1. Introduction

Portal hypertension (PH) is a common complication in the patients with advanced chronic hepatitis [1]. The increased hepatic vascular resistance and portal hyperemia are involved in the reversible pathogenesis as the potent therapy targets [2].

Salvianolic acid B (Sal B) is a molecule from the root of Salvia miltiorrhiza (Danshen), which is a traditional Chinese medicine widely used for cardiovascular diseases [3]. Sal B is effective for liver fibrosis and PH in patients [4] or animals [5]. In the endothelin-1-induced PH rats, Sal B could inhibit the constriction of hepatic stellate cells [5]. However, our previous study indicated that Sal B constrict portal veins of the isolated portal perfused rat livers (IPPRLs) at physiological status [6]. The underlying mechanisms of Sal B for PH remain unclear.

It is reported that nitric oxide (NO) and carbon monoxide (CO) play key roles in the pathogenesis of PH [7]. Both signal molecules directly relax portal veins through upregulation of cGMP via guanylate cyclase [8]. NO from endothelial NO synthase (eNOS) aggravates PH through systemic hyperemia [9], and inducible NO synthase (iNOS) exacerbates PH by producing peroxynitrite (ONOO⁻) [10]. It has been reported that the reduced NO bioavailability is involved in the increased hepatic vascular resistance [11]. There is an increase of superoxide release by NADPH oxidase in liver with chronic hepatitis [12] and an overproduction of iNOS from macrophages [10]. The iNOS-derived NO reacts with superoxide, leading to ONOO⁻ formation, with...
a decrease in NO bioavailability [10]. Heme oxygenase-1 (HO-1) is a rate-limiting enzyme catalyzing heme to CO, iron, and biliverdin. Biliverdin is then converted to bilirubin, which acts as a highly effective antioxidant and free radical scavenger against oxidation [13]. HO-1 also showed hepatoprotection against ischemia-reperfusion injury, endotoxicemia, hyperoxia-induced hepatic injury, and immune-mediated apoptotic liver damage [14]. Furthermore, HO-1/CO activation downregulates the inflammatory response by blocking the formation of ONOO− from iNOS [13]. While the ONOO− induces HO-1 protein expression but mediating its inactivation [15].

Sal B has an effect on [3] production of NO or CO from activated macrophages [16] under inflammatory cytokines [17]. In addition, Sal B could protect endothelium from the oxidation by blocking PI3K/Akt signal pathway [18]. Therefore, Sal B was proposed to rescue NO bioavailability or to maintain CO potency from the macrophage at portal triads in advanced chronic hepatitis.

The purpose of present study is to investigate the effects of Sal B on PH in IPPRL with chronic hepatitis and to analyze further the NO or/and CO signals through the relationship between the Sal B potency and the existed iNOS or HO-1 from the macrophages in portal triads.

2. Materials and Methods

2.1. Reagents. Carbon tetrachloride (CCI4), olive oil, and heparin sodium were purchased from Sinopharm Chemical Reagent Company. Acetylcholine chloride and phenylephrine hydrochloride were obtained from Sigma (USA). Salvianolic acid B (purity >99%) was purchased from Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

2.2. Animals. Thirty two six-week-old male Wistar rats (180–200 g) were purchased from Animal Centre of the Chinese Academy of Medical Sciences. All rats were kept under a 12 h/12 h light/dark cycle, temperature (25.0 ± 0.2 °C), and humidity (45 ± 2%) controlled SPF environment. The rats were fed standard rodent pellets and allowed free access to filtered water. All experiment procedures were performed in accordance with the Guidelines of Animal Experiments from the Committee of Medical Ethics, National Health Department of China.

2.3. Induction of Portal Hypertension with Chronic Hepatitis. PH with chronic hepatitis was induced by CCI4 in rat as described previously (Figure 1) [19]. Rats were injected subcutaneously with a mixture of 40% (v/v) CCI4 in olive oil (3 mL/kg) two times a week for 0, 28, 56, and 84 days, respectively [20, 21]; olive oil was the vehicle for age-matched control. Eighty four hours after the last CCI4 injection, rats were anesthetized with a subcutaneous injection of sodium pentobarbital (50 mg/kg). A midline incision was made to open abdominal cavity, and ascitic samples were collected and quantified as described previously [22]. The exuded liquid ratios were calculated as \( \frac{\text{exuded liquid weight}}{\text{body weight}} \times 100 \). The portal pressure in vivo was recorded. The blood sample was collected for analyzing the serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and albumin (Alb) levels by biochemistry and CD163 levels by immunoassay. Then the hepatic artery, portal vein, and hepatic vein were canulated [20, 21]. The liver, spleen, and kidneys were harvested, and the organ indexes were calculated as \( \frac{\text{organ weight}}{\text{body weight}} \times 100 \).

2.4. CD163 Immunoassay. The blood samples were centrifuged at 1200 g for 10 min at 4°C, and serum was stored at −80°C until the assays. Serum CD163 levels was measured using enzyme-linked immunosorbent assay kits (R&D Systems, Wiesbaden, Germany) following the manufacturer’s guidelines.

2.5. Histological and Morphometry

2.5.1. Histological Quantification. Formalin-fixed, paraffin-embedded liver sections were cut at a 6 μm thickness and then stained with Masson’s trichrome (Masson) [19]. Images were obtained using NanoZoomer Digital Pathology system (Hamamatsu, Japan). The collagen density was quantified using Image ProPlus analysis system 7.0.1 (no. 41N70000-60555, Media Cybernetics, USA) at 100 × magnification. The data were expressed as the one-ten thousandth of collagen (the ratio of collagen area per total analyzed field area ×100%). Values are expressed as the average of ten fields taken from each section.

2.5.2. Immunohistochemistry for Localization and Quantification of iNOS and HO-1. For immunohistochemical analysis, sections were incubated with rabbit polyclonal antibody against iNOS (1: 500 dilution, sc-8310, Santa Cruz Biotechnology) or HO-1 (1: 200 dilution, sc-10789, Santa
Cruz Biotechnology). Staining was visualized using avidin-biotin peroxidase immunostaining kit with diaminobenzidine (Boster, Wuhan, China). The mean optical density (OD), positive staining area (Ap), and observed area (AT) were determined with Image ProPlus 7.01 at 400× magnifications. The levels of iNOS and HO-1 were calculated by the formula [OD × (Ap/AT)]^{3/2}. The average of ten random fields generated a single data for statistic analysis [19].

2.6. Effect of Salvianolic Acid B on Isolated Portal Perfused Rat Livers with Chronic Hepatitis. The isolated portal perfusion system was performed with controlled velocity as described previously [20, 21]. At d₀, d₂₈, d₅₆, and d₈₄, the perfuse velocity was chosen 3935.50, 4720.63, 4753.35, or 5164.16 (µL/min), respectively [20, 21]. Phenylephrine hydrochloride was determined as 1.69 × 10⁻¹⁰, 2.64 × 10⁻¹⁰, 5.82 × 10⁻¹⁰, and 8.24 × 10⁻¹⁰ mol/L, respectively, to constrict portal veins [21]. After the phenylephrine constriction, Sal B (10⁻¹³–10⁻⁷ mol/L) was added into the recirculating perfusate. Dose-response curves were obtained from the Sal B concentrations and the changed percentage of the perfused pressure from the baseline of phenylephrine constriction.

2.7. Statistical Analysis. All data are expressed as mean ± S.E.M. Comparisons between groups were performed using Student’s t-test or Mann-Whitney. Significant differences were established at the 0.05 level. The equation, the EC₅₀ with its 95% confidence intervals of Sal B, and the area under the curve (AUC) of Sal B were analyzed using GraphPad Prism 4 (GraphPad Software). The EC₅₀ of Sal B (y) was regressed with the durations (0, 28, 56, and 84 days) and serum CD163 levels (x) in the progression of chronic hepatitis, and the AUC of Sal B (y) was regressed with the amounts of existed iNOS or HO-1 from immunohistochemical staining and the serum CD163 levels (x).

3. Results

3.1. General Characterization of Rats. The model of rat PH was confirmed by ascite levels, organ index, and serum biomarker levels (Figure 2). The exuded liquid ratios significantly elevated from d₀ to d₈₄ (P < 0.01) as the progression of chronic hepatitis (Figure 2). Hepatic indexes were the lowest at d₀, the highest at d₂₈, and reduced at d₅₆ and d₈₄ gradually (Figure 2). The splenic or renal indexes increased gradually from d₀ to d₈₄ (Figure 2). Serum ALT and AST levels increased from d₀ to d₂₈, then relived at d₅₆ and d₈₄. Serum ALP levels increased from d₀ to d₅₆, then relived at d₈₄. Serum Alb levels decreased from d₀ to d₂₈, then relived at d₅₆ and d₈₄ (Figure 3).

3.2. Portal Pressure and Serum CD163 Levels

3.2.1. Portal Pressure. The portal pressure in vivo significantly increased from d₀ to d₈₄ (P < 0.01) as the progression of chronic hepatitis (Figure 4).

3.2.2. Serum CD163 Levels. CD163 is a biomarker of the activated macrophages in PH. The serum CD163 levels were increased gradually from d₀ to d₈₄ (P < 0.01) as the progression of chronic hepatitis (Figure 4).

3.3. Pathological Changes and Morphometry

3.3.1. Pathological Changes. The hepatic pathological changes induced by CCL₄ were evaluated by Masson-stained sections. At d₀, the liver showed normal hepatic architecture, and the collagen only normally distributed at the portal areas and around vessels (Figure 5(a)). At d₂₈, the hepatic fatty degenerations and cellular swellings were obviously...
observed, and the hepatic sinusoid was severely narrowed without obvious collagen (Figure 5(b)). At \(d_{56}\), the hepatic fibrosis was observed and the collagen increased and mainly deposited in lobules. The relieved enlarged hepatic cords led to the hepatic sinusoid widen obviously. Some deposited collagen in interlobular had extended into and separated lobules incompletely, thus the directions of blood flow were not changed in hepatic sinusoid (Figure 5(c)). At \(d_{84}\), the hepatic cirrhosis was evident. The lobules were completely destructed by deposited collagen and the formation of pseudolobules was observed, so the directions of blood flow were completely changed in hepatic sinusoid (Figure 5(d)).

3.3.2. Collagen Ratio. Quantification of Masson staining by morphometry analysis showed that collagen ratios were increased along with the progression of chronic hepatitis (Figure 6).

3.4. Localization and Quantification of Synthases

3.4.1. iNOS Cellular Localization. The iNOS positive cells were the hepatocytes and scattered stellates in the lobules of the normal rats at \(d_0\) (Figure 5(e)). The iNOS expression was reduced in the scattered hepatocytes and mainly observed in stellates cells in the lobules of the rats with chronic hepatitis at \(d_{28}\) (Figure 5(f)). The expression of iNOS was completely quenched in the hepatocytes; the positive cells were the macrophages in the portal triads and the stellates in the lobules at \(d_{56}\) (Figure 5(g)). The main thick positive cells were the macrophages in the fibrous interval pseudolobules around vessels and the stellates with thin granules in the lobules at \(d_{84}\) (Figure 5(h)).

3.4.2. iNOS Quantification. The iNOS-IHC OD per volume (Figure 6) in the portal triads of the rats with chronic hepatitis was significantly increased at \(d_{28}\) (2-fold), \(d_{56}\) (1.5-fold), and \(d_{84}\) (3-fold) compared with that at \(d_0\), respectively, \((P < 0.01)\); these were decreased at \(d_{56}\) and increased at \(d_{84}\) with that at \(d_{28}\), respectively, \((P < 0.01)\); so did increased that at \(d_{84}\) with that at \(d_{56}\) \((P < 0.01)\).

3.4.3. HO-1 Cellular Localization. The main HO-1 positive cells were the hepatocytes near the central vein and the scattered stellates in the lobules, but the hepatocytes next to portal triads were absolutely negative in the normal rats at \(d_0\) (Figure 5(i)). Besides of the thinner granules in the hepatocytes, the main positive staining cells were the stellates in the lobules at \(d_{28}\) (Figure 5(j)). The thin granules have completely disappeared in the hepatocytes, while the positive cells were the macrophages in portal triads and the stellates in the lobules at \(d_{56}\) (Figure 5(k)). The main thick positive cells were the macrophages in the fibrous intervals out pseudolobules at \(d_{84}\) (Figure 5(l)).

3.4.4. HO-1 Cellular Quantification. The total HO-1-IHC OD per volume (Figure 6) in the rats with chronic hepatitis was significantly increased at \(d_{28}\) (1.6-fold), \(d_{56}\) (2-fold), and \(d_{84}\) (3-fold) compared with that at \(d_0\), respectively \((P < 0.01)\); these at \(d_{56}\) and \(d_{84}\) significantly increased compared with that at \(d_{28}\), respectively, \((P < 0.01)\); so did that at \(d_{84}\) compared with that at \(d_{56}\) \((P < 0.01)\).

3.5. Salvianolic Acid B Reducing PH

3.5.1. Dose-Effective Relation for Relaxing Portal Vein. At \(d_0\), Sal B constricted portal veins of normal rats (Figure 5(m)), the equation was \(y = 0.5290 + 2.2160/[1 + 10^{([−2.7600+0.6913x])}]\) \((R = 0.9983, P < 0.01)\); the \(EC_{50}\) with its 95% confidence intervals was \(2.04 \times 10^{-9}(1.02 \times 10^{-10}−4.10 \times 10^{-9})\) mol/L. At \(d_{28}\) (Figure 5(n)), \(d_{56}\) (Figure 5(o)), and \(d_{84}\) (Figure 5(p)) of the progression in the rats with chronic hepatitis, Sal B relaxed portal veins, the equations were \(y = −0.0563 + 0.0150/[1 + 10^{(−8.6695+0.4685x)}]\) \((R = 0.9953, P < 0.01)\), \(y = −0.0672 + 0.0585/[1 + 10^{(−8.4420+0.6878x)}]\) \((R = 0.9994, P < 0.01)\), and \(y = −0.1203 + 0.0918/[1 + 10^{(−6.0860+0.5903x)}]\) \((R = 0.9955, P < 0.01)\), respectively; the \(EC_{50}\) with their 95% confidence intervals were \(7.28 \times 10^{-11}(1.23 \times 10^{-11}−4.30 \times 10^{-10})\) mol/L, \(1.52 \times 10^{-11}(3.90 \times 10^{-12}−5.90 \times 10^{-11})\) mol/L, and \(8.44 \times 10^{-11}(1.21 \times 10^{-11}−1.97 \times 10^{-10})\) mol/L, respectively.

3.5.2. Time-Effective Relation with Pathological Progression. The liner regressive equation was \(y = 2.2170x – 140 (R = 0.7861, P < 0.05)\) from the \(EC_{50}\) \((y \times 10^{-11}\) mol/L) of Sal B to the durations \((x = d \times 24 + 11.47\) (hours)\); \(d = 0, 28, 56, \) and \(84\) days) of chronic hepatitis progression. So did the

![Figure 4: Changes of portal pressure and serum CD163 levels in portal hypertensive rats with chronic hepatitis. Data represent mean ± S.E.M. (n = 8), *P < 0.05, **P < 0.01 compared with rats at \(d_0\); \(bP < 0.05\) and \(cP < 0.01\) compared with rats at \(d_{28}\), \(dP < 0.05\) and \(eP < 0.01\) compared with rats at \(d_{56}\).]
Figure 5: Salvianolic acid B reducing portal hypertension in IPPRL with chronic hepatitis. (1) Masson staining was performed to evaluate collagen deposition (100×). (a) Liver with normal structure in normal rats at d0. (b) Hepatic degeneration in the portal hypertensive rats at d28. (c) Hepatic fibrosis in the portal hypertensive rats at d56. (d) Hepatic cirrhosis in the portal hypertensive rats at d84. The inserted micrographs in the upper left corner were the portal triad (Masson × 630) from the original ones (black rectangle). (2) Existence of iNOS was detected by immunohistochemistry staining (400×). (e) iNOS was located at the hepatocyte at d0. (f) iNOS was located at stellates in the lobules at d28. (g) iNOS was located at stellates and macrophages at d56. (h) iNOS was located at macrophages out lobules at d84. The inserted micrographs in the upper left corner were the portal triad (630×) from the original ones (Black rectangle). (3) Existence of HO-1 was detected by immunohistochemistry staining (400×). (i) HO-1 was located at the hepatocytes only at d0. (j) HO-1 was located at the macrophages in portal triads with less at the hepatocytes at d28 than that at d0. (k) HO-1 was located at the macrophages out lobules with less at the hepatocytes at d56 among the durations of chronic hepatitis. (l) HO-1 was located at the macrophages in portal triads only at d84. The inserted micrographs in the upper left corner were the portal triad or its partners (630×) from the original ones (black rectangle). (4) (m) Sal B increased the portal pressure in the IPPRL at d0. (n) Sal B decreased the portal pressure in the IPPRL at d28. (o) Sal B decreased the portal pressure in the IPPRL at d56. (p) Sal B decreased the portal pressure in the IPPRL at d84.

The inserted micrographs in the upper left corner were the portal triad or its partners (630×) from the original ones (black rectangle). (4) (m) Sal B increased the portal pressure in the IPPRL at d0. (n) Sal B decreased the portal pressure in the IPPRL at d28. (o) Sal B decreased the portal pressure in the IPPRL at d56. (p) Sal B decreased the portal pressure in the IPPRL at d84.

3.5.3. Salvianolic Acid B-AUCs Correlated with Existed iNOS. The liner regressive equation was $y = 0.3587x - 8.0364$ ($R = 0.83391, P < 0.05$) from the AUCs of Sal B to the iNOS-OD/V (%) in portal triads at $d_0, d_{28}, d_{56}$, and $d_{84}$ in the progression of CCl4-induced chronic hepatitis.

3.5.4. Salvianolic Acid B-AUCs Correlated with Existed HO-1. The liner regressive equation was $y = 0.4120x - 9.3727$ ($R = 0.9062, P < 0.05$) from the AUCs of Sal B to the HO-1-OD/V (%) in portal triads at $d_0, d_{28}, d_{56}$, and $d_{84}$ in the progression of CCl4-induced chronic hepatitis.

3.5.5. Salvianolic Acid B-AUCs Correlated with Serum CD163 Levels. The liner regressive equation was $y = 0.8531x + 26.2360$ ($R = 0.7838, P > 0.05$) from the AUCs of Sal B to the serum CD163 levels at $d_0, d_{28}, d_{56}$, and $d_{84}$ in the progression of CCl4-induced chronic hepatitis. It was $y = 22.8210x + 19.3530$ ($R = 0.9889, P < 0.01$) from the AUCs to the serum CD163 levels at $d_{28}, d_{56}$, and $d_{84}$ in the progression of CCl4-induced chronic hepatitis.
4. Discussion

It was demonstrated in the present study that Sal B relaxed portal veins in IPPRLs of CCl\textsubscript{4}-induced chronic hepatitis. Its mechanisms are related to the inhibition of oxidative stress from macrophages and the increase of NO bioavailability or CO potency in portal triads. Sal B is the most active antioxidant extracted from Danshen and has obvious effects for liver fibrosis, chronic hepatitis, or PH in clinic [4]. The mechanisms responsible for the protective effects of Sal B in PH remain unclear.

It has been reported that the portal resistance is mainly located at the terminal portal venules (TPV) in portal triads [23]. The activated macrophages release vasoactive substances concomitantly and increase the perfusion resistance [24]. Accordingly, we have previously demonstrated that the macrophages out lobules express more iNOS, produce more NO, and generate ONOO\textsuperscript{−} to further reduce NO bioavailability and aggregate PH [22]. The HO-1/CO activation decreases iNOS expression, enhances antioxidative effect, and upregulates extracellular superoxide dismutase (ecSOD) [13]. The local ecSOD could scavenge superoxide and block ONOO\textsuperscript{−} generation [11]. Therefore, macrophage-derived NO or CO in portal triads was considered as the most effective target. Sal B, a molecule from medical plants [3] for PH [4–6, 20, 21, 25], has benefits to elevate NO or CO potency in portal triads. Sal B increased further phenylephrine-induced elevated portal pressure in the rats without chronic inflammation [6, 20, 21]. It suggested that the macrophages infiltrated in portal triads being the indirect cellular targets of Sal B to reduce PH in the rats with chronic hepatitis. There were at least four possible pathways for Sal B decreasing PH from oxidative chronic hepatitis (Figure 7). (1) NO signal: Sal B inhibited oxidative stress of activated macrophages [17], blocked ONOO\textsuperscript{−} generation [3], rescued iNOS activity from the inactivation by nitrate modification [10], and consequently increased local NO level to relax the TPV. Especially the AUC of Sal B for reducing PH correlated positively with the existed level of iNOS from the macrophages [8–11, 23]. Sal B relaxed indirectly portal vein via restoring NO bioavailability [29]. (2) CO signal: Sal B increased the expression of HO-1 from activated macrophages [16] and elevated local CO level to dilate TPV [8, 17]. Especially the AUC of Sal B for reducing PH correlated positively with the existed level of HO-1 from the macrophages in the portal triads. Meanwhile, HO-1-derived bilirubin directly inhibits NADPH oxidase and increases ecSOD and then decreases superoxide production and ONOO\textsuperscript{−} formation [13]. (3) EcSOD protection: Sal B might indirectly upregulate ecSOD expression, which converts superoxide to hydrogen peroxide and blocks ONOO\textsuperscript{−} generation from NO [11, 30]. Then the hydrogen peroxide could enhance iNOS, HO-1, and ecSOD expression itself to against the vicious cycle in PH. (4) Calcium signal: being considered as a cardiovascular protective agent [31], macrophages, which was consistent with the PH patients [24]. We found Sal B reduced PH as a candidate from a medical plant for PH patients. Sal B increased the portal pressure of the IPPRLs at physiological status and reduced the PH of the IPPRLs at chronic hepatitis status in this study. EC\textsubscript{50} of Sal B relaxation was positively correlated with the duration of CCl\textsubscript{4}-induced chronic hepatitis, indicating the action of Sal B which was pathological dependent. Our results demonstrated that increased iNOS or HO-1 levels in the macrophages infiltrated in portal triads are involved in the mechanism of Sal B relaxation. The existed levels of iNOS or HO-1 in lobules disappeared gradually, these in portal triads strengthened continuously along with the progression of CCl\textsubscript{4}-induced chronic hepatitis, especially in the infiltrated macrophages. We also reported here that iNOS and HO-1 levels in portal triads are correlated positively with the AUCs of Sal B for reducing PH.

The IPPRL was used in this study to evaluate the effect of Sal B on PH. The hepatic artery was ligated to ensure that the portal resistance originated mainly from the smooth muscle cells in terminal portal venule (TPV) and the sphincter-like endothelia at hepatic sinusoid inlets [23]. In PH rodents, the TPVs were the major resistance in portal microcirculation without enough collateral (like pre-TPV) or sinusoidal (post-TPV) networks to compensate a blood pressure increase [26]. Furthermore, the infiltrated activated macrophages in portal triads were next to TPVs in the rats with oxidative chronic hepatitis (Figure 7 inserted micrographs). Sal B relived endothelin-induced elevated portal pressure in physiological rats [27] or mice [28]; these did not agree with the data in this research that Sal B increased further phenylephrine-induced elevated portal pressure in the rats without chronic inflammation [6, 20, 21]. It suggested that the macrophages infiltrated in portal triads being the indirect cellular targets of Sal B to reduce PH in the rats with chronic hepatitis. There were at least four possible pathways for Sal B decreasing PH from oxidative chronic hepatitis (Figure 7).

![Figure 6: Collagen ratio and the levels of iNOS and HO-1 in portal triads. Data represent mean ± S.E.M. (n = 8). *P < 0.05, **P < 0.01 compared with rats at d\textsubscript{0}; bP < 0.05 and bbP < 0.01 compared with rats at d\textsubscript{28}; cP < 0.05 and ccP < 0.01 compared with rats at d\textsubscript{56}.](image-url)
Sal B acted on TPV endothelia and smooth muscles. On human endothelia, Sal B activated transcription factor 4 or 6, consequently regulated upwards glucose-regulated protein 78, to protect the cellular damage from oxidative stress [30]; Sal B suppressed JAK/STAT1 activation in endothelia to relieve vessel inflammation [32]. On human vascular smooth muscle, Sal B limited calcium channel to decrease Ca^{2+} influx [33]. It’s a challenge that the exact mechanism of Sal B actions from the physiological constriction switches to pathological relaxation. The clinical aspects of heme oxygenase hinted its pharmacological actions in pathological status [13]. Further research on Sal B mechanisms might go on the way of systems biology [34].

Sal B for reducing PH might be used to explain the actions of medical plants in Chinese prescription for the ascitic patients with chronic hepatitis. It is an interesting clue to discover more effective candidates depending on the macrophage iNOS or HO-1 in portal triads, at least partly. Consequently, Sal B or its derivative might be exploited as a candidate to increase NO bioavailability or CO potency, especially from free radical damages in inflammatory diseases.

Authors’ Contribution

X. Zhao and H. Jia have the same contribution in this research work.

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