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Zingerone Ameliorates Hepatotoxicity

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ABSTRACT

In medical sciences, toxicity is an area wherein extensive studies have been carried to improve the diseases as well as to prevent. So, there is a high requirement for novel and improved alternative therapeutic strategies to manage diseases. The liver is the largest gland in the body, which executes several important mechanisms; it stores minerals and vitamins and releases them in periods of need. The main aim of this study was to give a closer insight into potent non- toxic compounds that is capable of modifying the responses. Animals were divided into five equal groups viz control (Group 1), administered with food and water ad libitum, (Group 2) administered with olive oil, (Group 3) administered with zingerone, (Group 4) administered with concanavalin A, (Group 5) administered with cyclosporine A followed by zingerone. Our results revealed significant changes in liver marker enzymes and liver histology of zingerone treated rats when compared to control rats. A corollary, zingerone has no toxic effect on hepatocytes and was found to be safe at a dose of 10mg/kg b wt and also ameliorates hepatotoxicity.

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INTRODUCTION

Hepatotoxicity is a leading disease caused by chemicals and drugs, which induce acute liver injury (Safhi, 2018; Sarfaraz and Eraj, 2016). The liver is a solely vital organ where the integration of metabolism and mainly detoxification process takes place (Dash *et al.*, 2007; Talluri *et al.*, 2018). Liver disease is a leading remarkable global health problem (Zhou *et al.*, 2015). It is very important to maintain a healthy liver for a good life condition (Sharma and Majumdar, 2009). Liver dysfunction may result from a viral infection, chronic excess alcohol intake, hepato-toxins, and transplant (Bishayee *et al.*, 2010). The current lifestyle changes cause different illnesses (Grant and Rickey, 2012), the drugs used for illness are getting resistant to disease and cause severe side effects, which leads to iatrogenic disease (Murray *et al.*, 2008; Reuben *et al.*, 2009). The drugs mainly target the vital organs like the liver (Sarfaraz and Eraj, 2016). The drugs used for the treatment of hepatotoxicity leads to severe adverse effect, and the drug itself causes liver damage (Syed *et al.*, 2017). Natural products and their active compounds are the sources for the formulation of many new drugs in the medicinal field (Al-Kushi *et al.*, 2013). In India, numerous medicinal plants are used to improve impaired liver damage cells have enticed attention in recent years (Rajesh and Latha, 2004). Several studies reported that zinger has many health benefits in traditional medicine. Zingerone is an active component of dried zinger rhizome, having a wide range of essential pharmacological properties (Ahmad *et al.*, 2018).

MATERIALS AND METHODS

Experimental Design

The treatment regimen was as follows

Thirty rats were divided into five equal groups.

Group I- Normal control, Administered Food, and water only.

Group II- Olive oil (Vehicle control)

Group III- Zingerone was orally given at a dose of 10 mg/kg B wt, daily for 10 days.

Group IV- Concanavalin was orally given at a dose of 50 mg/kg B wt, daily for 10 days.

Group V- Cyclosporine A (CsA) was orally given at a dose of 20mg/Kg B wt, followed by Zingerone orally at a dose of 10 mg/kg B wt, for 10 days.

Chemicals

All the chemicals used in the experiment were purchased from Sigma Aldrich Chemicals, India

Biomarkers assay

The following biomarkers as aspartate aminotransferase (AST) (EC 2.6.1.1), alanine aminotransferase (ALT) (EC 2.6.1.2), and alkaline phosphatase (ALP) (EC 3.1.3.1) were measured using Dimension Xpand Automatic Analyzer (Siemens).

Histological evaluation

The flattened sections were collected on clean poly – L – lysine coated glass slides and dried overnight. For optimal adhesion, the slide was placed in a 60°C oven for 1h. Sections cut from formalin-fixed paraffin-embedded specimens were used for H & E staining.

RESULTS AND DISCUSSION

Figure 1 and Figure 2 respectively represent the liver marker enzymes estimated in blood and tissue samples.

Figures 3, 4, 5 and 6, respectively represents the histology of liver cells.

Aminotransferases are involved in the interconversion of metabolic intermediates to relative energy metabolism (Babu, 1999).

In the current study, when rats are treated with zingerone (Group 3), the activity of serum liver marker enzymes did not show any statistically significant increase when compared to that of control rats indicating that zingerone is not harmful to liver cells. This may be due to the fact that zingerone stabilizes hepatocytes plasma membrane and prevents the leak of hepatic enzymes to the extracellular fluid (Osama *et al.*, 2014; Darbar *et al.*, 2010). The normal level of serum enzymes was reported by (Al-Kushi *et al.*, 2013; Mani *et al.*, 2016; Ahmad *et al.*, 2018) when rats were treated with zingerone or zingiber officinalis respectively. The above results are in accordance with our report. The normal level of liver marker enzymes in serum stipulate the hepatoprotective effect of zingerone. Therefore zingerone has a protective effect in liver cells. The increased level of hepatic enzymes was observed in Con A treated rats (Group 4), which might be due to the degradation of the liver architecture and subsequent release of the enzymes in the serum. The results were compared with (Zhao *et al.*, 2017) after Con A injection. A statistically significant increase in hepatic enzyme levels was observed. Our results were supported by (Zhou *et al.*, 2015; Chen *et al.*, 2015), indicating the elevated level of hepatic enzymes in Con A treated group. Increased levels of liver enzymes may be observed during liver metastasis, fatty liver, biliary cirrhosis, acute hepatitis, liver cirrhosis (Janakiraman and Parameswari, 2016). Increased levels in Con A treated group narrates the toxic effects of concanavalin A besides its immunostimulatory effect. Con A-induced liver injury is a model of immune-mediated liver injury that involves viral and autoimmune hepatitis in humans (Imose *et al.*, 2004; Chen *et al.*, 2010; Bishayee *et al.*, 2010). Intravenous injection of Con A activates T cells, which infiltrates the liver, result in subsequent process of hepatocyte apoptosis, and necrosis finally increased the level of serum liver marker enzymes (Zhou *et al.*, 2013; Shen *et al.*, 2014; Chen *et al.*, 2014). Con A-induced T cell activation results in an increased level of inflammatory cytokines, including tumor necrosis factor (TNF-α), Interferon (IFN-), and interleukin (IL-6) (Mann *et al.*, 2009). Administration of CsA to rats suppress immune response mainly by inhibiting the production of immune reactive cytokines (Shaw *et al.*, 1995). The liver is responsible for detoxification and elimination of potentially harmful substances. CsA induced hepatotoxicity could be due to either be a direct effect of CsA itself or from reactive oxygen species (Mostafavi-Pour *et al.*, 2013). Adverse effects caused by CsA include hepatotoxicity that may lead to the development of cholestasis (Dandel *et al.*, 2010), fatty liver (Pagadala *et al.*, 2009), and cardiovascular complications (Hulzebos *et al.*, 2004). In (Group 5) Cyclosporine A/zingerone treated group showed significantly increased levels of hepatic enzymes as compared to the control and zingerone treated group. Cyclosporine A-induced hepatotoxicity is indicated by a significant increase in the activities of hepatic enzymes in the circula-

tion. Supplementation with zingerone decreased the activities of hepatic enzymes near those of the control values, which could be attributed to the ability of zingerone to prevent hepatic damage and dysfunction. Similar hepato-protective findings were observed by previous researchers (Swaroopa *et al.*, 2012; Elsayed *et al.*, 2016; Korolczuk *et al.*, 2016). To confirm the hepatoprotective effect of zingerone, in our present study, the activity of AST & ALT was measured in liver tissues. No significant change was observed in the zingerone treated group when compared to that of the control group.

In the present study, liver histopathology of a control rat showing normal architecture with normal appearance of the hepatocytes and central vein. Zingerone treated rats also show the normal architecture of hepatocytes, and the central vein indicates zingerone is normally metabolised in the cells without any toxic effect. Histological alterations in the con A treated group cause liver damage, as evidenced by the structural change by disruption of normal architecture, periportal inflammation, cellular infiltration, and leading to pathological damage. Many researchers had been reported that after con A injection, exacerbated liver damage was observed (Zhao *et al.*, 2017; Chen *et al.*, 2015). Cyclosporine/zingerone treated rat showing the normal architecture of hepatocytes revealed that zingerone treatment clearly attenuated the acute liver injury induced by cyclosporine and also due to the antioxidant efficacy of zingerone, which helps in wiping out the generation of free radicals and thereby preventing the destruction of hepatic cells. The author (Mani *et al.*, 2016) reported that supplementation with zingerone reduced the pathogenicity and restoring the healthy state of the liver.

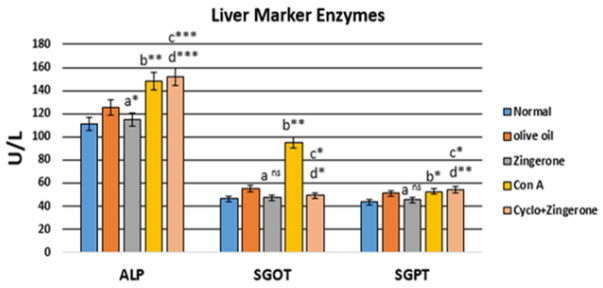

Figure 1: Activity of Liver Marker Enzymes in control and treated rats

Comparisons were made between a- control vs zingerone; b - zingerone vs Con A; c - Zingerone vs CsA +Zingerone; d - Control vs CsA +Zingerone. Results are expressed as mean ± SEM (n=6), ns-non significant *(p<0.05) ** (p<0.01) *** (p<0.001) were considered to be statistically significant.

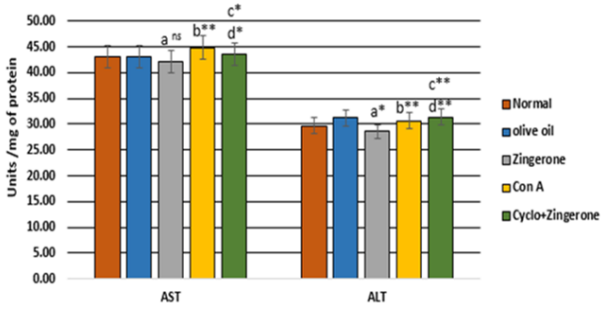

Figure 2: Activity of AST & ALT in control and treated rats

Comparisons were made between a- control vs zingerone; b - zingerone vs Con A; c - Zingerone vs CsA +Zingerone; d - Control vs CsA +Zingerone. Results are expressed as mean ± SEM (n=6), ns-non significant *(p<0.05) ** (p<0.01) *** (p<0.001) were considered to be statistically significant.

Histopathology of Liver Tissue

Histopathological observations in the control and experimental group of rats (H and E staining, 200X)

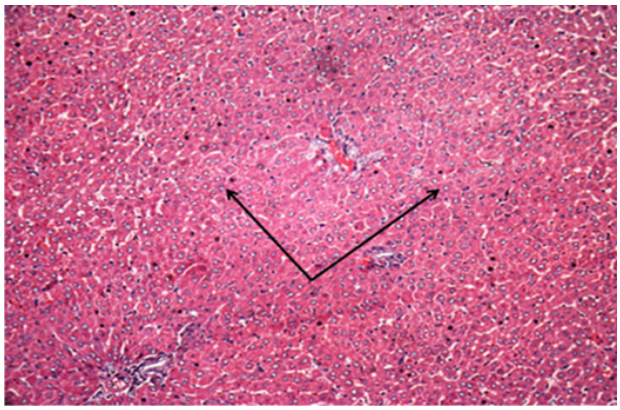

Figure 3: Control group of Liver showing normal histology of hepatocytes

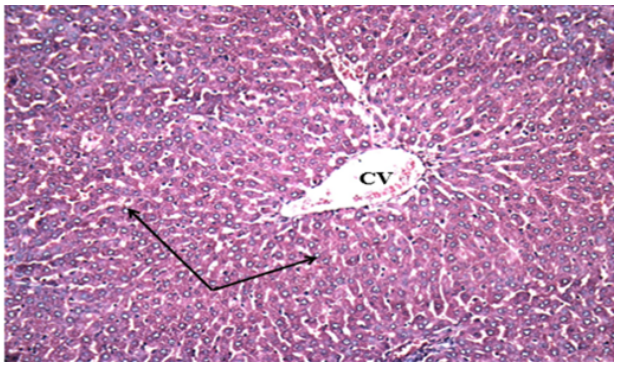

Figure 4: Zingerone group of Liver showing normal histology of hepatocytes and central vein

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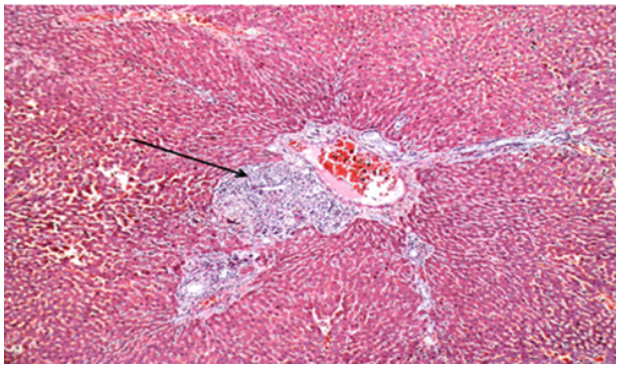

Figure 5: Concana vallin A group showing a mild degree of periportal inflammation

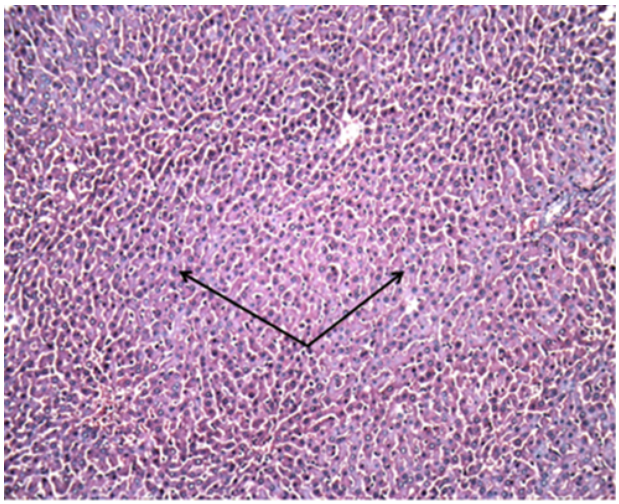

Figure 6: Cyclosporine A/Zingerone group of Liver showing normal histology of hepatocytes

CONCLUSION

The present study results in aid in proving that zingerone being non-toxic to hepatic cells can be developed as a full-fledged immunomodulatory in the near future.

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