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Hepatoprotective effects of Solanum nigrum Linn extract against CCl₄-induced oxidative damage in rats

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Abstract

Solanum nigrum L. (SN) is an herbal plant that has been used as hepatoprotective and anti-inflammation agent in Chinese medicine. In this study, the protective effects of water extract of SN (SNE) against liver damage were evaluated in carbon tetrachloride (CCl₄)-induced chronic hepatotoxicity in rats. Sprague-Dawley (SD) rats were orally fed with SNE (0.2, 0.5, and 1.0 g kg⁻¹ bw) along with administration of CCl₄ (20% CCl₄/corn oil; 0.5 mL kg⁻¹ bw) for 6 weeks. The results showed that the treatment of SNE significantly lowered the CCl₄-induced serum levels of hepatic enzyme markers (GOT, GPT, ALP, and total bilirubin), superoxide and hydroxyl radical. The hepatic content of GSH, and activities and expressions of SOD, GST Al, and GST Mu that were reduced by CCl₄ were brought back to control levels by the supplement of SNE. Liver histopathology showed that SNE reduced the incidence of liver lesions including hepatic cells cloudy swelling, lymphocytes infiltration, hepatic necrosis, and fibrous connective tissue proliferation induced by CCl₄ in rats. Therefore, the results of this study suggest that SNE could protect liver against the CCl₄-induced oxidative damage in rats, and this hepatoprotective effect might be contributed to its modulation on detoxification enzymes and its antioxidant and free radical scavenger effects.

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Keywords: Solanum nigrum Linn; Carbon tetrachloride; Liver fibrosis; Hepatoprotection

1. Introduction

Numerous medicinal plants and their formulation are used for liver disorders in ethnomedical practice as well as traditional medicine in Chinese. Solanum nigrum L. (SN) is a common herb that grows wildly and abundantly in open fields. It has been used to treat inflammation, edema, mastitis and hepatic cancer for a long time in oriental medicine. A freshly prepared extract of the herb is effective in treating cirrhosis of liver, and juice of the leaves alleviates pain in inflammation of the kidney and bladder, and internally for cardialgia.

Previous investigations showed that extracts of SN suppressed the oxidant mediated DNA–sugar damage,
and the plant exerted cytoprotection against gentamicin-induced toxicity on Vero cells and anti-neoplastic activity against Sarcoma 180 in mice. More recent studies revealed an inhibitory effect of extracts of SN on 12-0-tetradecanoylphorbol 13-acetate (TPA)-induced tumor promotion in HCT-116 cells, and a remarkable hepatoprotective effect of the ethanol extract of dried fruits of SN against CCl4-induced liver damage [1]. These studies suggest that SN possesses a beneficial activity as an antioxidant, and antioxidant-promoting, and hepatoprotective agent, although the mechanism for the activity remains to be elucidated.

CCl4 is a classical hepatotoxicant that causes rapid liver damage progressing from steatosis to centrilobular necrosis. Long-term administration of CCl4 causes chronic liver injury, and is a widely accepted model to produce hepatic fibrosis [2,3]. CCl4 is known to induce reactive oxygen formation, deplete GSH of phase II enzyme, and reduce antioxidant enzyme and antioxidant substrates to induce oxidative stress that is an important factor in acute and chronic liver injury. The liver injury induced by CCl4 is resulted from free radicals and lipid peroxidation that cause hepatic cell damage. CCl4 requires bioactivation by phase I cytochrome P450 system in liver to form reactive metabolic trichloromethyl radical (CCl3+) and proxy trichloromethyl radical (*OCCl3). These free radicals can bind with polyunsaturated fatty acid (PUFA) to produce alkoxy (R•) and peroxy radicals (ROO•), that, in turn, generate lipid peroxide, cause damage in cell membrane, change enzyme activity and finally induce hepatic injury or necrosis [4–6].

Recently, we have demonstrated that the water extract of SN (SNE) contains several antioxidants, such as gallic acid, PCA, catechin, caffeic acid, epicatechin, rutin and naringenin, and possesses strong antioxidative activity in vitro [1]. In this study, we investigated the antioxidative activity and potential protective effects of SNE in the CCl4-induced hepatic damage in rats. The protection activity of SNE was compared with silymarin, which has been used for over 20 years in clinical practice for the treatment of toxic liver disease [7]. It has been described to be an antioxidant and exhibits anti-inflammatory, anticarcinogenic, growth-modulatory and hepatoprotection effects [8]. The effect of SNE on the expression of phase II detoxifying and antioxidative enzymes was also examined. The results of this study showed that SNE could be used as a protective agent against the chemical-induced oxidative damage in rats, and the hepatoprotective effect might be correlated with its antioxidative and free radical scavenger effect.

2. Materials and methods

2.1. Preparation of water extracts of SN (SNE)

The whole plant of SN was collected from the mountain in Miaoli, Taiwan. The plants were washed, cut into small pieces, shade dried for 3 days, and then dried overnight in an oven. The dried SN (800 g) was mixed with water (5000 mL) for 30 min, and subjected to continuous hot extraction (100 °C, 40 min). The resulting water extract was filtered and subsequently concentrated with a water bath (90 °C) until it became creamy, and then dried in an oven (70 °C) that finally gave 185 g (23.125% of initial amount) of powder (SNE, water extract of SN). The concentration used in the experiment was based on the dry weight of the extract.

2.2. Animals and treatment

SD rats weighing 150–180 g were housed in conventional cages with free access to water and rodent chow at 20–22 °C with a 12-h light–dark cycle. All procedures involving laboratory animal use were in accordance with the guidelines of the Instituted Animal Care and Use Committee of Chung Shan Medical University (IACUC, CSMU) for the care and the use of laboratory animals. Rats were treated orally with CCl4 (20% CCl4/corn oil; 0.5 mL kg−1 body weight twice a week; Monday and Thursday) for 6 weeks to cause chronic reversible cirrhosis as described previously with some modification [9]. At the same time, the rats were fed with a diet containing SNE (0.2, 0.5 and 1.0 g kg−1 body weight), or given silymarin orally (0.2 g kg−1 body weight; four times a week; Tuesday, Wednesday, Friday and Saturday) [10,11]. The control rats were treated with corn oil and fed with a normal diet. Blood samples (0.2 ml) with heparin (10 U mL−1) were collected from the tail vein before the first CCl4 treatment and at the end of the third and sixth weeks. At the end of the experiment, blood and livers were immediately obtained after the animals were sacrificed. Liver tissue samples were taken from the left liver lobe, and cut into two pieces. One piece was fixed in formalin for pathological examination. The other piece was utilized for the following biological analyses. Liver homogenates (10%, w/v) were obtained in 50 mM phosphate buffer (pH 7.0) and stored at −80 °C for analysis within 2 weeks.

2.3. Histological examinations

A portion of the liver was fixed in 10% formalin, processed by routine histology procedures, embedded in
paraffin, and cut into 5 μm sections. The samples were stained with hematoxylin and eosin for histopathological examination and stained with Masson’s trichrome for assessment of fibrosis [12]. Liver steatosis was graded on a three-point scale: 1+, hepatocytes in the area of one third of the lobules showed fatty accumulation, 2+ for two thirds and 3+, for all hepatocytes. The criteria used for scoring fibrosis severity were as follows: 0, normal; 1+, fibrosis present (collagen fiber present that extends from portal triad or central vein to peripheral region); 2+, mild fibrosis (the collagen fiber present with extension without compartment formation); 3+, moderate fibrosis (the collagen fiber present with some pseudo lobe formation); and 4+, severe fibrosis (the collagen fiber present with thickening of the partial compartments and frequent pseudo lobe formation).

2.4. Determination of biochemical markers of hepatic injury

Blood were placed at room temperature for 1 h, and then centrifuged at 1000 × g for 10 min to obtain serum. Serum biochemical parameters (GOT, GPT, ALP, and total-bilirubin) were assayed by the Boehinger Mannheim reagents (International Federation of Clinical Chemistry (IFCC) Scientific Committee recommended) [13,14].

2.5. Determination of glutathione (GSH) content

The procedure used for determining GSH with α-phtalaldehyde (OPA) was performed as previous described [15]. Liver GSH levels were determined using 1–10 mL of deproteinized homogenate. OPA-derived fluorescence was measured at 365 nm excitation and 430 nm emissions in a F4500 fluorescence spectrophotometer (Hitachi, Japan).

2.6. Assay of superoxide dismutase (SOD) activity

The SOD activity was measured according to the method of Beauchamp and Fridovich [16]. An adequate amount of the liver supernatant was mixed with the reaction mixtures, which contained 0.1 mM EDTA, 25 mM NBT, 0.1 mM xanthine, 50 mM sodium carbonate buffer (pH 10.2), and the final volume of the reaction mixture was brought up to 3 mL with distilled water. The reaction was initiated by the addition of 2 μM mL−1 xanthine oxidase and maintained under two 40 W lamps at 25 °C. After 15 min, the inhibition rate of NBT reduction was spectrophotometrically determined at 560 nm. One unit of SOD is defined as the amount of enzyme required to reduce NBT by 50%. The specific activity of SOD was expressed as a unit mg−1 protein in each supernatant.

2.7. Assay of glutathion-S-transferase (GST) activity

Total GST activity and the activities for specific GST isoform were measured according to the method of Habig et al. [17] using 1-chloro-2,4-dinitrobenzene (CDNB; Sigma Chemical, St. Louis, MO) as substrate for total activity, 4-chloro-7-nitrobenzofurazan (NBD-Cl) for GST Al, ethacrynic acid (EA) for GST Pi, and 1,2-dichloro-4-nitrobenzene (DCNB) for GST Mu. Enzyme activity was expressed as nanomoles of substrate–GSH conjugate produced per minute per milligram of cytosolic protein. The change in absorbance of total GST, GST Al, GST Pi and GST Mu was obtained at 340, 419, 270, and 345 nm, respectively, and the enzyme activity was calculated as nmol of CDNB, NBD-Cl, EA, and DCNB conjugate formed min−1 mg−1 protein using a molar extinction coefficient of 9.6 × 103 M−1 cm−1, respectively. Protein concentration was determined with a standard commercial kit (Bio-Rad Lab. Ltd., Watford, England) with bovine serum albumin as a standard.

2.8. Immunohistochemistry

Liver sections were deparaffinized in xylene, rehydrated in graded alcohol series, and blocked for the endogenous peroxidase by incubating in a solution of 3% hydrogen peroxide (H2O2) in methanol for 10 min. Tissue sections were washed with PBS, and then immunostained with primary antibodies for GST Al, GST Pi and GST Mu (1:300, Oxford Biomedical Research, USA). The antigen–antibody complex was visualized by a labeled streptavidin–biotin method using a Histostatin-PLUS Bulk Kit (Zymed Laboratories Inc., USA) followed by diaminobenzidine (DAB) as a chromogen. After washing, sections were counterstained with Meyer’s hematoxylin and washed with tap water.

2.9. Determination of superoxide and hydroxyl free radical in blood samples

For the measurement of superoxide and hydroxyl radical in whole-blood, blood samples from the carotid artery were obtained immediately after sacrifice using heparin as anti-coagulator, wrapped with aluminum foil and kept on ice until Chemiluminescence measure-
ment within 2 h [18]. Right before Chemiluminescence measurement, 0.1 mL of phosphate-buffered saline (pH 7.4) was added to 0.2 mL of blood sample. Chemiluminescence was measured in the dark chamber of a Chemiluminescence Analyzing System. After a 100 s background level determination, 1.0 mL of and 0.1 mM lucigenin and lucigenin in phosphate-buffered saline (pH 7.4) were injected into the sample, respectively. The chemiluminescence was monitored continuously for additional 600 s. The total amount of chemiluminescence was calculated by integrating the area under the curve and subtracting the background level from it. The assay was performed in duplicate for each sample and expressed as chemiluminescence counts/10 s. The mean ± S.E. of chemiluminescence level of each sample was calculated.

2.10. Statistical analysis

The experimental results were expressed as mean ± S.D. Statistical significance was analyzed by one-way analysis of variance (ANOVA). Duncan’s multiple tests were used to determine the difference among groups. Student’s t-test was used in the two-group comparison. A p-value <0.05 were considered statistically significant (Sigma-Stat 2.0, Jandel Scientific, San Rafael, CA).

3. Results

3.1. Effect of SNE on the body and organ weight of rats

In the present design of animal experiment as described in Section 2, the body weights, and relative liver and spleen weights of the CCl4-treated rats were significantly higher than those of control group (**P < 0.05, **P < 0.01, Table 1). The supplement of silymarin or SNE (0.5 and 1 g kg⁻¹ of body weight) for 6 weeks reversed significantly the CCl4-induced body and organ weights.

3.2. Effect of SNE on CCl4-Induced liver morphological change and fibrosis in rats

The general liver morphological changes and fibrosis induced by CCl4 administration were evidenced by both qualitative and quantitative histopathological examination. As compared to normal rat liver, the tissue section in Fig. 1A, b showed that the CCl4-induced chronic liver injury revealed concave on the liver surface and lymphocytes infiltration in the central vein. The hepatic cells were found to be cloudy swelling, and necrosis, cytoplasmic vacuolization and fatty degeneration were observed in central zone and mid-zone. Masson trichrome stain clearly demonstrated that the CCl4-intoxicated liver become fibroic with fiber extension and collagen accumulation (Fig. 1B, b). These pathological changes (such as fibrosis and inflammation) were ameliorated by the co-treatment of silymarin and SNE that, especially, showed a dose-dependent effect (Fig. 1A and B). The severity of the liver morphological changes and fibrosis induced by CCl4 treatment were scored and summarized in Table 2. As shown, six out of eight CCl4-exposed rats had liver morphological change greater than grade 3+, and seven out of eight had liver fibrosis and necrosis greater than grade 2. SNE exposure greatly improved liver morphological changes, fibrosis and necrosis. The average severity scores of SNE-treated rats were markedly reduced in a dose-dependent manner.

Table 1: Body weight, relative liver and spleen weight of CCl4-treated rats with or without the gavage of extract of Solanum nigrum L. (SNE) for 6 weeks.

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight</th>
<th>Relative organ weighta (g 100 g⁻¹ of bw)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Liver</td>
</tr>
<tr>
<td>Control</td>
<td>314 ± 22</td>
<td>3.5 ± 0.2</td>
</tr>
<tr>
<td>CCl4 (20%)</td>
<td>221 ± 18##</td>
<td>5.1 ± 0.6##</td>
</tr>
<tr>
<td>Silymarin</td>
<td>0.2 g kg⁻¹ of bw + CCl4</td>
<td>270 ± 17*</td>
</tr>
<tr>
<td>SNE</td>
<td>0.2 g kg⁻¹ of bw + CCU</td>
<td>259 ± 19*</td>
</tr>
<tr>
<td></td>
<td>0.5 g kg⁻¹ of bw + CCl4</td>
<td>272 ± 24*</td>
</tr>
<tr>
<td></td>
<td>1.0 g kg⁻¹ of bw + CCl4</td>
<td>282 ± 26*</td>
</tr>
</tbody>
</table>

a Significantly different from the group treated with CCl4, *p < 0.05, **p < 0.01. #Significantly different from control group, *p < 0.05, ##p < 0.01.

a Valued are mean ± S.D., n = 8.
3.3. Effect of SNE on serum biochemical parameters of liver function

The serum levels of hepatic enzymes, such as GOT, GPT, ALP, and total bilirubin, used as biochemical markers for evaluation of early hepatic injury were significantly elevated in the CCL4-treated animals (Fig. 2). SNE administration at the dose of 0.2, 0.5 or 1.0 g kg\(^{-1}\) body weight during CCL4 treatment significantly lowered, in a dose-dependent manner, the serum GOT, GPT, ALP, and total bilirubin activities as compared with those of CCL4 treatment group. The supplement of silymarin (0.2 g kg\(^{-1}\) body weight) showed a similar effect as that of high dose SNE.

3.4. Effect of SNE on GSH content and SOD level

GSH constitutes the first line of defense against free radicals. The toxicity of CCL4 significantly decreased the hepatic GSH levels (\(\mu\)mol mg\(^{-1}\) protein) from 3.3 ± 0.46 in the control group to 2.3 ± 0.37 (Fig. 3). An addition of silymarin and SNE at doses of 0.5 and
Table 2: The effect of SNE on histopathological evidence of CC14-induced liver fibrosis in rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Severity score of fatty metamorphosis (incidence)</th>
<th>Severity score of hepatic fibrosis (incidence)</th>
<th>Severity score of necrosis (incidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Control</td>
<td>80</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CC14 (20%)</td>
<td>80</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Silymarin 0.2 g kg⁻¹ of bw + CC14</td>
<td>80</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>SNE 1.0 g kg⁻¹ of bw + CC14</td>
<td>80</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

*Significantly different from the group treated with CC14. *p < 0.05. **p < 0.01. #Significantly different from control group, ##p < 0.01.

a SNE and CC14 were given as described in Section 2.
b Data represent the number of rats rated with a given level of fatty metamorphosis, hepatic fibrosis or necrosis. See Section 2.
c The individual severity rates in rats were expressed as mean ± S.D. n = 8.

d 1.0 g kg⁻¹ body weight in diet reversed the GSH level. Especially both high dose of SNE (1.0 g kg⁻¹ body weight) and silymarin restored almost completely the GSH content to the normal level. The hepatic level of SOD was also significantly reduced in the CC14 group. Silymarin effectively, however only partially, lessened the influence of CC14. A significant dose dependent and partial reversal of the SOD level was observed by SNE at 0.5 and 1.0 g kg⁻¹ body weight.

3.5. Effect of SNE on hepatic GSTs activity

GSTs are a family of dimeric enzymes responsible for the metabolism of a broad range of xenobiotics and carcinogens. As shown in Fig. 3, CC14 caused a decrease in the activity of total GST, GST Al, and GST Mu to 48%, 58% and 57% of control level, along with a two-fold increase in GST Pi activity in liver tissue. SNE treatment at doses of 0.5 and 1.0 g kg⁻¹ body weight for 6 weeks diminished the CC14-caused reduction in hepatic total GST, GST Al and GST Mu enzyme activities and induction in GST Pi activity. Silymarin showed a similar effect as SNE.

3.6. Immunohistochemical examination of hepatic GST subunits

In order to confirm the effect of SNE on the hepatic GST system under CC14 toxicity, the protein levels of GST subunits were examined by immunohistochemistry. The results demonstrated that the expression of GST Al and GST Mu was repressed in the hepatocytes of CC14-induced liver chronic damage and, on the other hand, GST Pi was induced (Fig. 4). The supplement of SNE at high dose in diet reversed the expressions of GST subunits comparable to the control levels, that were increasing the levels of GST Al and GST Mu and reducing GST Pi, even though the animals were toxicated by CC14. These effects were also demonstrated by the co-treatment of silymarin.

3.7. Effect of SNE on serum free radicals

The serum levels of superoxide and hydroxyl radical were increased to 13-fold and 8-fold of those of control in the CC14-treated animals (Fig. 5). This inductions in free radicals caused by CC14 were diminished by oral addition of SNE dose-dependently. Silymarin was also able to reduce the CC14-induced free radicals with an effect comparable to high dose of SNE.
4. Discussion

Hepatic fibrosis represents the wound healing response of the liver to repeated liver injuries, and is associated with increased inflammatory cell infiltration and may involve the interplay of different inflammatory mediators, which is a common stage in most chronic liver disease. It is well known that constant fibrosis can lead to the development of hepatocellular carcinoma [19]. If treated properly in this stage, hepatic fibrosis can be reversed and its progression to irreversible cirrhosis that often leads to lethal complications and high mortality may be prevented. Interrupting or reversing hepatic fibrosis may well be a new approach to avoiding its progression to hepatocellular carcinoma [20]. However, the prevention for liver fibrosis is not yet well established.

In this study, we demonstrated that SN, a traditional Chinese medicine, had preventive effects on hepatic fibrosis induced by CCl4 exposure in rats. Our study possesses some unique features as compared to the other published literature including, the use of the water extract of whole plant, long-term (6 weeks) animal exposures, induction of liver fibrosis, and identification of the mechanisms of action of SN on detoxification and antioxidative ability, especially the effect on the activity and expression of GST subunits. CCl4 has been widely used for inducing experimental hepatic damage due to free radical formation during its metabolism by hepatic microsome, which, in turn, to causes lipid peroxidation of the cellular membrane leading to the necrosis of hepatocyte. Rats treated with CCl4 developed significant hepatic damage and oxidative stress as evidenced by substantial increases in the serum activities of GOT, GPT, ALP, and total bilirubin that are indicators of cellular leakage and loss of functional integrity of cell membrane in liver [21,22]. The reduction in the levels of these parameters toward the respective normal values by SNE at two doses (0.2 and 0.5 g kg⁻¹ body weight) is an indication of the stabilization of plasma membranes as well as repair of hepatic tissue damage caused by CCl4. This effect is in agreement with the commonly accepted view that serum levels of transaminases would return to normal after the healing of hepatic parenchyma and regeneration of hepatocytes. This indicates that the anti-lipid peroxidation and/or adaptive nature of the systems brought about by SNE acted against the damaging effects of free radicals produced by CCl4. During hepatic injury, superoxide and hydroxyl radical generate at the site of damage, and SOD is exhausted as a result of oxidative stress caused by CCl4 that further leads to accumulation of free radicals. The SOD activity was brought to increase and free radicals were decreased by the co-treatment of SNE in the CCl4-treated rats. These results evidently demonstrate the antioxidant
property of SNE against superoxide and hydroxyl free radical.

To avoid redox imbalance and oxidative damage, aerobic organisms possess an efficient biochemical defense system including enzymes, such as SOD and GSTs, and GSH, which, however, could not provide complete protection against the attack of ROS in conditions of severe oxidative stress [23,24]. Therefore, scientists have been trying to find bioactive substances possessing cytoprotective ability against cellular oxidative damage, as well as enhancing ability on antioxidant enzymes activities [25,26]. GSTs are a family of dimeric enzymes responsible for the metabolism of a broad range of xenobiotics and carcinogens [27]. Numerous studies showed that the regulation of different GST isoforms was associated with various pathological processes. For example, the up-regulation of GST Pi, which is absent from normal rat and human hepatocytes, is associated with carcinogenesis [28,29] and drug resistance of tumor tissue [30,31]. The absent expression of GST Mu and GST Theta, on the other hand, is related to cancer susceptibility in human studies [32,33]. Chemicals like chloroform and CCl₄ alter the hepatic GST activity [34]. In this study, CCl₄ treatment decreased the activity and expression of GST Al, and GST Mu and increased those of GST Pi, indicating that the hepatic GST system had been shifted to a direction that may lead to tumorigenesis during chronic liver damage. The GSH content and the expression of GST subunits were brought back to control levels by the use of SNE. Whether these effects of SNE are attributed to its direct action on GST system or its detoxification of CCl₄ remains to be elucidated. Anyhow, the ability of
Fig. 4. Effects of SNE on GSTs expression in rats with hepatic fibrosis. Immunohistochemistry (400×) of GST Al (A), Pi (B), and Mu (C) in rat liver of (a) control group, (b) CCl4 group, (c) CCl4 + 0.2 g silymarin kg⁻¹ bw group, (d) CCl4 + 0.2 g SNE kg⁻¹ bw group, (e) CCl4 + 0.5 g SNE kg⁻¹ bw group, and (f) CCl4 + 1.0 g SNE kg⁻¹ bw group.

SNE to sustain hepatic GSTs expression at normal physiological condition under the toxicity of CCl4 suggests that it is effective in protecting liver from chemical damage and preventing further progression of pathological condition.

In conclusion, our results demonstrate that SNE was able to reverse the pathological parameters, such as fibrotic histological feature and serum levels of GOT, GPT, ALP, and total bilirubin, of chronic liver damage induced by CCl4. This protecting ability of SNE was due to, at least partially, its modulation on detoxification enzymes (GSTs) and antioxidative enzyme (SOD) that, in turn, repressed the production of free radicals and the subsequent liver damage. Furthermore, the high content of polyphenols, alkaloids and saponins in SNE [11] contributes free radical scavenging and antioxidation activities. Although it seems difficult to entirely recuperate the chronic hepatic damage-induced by CCl4 through the supplement of phytochemicals, SNE indeed retarded the liver injury by blocking the oxidative stress. Therefore, dietary SNE may be useful as a hepatoprotective agent against chemical-induced chronic liver fibrosis in vivo.

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References


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