Ameliorative Effect of *Padina Pavonia* on *Liver Fibrosis* by Down-regulating Inflammatory Mediators

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ABSTRACT

Introduction: Oxidative stress is potent physiological mechanism which induced during cell division, wound healing process and metabolism. Its over-production initiates various pathological condition in body. Excessive oxidative stress induces the cascade mechanism by activating inflammatory mediators followed by triggering tumor suppressor gene p-53 which ultimately activates apoptotic gene to recruits apoptosis (Somade et al.2020). In response to rapid generation of ROS, GSH production dramatically decreased and it caused induction of cellular apoptotic pathway, furthermore depletion in GSH level also accelerates autophagy of cancerous cells.CCl_4 widely used chemical for developing oxidative stress in animal model. er, monooxygenase system (CYP450) converts CCl_4 into CCl_3OO^- as a result it to cross the bilayer membrane results in excessive production of ROS/RNS results in excessive release of inflammatory cytokines which mainly recruited by T- helper cells and hepatic macrophages and promotes inflammatory response of liver (Mannaa & Abdel-Wahhab. 2016). Phyto-constituents from algal source showed striking pharmacological activities against variety of diseases condition. Brown seaweeds are a cheap natural source of phyto-constituents such as rare carbohydrates, amino-acids, lipids and phenolic compounds like terpenoids, pholrotanin, flavonoids and alkaloids (Wells et al. 2017).

Objectives: Present work is design to elucidate the pharmacological effect of solvent fractions *(hexane and chloroform)* of brown alga; *Padina pavonia* against liver fibrosis induced by chronic exposure of CCl_4.

Methodology: Hexane and chloroform fractions were prepared using HPLC grade solvents using ethanol extracts.Female Wistar rats (120-160 g) were categorized into 6 groups (n=6), Rats were injected with CCl_4 (50%), dissolved in olive oil, thrice a week for 30 days to induce liver fibrosis. Rats were supplemented either with *hexane and chloroform of P. pavonia* (150mg/kg b.w.) daily for 30 days. On day 31st rats were decapitated, serum and liver tissue sample were dissected for evaluation of liver specific serum enzymes, hepatic tissue induced oxidative stress, hepatic tissue antioxidant status, serum inflammatory and apoptotic mediators and morphological improvement were evaluate. Hexane soluble fractions were further evaluate for possible active components using GC/MS.

Conclusion/Results: *Hexane soluble fraction* of *P. pavonia* showed significant ($p \leq 0.05$) alleviation in ALT -53.20% AST -62.33%, ALP -77.32%, LDH 57.8% and total bilirubin -47.08% level respectively levels respectively . Similarly, chloroform soluble fraction of *P. pavonia* also represent similar pattern by reducing ALT -51.28%, AST -57.78%, ALP -47.32%, LDH -52.34% and total bilirubin --49.2%levels respectively. Solvent fractions notable reduced the production of ROS/ RNS in hepatic tissues. *hexane soluble fraction* of *P. pavonia* showed significant reduction in lipid peroxidation indicated by decreased hepatic level of MDA -52.2% . However, it also reduced the production of RNS, evident by alleviated level of i-NO -62.4% level. Besides that, intoxicated rats treated with *chloroform soluble fraction* of *P. pavonia* showed significant ($p \leq 0.05$) alleviation in lipid peroxidation and generation of RNS followed by low concentration of MDA -2 -58.1% and i-NO -50.2%. These fraction also improved antioxidant status of hepatic tissue by improving GPx and Catalase activities followed by enhancing GSH concentarion in hepatic tissue. They also decreased serum concentrations of inflammatory mediator (IL-6) by (-8.2%, -0.78%). it

has been reported that increased caspase-3 activity have central role in progression of cellular necrosis activities (Alkhouri *et al*., 2010). In present study, increased serum concentration of caspase-3 demonstrates acceleration of apoptotic activity which is evident by presence of massive necrotic bodies along the portal areas of fibrotic rats. Apoptotic protein (caspase-3) -25.7% and -22%. Further they also improved hepatic morphology by decreasing collagen deposition in hepatocytes along with significant reduction in necrotic bodies and fatty degenration. HSF of ethanol extract of *P. pavonia* reveals the presence of several fatty acids such as palmitic acid, stearic acid, oleic acid, linoleic acid, lauric acid, (hexadecanoic acid methyl ester, Octadecanoic acid ethyl ester, ethyl Oleate, 9,12-Octadecadienoic acid (Z,Z)-, methyl ester, dodecanoic acid) which previously reported to possess anticancer, antifibrotic, anti-nonalcoholic fatty liver diseases activities (Breeta et al. 2021, Kim et al. 2017, Ronis et al. 2013). These phytoconstituents previously showed anti-inflammatory, anti-oxidant activities. Suggestively, *P. pavonia* showed antifibrotic activities since they suppressed the inflammatory mediators as well as they also ameliorates the excessive secretion of ECM in disse spaces by attenuating th collagen deposition in disse spaces. Conclusively, solvent fractions of *P. pavonia* have capability to reverse the tissue oxidative stress induced in response of repeated administration of CCl_4 and they also have promising phytoconstituents which may induce effect by blocking toll-like receptors followed by suppression of MAPK and NF- kβ pathways which ultimately reduces level of inflammatory cytokines and apoptotic protein. Thereby, contributing in delay the onset of liver fibrosis.

Keywords: Cytokines, Hepatic fibrosis, Marine algae.

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