III. 1.1 Theoretical framework

Smoking induces three major adverse effects on the liver: toxic effects either direct or indirect, immunological effects and oncogenic effects. And the _curcuma longa_ extract has counter-effect for it.\(^{29}\)

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 ribonucleotide 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-\(\alpha\)).

The curcumin is a potent anti-inflammatory agent. First, curcumin suppresses the activation of the transcription factor NF-\(\kappa\)B, which regulates the expression of pro-inflammatory gene products. Also curcumin downregulates the expression of various inflammatory cytokines, including TNF, IL-1, IL-6, IL-8, and chemokines.\(^{46}\)

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. 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.

Curcumin suppresses lipid peroxidation. Curcumin increases the expression of intracellular glutathione, curcumin could also play an antioxidant role through its ability to bind iron.

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.

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 p53.
Liver Odeama Cell & Karyolysis and Karyopiknotic

Oxidative stress inside liver cell

Liver tissue expression of TNF-α

Tissue Hypoxia

Immune response

Macrophage activation

Pro-inflammatory cytokines production

Curcuma Longa Rhizoma Extract

TGF-β
TNF-α
IL-1
IL-6

TGF-β
TNF-α

Figure 7. Theoretical Framework
III.1.2 Conceptual Framework

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Dependent Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcuma longa rhizome extract</td>
<td>Liver Odeama Cell &amp; Karyolysis and Karyopiknotic</td>
</tr>
<tr>
<td></td>
<td>Liver tissue TNF-α expression</td>
</tr>
</tbody>
</table>

**Fig 8.** Conceptual Framework of study

III.7. Hypothesis

III.7.1 Major hypothesis

_Curcuma L_ extract has regenerative effect to SD rat’s liver cell damage induced by passive cigarette smoking

III.7.2. Minor hypothesis

e. SD rats that received curcuma longa rhizome extract have liver cell change (Odeamatus cell and karyopiknotic, karyolysis of the nucleaus ) lower than those SD Rats did not received _curcuma longa rhizome extract_ after exposure to passive cigarette smoke

d. SD rats that received curcuma longa rhizome extract have liver cell TNF-α expression lower than those SD Rats did not received _curcuma longa rhizome extract_ after exposure to passive cigarette smoke