II.4.7 Spraque Dawley rats

The Sprague Dawley rat is an outbred multipurpose breed of albino rat used extensively in medical research. Its main advantage is its calmness and ease of handling. This breed of rat was first produced by the Sprague Dawley farms (later to become the Sprague Dawley Animal Company) in Madison, Wisconsin. These rats were first bred in 1925. The breeding facilities were purchased first by Gibco and then by Harlan (now Harlan Sprague Dawley) in January 1980.[53]

Strain characteristics related to the Spraque rats

1.Selected stock for high lactation
2.Rapid grow
3.Vigor
4. Good Temperature
5.high resistance to arsenic trioxide