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ORIGINAL ARTICLE

Green biosynthesis of Pt-nanoparticles from Anbara fruits: Toxic and protective effects on CCl_4 induced hepatotoxicity in Wister rats

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KEYWORDS

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Liver enzymes

Abstract Platinum Nanoparticles (PtNPs) are synthesized from the Anbara fruit (*Phoenix dactylifera* L.) and are characterized using various spectroscopic analytical methods. These PtNPs were used to study the Hepatotoxic and Hepatoprotective effects on acute liver damage caused by CCl_4 in Wister rats. Seventy-two rats of both sexes are divided into twelve groups and are treated with PtNPs and aqueous Anbara extract (AAE). Histopathological examinations were performed to identify the toxic effects on the vital organs of the rats. Hepatoprotective activity was monitored by observing the serobiochemical and hematological parameters and the intensity of hepatic marker enzymes alanine transferase (ALT), aspartate amino transferase (AST) and alkaline phosphatase (ALP) in the organs such as liver, intestine and kidney. Considerable experimental results were obtained when compared with the standard drug Silymarine. The PtNPs and AAE were proven to have protective activity of enzymes in the liver of Wister rats.

1. Introduction

Nano-chemistry is attributed as a rapidly growing family of research in the empire of chemistry in these days (Al-Radadi, 2018; Barua and Mitragotri, 2014; Cai et al., 2010; Ferreira et al., 2017; Mahdavi et al., 2013; Reddy, 2017; Sathishkumar et al., 2013; Thakkar et al., 2010). Noble metals such as Au, Pt and Ag contained nanoparticles explored interesting applications in the areas of biomedical devices and in biosensors (Al-Radadi and Al-youbi, 2018a; Aswathy Aromal and Philip, 2012; Deokar and Ingale, 2016; Kumar et al., 2011; Mukherjee et al., 2017; Rajan et al., 2017; Rao et al., 2000; Sanchez-Mendieta and Rafael, 2012; Shah et al., 2015; Shipway et al., 2000; Smitha et al., 2009; Vinod et al., 2011; Yu et al., 2016). These metal nanoparticles are gaining popularity as they are widely used in the manufacturing of cosmetics, soaps, detergents, shoes, toothpastes and shampoos (Al-Radadi and Al-youbi, 2018; Bankar et al., 2010; Bavykin et al., 2006; Meena and Chouhan, 2015; Prokop and Davidson, 2008; Vedelago et al., 2018). In addition, these

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metal based NPs are used for drug synthesis and as drug delivery systems. In particular, Platinum nanoparticles (PtNPs) in recent years have gained attention for their thriving applications in the treatment of coronary artery disease, brain aneurysms (Chanda et al., 2011; Da Rocha et al., 2014; Dreaden et al., 2011; Lin et al., 2012; Mirza and Siddiqui, 2014; Muniyappan and Nagarajan, 2014; Ramalingam et al., 2016; Yew et al., 2020; Yoon et al., 2016) and in chemotherapy due to their size and shape dependent therapeutic properties, volume to large surface area ratio, and electrocatalytic properties. PtNPs are also finding significant role in energy related industrial fields such as fuel cells, hydrogen storage and electro catalysis (Bendale et al., 2017; Miklášová et al., 2012; Pansare et al., 2016; Vrana et al., 2016). PtNPs are also combined with other metal nanoparticles in the form of bimetallic nanoclusters (Ganaie et al., 2016; Majzik, 2008; Sahu et al., 2015; Zhan et al., 2011), core-shell (Chaudhuri and Paria, 2012; Wang et al., 2013), or as alloys (Malathi et al., 2014; Rashid et al., 2018; Valodkar et al., 2011; Xu et al., 2012) and are extensively used in biomedical applications. Biomimetic synthetic approaches accompanied with plant extracts, live plants, and microorganisms (El-Sherbiny et al., 2016; El Khoury et al., 2015; Ibrahim, 2015; Mavukkandy et al., 2016; Puišo et al., 2014; Rivera-Rangel et al., 2018; Sathishkumar et al., 2009) are considered as a probable non-toxic and eco-friendly techniques which are alternatives to the conventional chemical and physical methods (Abdel-misih and Bloomston, 2010; Cruz-López et al., 2015; David et al., 2014; Dubey et al., 2010; Dzimitrowicz et al., 2016; Ghorbanpour, 2015; Ghoreishi et al., 2011; Karthik et al., 2016; Kumar et al., 2013; Molnár et al., 2018; Muthu and Priya, 2017; Philip, 2009; Wang et al., 2015; Yadav et al., 2017).

Liver is one of the vital organs which regulate the homeostasis inside the body. It works with almost all biochemical pathways associated with nutrient supply, energy stipulation, growth, fight against diseases and reproduction. This detox organ also protects us from harmful chemicals including drugs (Althnaian et al., 2013; Diniz-santos et al., 2004). In recent years, increased deaths are observed due to morbidity and co-morbidities of liver problems including hepatitis and Jaundice. Inadequate pharmacotherapeutic agents to cure the liver diseases scares and increase the demand to propel the requirement of novel and effective drugs for the medication of hepatic disorders (Adam et al., 2011; Czaja, 2014).

Carbon tetrachloride (CCl_4) is generally used for liver injury in the research experiments. It decreases antioxidant enzymes activities and generate free radicals leads that to hepatocyte damage in both *invitro* and *invivo* conditions (Johnston and Kroening, 1998). CCl_4 causes damage associated with free radical and oxidative stress mediate dliver tissue damage was determined in humans and rats (Mohammadinejad et al., 2016). It creates critical effects on membranes by raising the levels of plasma aminotransferases of the hepatocyte, causing leakage of the enzyme present in the cell. It directs the decomposition of fat in the liver due to obstacle of secretion of hepatic triglycerides into plasma. CCl_4 toxicity intricate the splitting of C—Cl bond forms (CCl_3O_2) free radical which occurs in endoplasmic reticulum and mediated by cytochrome *p*-450 oxidase system. The free radicals are then bound to lipids and hepatic proteins (Das and Brar, 2013).

Green synthetic approach of metal nanoparticles is an intriguing research area showed increased consideration due to its simplicity. It has several advantages over traditional techniques such as it is non-toxic, clean, environmental friendly, cost effective, simple and high productivity. They can be synthesized from extracts of plant materials by several chemical, physical and biological methods and obtained functioning in the prevention of chronic diseases such as cancer due to their unique interactions at the molecular & cellular levels (Abdul Salam et al., 2012; Alshatwi et al., 2015; Banerjee et al., 2014; Jee et al., 2012; Mishra et al., 2014; Nair, 2013; Taylor et al., 2012).

Date palm fruits have commercial importance in countries like Saudi Arabia, Oman, Emirates, Bahrain, Iraq, North Africa and South Africa (Al-farsi et al., 2007; Al-orf et al., 2012; Aron and Hahidi, 2005; Vayalil, 2012). In most of the Arabian countries, dates are fundamental components of diet and clipped food which are assumed to be a good resource of energy. Fruits of date palm composed of proteins (0.2–0.5%), minerals (2.3–5.6%), dietary fiber (6.4–11.5%) in addition to high percentage of carbohydrates (44.8%) and vitamins. These fruits have rich contents made up of antioxidants, amino acids, sugars, macro minerals, trace elements and several fatty acids like linolenic, oleic and palmitoleic acids (Abdul Salam et al., 2012; Alshatwi et al., 2015; Jee et al., 2012; Khan et al., 2016; Kumar and Yadav, 2009; Nair, 2013).

There are several reports on anticancer, antiviral and liver protective activities of dates (Al-qarawi et al., 2004; Al-Radadi, 2019; Al-yahya et al., 2016; El-far, 2014; Nadaroglu et al., 2017; Saafi et al., 2011). The aqueous extract of date fruit was used *invivo* for hepatoprotective properties and induced hepatic injury in mice, besides some information indicate that this fruit could be helpful to prevent the oxidative stress induced hepatotoxicity (Martins et al., 2012). Liver damage caused by CCl_4 were reorganized by the treatment of dates flesh or pits extractin rats and rabbits (Dobrucka, 2015; Nadaroglu et al., 2017; Yew et al., 2020). The extract of date palm Ajwa from almadine-almonawara shows strong hepatoprotective activity against ochratoxin (Al-Radadi, 2019). The effect of particle size of Pt-Anbara NPs and aqueous Anbara extract (AAE) on the hepatic and kidney tissues of rats, identification of potential threats of diagnostic and therapeutic use and hepato-toxicity with the time of exposure is studied in the present work.

2. Experimental

2.1. Materials

The UV–visible absorption spectra were recorded on Agilent, Cary 100 UV–VIS spectrophotometer, IR spectra was performed using Thermo Nicolet 6700 FTIR Spectrometer, powder X-Ray diffraction was recorded with a Shimadzu XRD-6000 with Cu Kα radiation (λ = 1.54056 Å). The size and surface morphology of NPs were identified with Energy dispersive X-ray (EDX) with modelNOVA-450 instrument and Transmission electron microscope (TEM).

2.2. Animals

Seventy-two clinically healthy Wister rats with standard husbandry conditions such as temperature, diet and drinking

water having 3 months of age of two sexes with an average body weight of 120–152 g, were housed in the animal house of collage of Science and Technology, Al Neelain University, Khartoum, Sudan. Animals were prepared to the experimental conditions for a period of two weeks prior to the initiation of the experiments. Animal experiments were designed and conducted according to the guidelines of institutional animal ethical committee.

2.3. Synthesis of Pt nanoparticles (Pt NPs)

Anbara (*Phoenix dactylifera*) date fruits were obtained from a local farm in Madinah Monawara, Saudi Arabia. The fruits were washed with distilled water to remove the impurities, dried at 60 °C and preserved under vacuum. An Anbara stock solution was prepared where Anbara was mixed with 4 ml of 10^{-3} M H_2PtCl_6 solution and make up to 10 ml with deionized water. The reduction of Pt^{+4} to Pt^0 NPs was confirmed when the solution color changed to yellow to yellowish-brown. The pH of the solution was adjusted by the addition of 0.1 M NaOH or 0.1 M HCl. The solid black colored Pt NPs were obtained when the mixture was boiled for about 7 h. The solvent was reduced to 1/4th of its original volume, centrifuged and washed several times with water and ethanol to get the pure product.

2.4. Preparation of the aqueous Anbara extract (AAE)

Anbara stock solution was prepared by taking 9 g. of Anbara and was boiled in 200 ml water for 15 min. and was reduced to a volume of 100 ml. The solution obtained was filtered, kept in dark at 100 °C and the filtrate was used as a reducing agent and utilized with 24 h.

2.5. Preparation of AAE concentrations

The Anbara dissolved in distilled water at a dose of 0.78 g/kg/day (low dose), equivalent to 7 units Anbara dates ~47.25 g/200 ml water/60 kg/body weight per person per day (according to the words of our prophet mohammed (peace be upon him) who eats seven Anbara dates in a day which is equal to 1.56 g/kg/body weight (high dose).

2.6. Preparation of Pt NPs dose concentration

The Pt NPs prepared every day at 5 μg (low dose), and 10 μg (high dose) dissolved in phosphate buffer saline (PBS).

2.7. Experimental design

2.7.1. Toxicity assessment

Thirty male adult Wistar rats were divided randomly to 6 rats each in 5 groups. Group-1served as control allowed for feed the normal diet. Groups 2 and 3 were given AAE at 0.78 g/kg/ day and 1.56 g/kg/day orally. To the groups 4 and 5 rats, PtNPs were given at 5 μg/g/day and 10 μg/g/day orally by cathedral tube, respectively. The dosage of all rats was given for 7 days according to their designated experimental oral doses. Body weights of rats were measured on day 0 and the 7th day of the treatment. Tissue samples for histopathology were taken at the end of the experiment after scarifying animals under mild chloroform anesthesia.

2.8. Evaluation of hepatoprotective activity

After two weeks of acclimation, forty-two Wistar rats of both sexes were divided into seven groups contain 6 rats in each group. Group 1 represents control in which the rats were fed with normal diet and distilled water for 21 days. Group 2 represents induction control received 3 ml/kg CCl_4 subcutaneously and diluted on 7th day in 1:3 with olive oil. Group 3 received 70 mg/kg/day Silymarin for 15 days and CCl_4 injected on 7th day. Groups 5 received 10 μg/g/day of Pt NPs orally for 7 days and CCl_4 injected on 7th day. Group 6 received 0.78 g/kg (lower dose) of AAE orally for 7 days and CCl_4injected on 7th day. Group 7 received 1.56 g/kg (higher dose) of AAE orally for 21 days and CCl_4injected on 7th day. Clinical signs were recorded throughout the experimental period where body weights were weekly reported for each group. Animals were killed on 21st day under mild chloroform anesthesia whereas blood samples for serum and hematological analysis were collected immediately. To identify the gross lesion, all rats were examined at necropsy and the small intestine, liver and kidney specimens were quickly recovered after autopsy and fixed in 10% formalin for histopathological study.

2.9. Hematological analysis

Ethylene diamine tetra acetic acid (EDTA) contained dry test tubes were taken and collected the blood samples of rats to determine the red blood cells (RBC) count, differential white blood cell (WBC) count, packed cell volume (PCV), mean corpuscular volume (MCV), hemoglobin concentration (Hb), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). Automated heamatology analyzer was used to perform the measuring techniques.

2.10. Serobiochemical analysis

Blood samples were collected in a plain container and allowed to clot. Serum was separated after centrifugation and stored at −20 °C. This serum was used to analyze the serum activities on alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and for total protein concentration, urea, albumin, globulin, bilirubin, and creatinine.

2.11. Histological examination

To identify the gross lesion all rats were examined and Necropsy was conducted. Kidney, small intestine and liver specimens were collected, fixed in 10% formalin immediately, covered with paraffin wax, sectioned at 5 μm thickness and stained with eosin and haematoxylin (H&E) using Harris's haemalum.

2.12. Statistical analysis

Statistical Package for Social Science (SPSS) used for the data analysis. For the T-test classified data Duncan's multiple range tests were performed to compare the difference between means

at each point after ANOVA. The obtained results were presented as mean ± Standard error (M ± S.E). $P < 0.05$ was considered as the statistically significant difference.

3. Results and discussion

The characterization of synthesized Pt NPs under different conditions were analyzed using UV–visible absorption spectra, Transmission Electron Microscope (TEM) analysis, Fourier Transform Infra Red (FTIR), Powder XRD and Energy Dispersive X-ray spectroscopy (EDX).

3.1. UV–Visible absorption and Transmission electron microscope (TEM) analysis

The formation of Pt NPs was monitored using UV–visible absorption spectra. The UV–visible absorption spectra were taken for in three batches. For the first batch the UV–visible absorption spectra were measured for the mixture of a constant 4 ml of 10^{-3} MH_2PtCl_6 solution and different volumes of aqueous Anbara extract. The UV–Visible spectra showed a prominent peak at a wavelength (λ_{max}) of 380 nm. There is a gradual increase in the absorbance intensity upon increasing the Anbara extract volume from 1 ml to 6 ml, with a slight red shift in the peak position in the UV–visible spectra was observed (Fig. 1).

The peak at 380 nm is an indication for the formation of Pt^0 species which is the ideal surface plasmon resonance (SPR) of Pt NP (Huang et al., 2004; Link and El-Sayed, 2005; Rajathi and Nambaru, 2014; Riddin et al., 2010; Song et al., 2010; Soundarrajan et al., 2012). Whereas the red shift in the peak position indicates the completion of reaction and no more Pt^0-will be formed. Furthermore, the TEM images of synthesized Pt NPs were taken for the mixtures of 4 ml 10^{-3} MH_2PtCl_6 with 4,5 and 6 ml solutions of Anbara extract. The images showed the presence of homogeneous, quasi- spherical and smaller size with an average size range of 2.3–3.0 nm nanoparticles (Fig. 2).

For the second batch the UV–visible absorption spectra were measured for the mixture of a constant 6 ml of Anbara extract and different volumes (0.5–4 ml) of H_2PtCl_6 solution. A prominent peak at λ_{max} = 380 nm was obtained. Red shift in the peak position was observed with increase in the concentration of H_2PtCl_6 solution from (0.5 ml) to (4 ml) (Fig. 3). TEM images of the synthesized Pt NPs were taken for the mixtures of 6 ml Anbara extract and 2, 3 and 4 ml H_2PtCl_6 solutions. The images showed the presence of smaller size homogeneous quasi- spherical nanoparticles with an average size range of 2.3–3.0 nm (Fig. 4). From the TEM images it was observed that the NPs size decreased with the addition of the volume of H_2PtCl_6 solution from 0.5–4 ml to 6 ml Anbara extract.

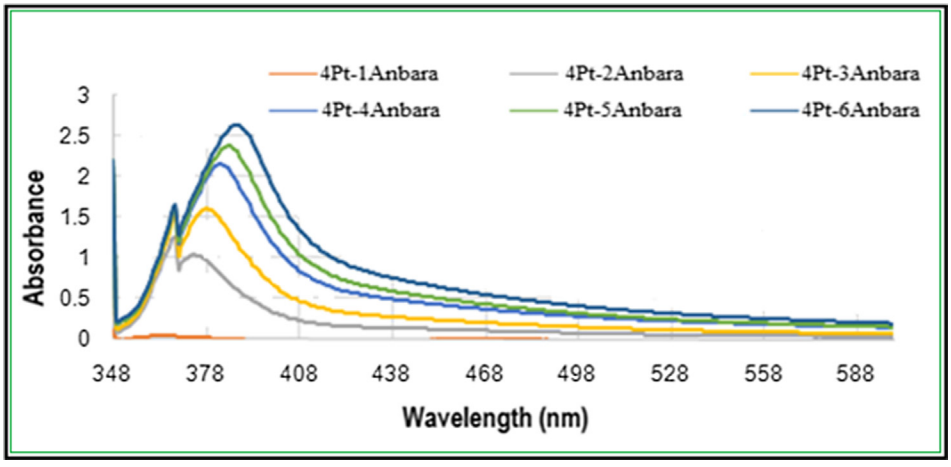


Fig. 1 UV–visible absorption spectra of Pt NPs synthesized with different concentrations of Anbara extract and 4 ml H_2PtCl_6 stock solutions after 7 h of addition at 25 °C.

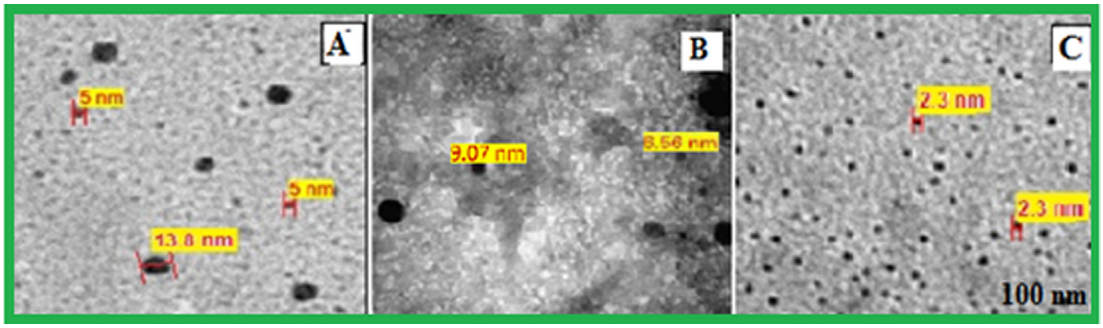


Fig. 2 TEM micrograph of Pt NPs prepared with different mixtures of 4 ml of H_2PtCl_6 and Anbara extract (A) 4 ml (B) 5 ml and (C) 6 ml, after 7 h of addition at 25 °C.

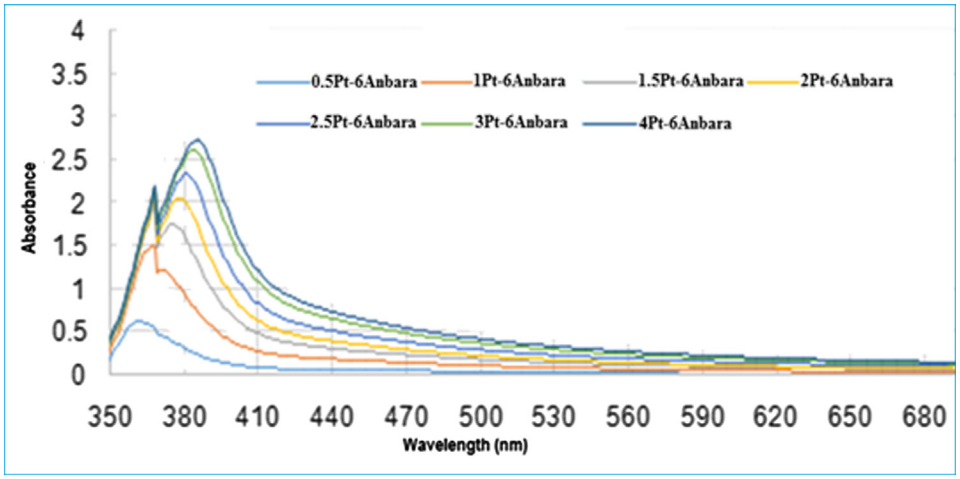


Fig. 3 UV–visible absorption spectra of Pt NPs prepared with different volumes of 10^{-3} M H_2PtCl_6 stock solutions with 6 ml Anbara extract after 7 h of addition at 25 °C.

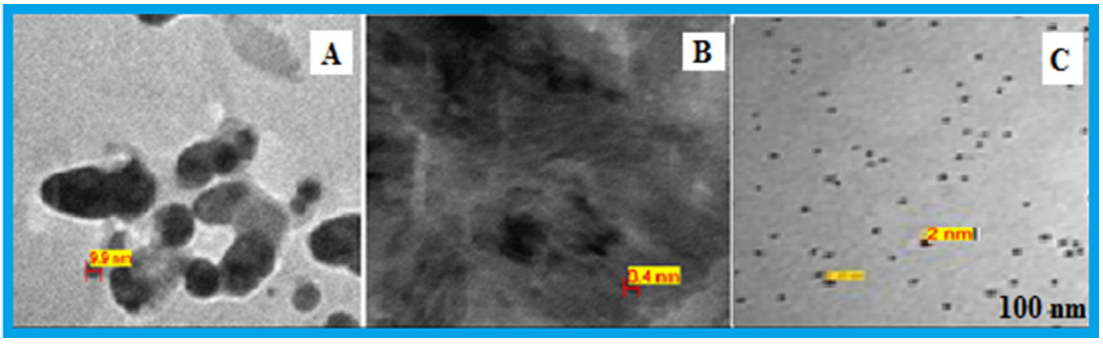


Fig. 4 TEM micrograph of Pt NPs formed with different mixtures of 6 ml Anbara extract and 10^{-3} M H_2PtCl_6 stock solutions (A) 2 ml (B) 3 ml and (C) 4 ml, after 7 h of addition at 25 °C.

The third batch UV–visible absorption spectra were measured for the Pt NPs synthesized with 4 ml of 10^{-3} MH_2PtCl_6 and 6 ml Anbara extracts a function of time at room temperature. Two peaks were obtained at 310 nm and 380 nm up to 1 h. The intensity of the peak at 310 nm increased and the 380 nm peak intensity was decreased initially for 30 min. Further increasing the time the peak at 310 nm decreased, and then vanished, but the peak intensity at 380 nm increased and stabilized at 7 h and no subsequent increase in intensity occurred up to48 hours (Fig. 5). The peak at 310 nm is corresponding to Pt^{4+} species which increased up to 30 min. and converted to 380 nm peak which corresponding to the formation of Pt^0 NPs. The absorbance to time spectrum showed the variation in the absorbance and the time required for maximum stability of Pt^0 NPs (Fig. 6).

These results suggests that the highest concentration of Pt^0 NPs were achieved within first 420 min (7 h) and then stabilized. It optimized the reaction time for the synthesis of Pt^0 NPs with 4 ml of 10^{-3}M H_2PtCl_6 and 6 ml Anbara extract. The color of the solution turns darker with increasing the reaction time. The TEM images of Pt NPs reactions at 4, 7 and 11 h were taken for the third batch compound mixture. The most adequate time at 7 h (Fig. 7) offers the optimum reaction time to obtain Pt NPs which is in good agreement with the TEM images of the proposed reactions conditions. More over the TEM analysis showed that the desired Pt NPs formed acquired nearly spherical shape contained the particle size of 2.3–3.0 nm.

3.2. Ftir

FTIR was recorded to identify the presence of functional groups in AAE and PtNPs. Similar pattern of IR bands at 3550–3150, 1732, 1626, 1347, 1226 and 1042 cm^{-1} were obtained in both spectra (Thirumurugan et al., 2016; Venu et al., 2011). A broad band at 3550–3150 cm^{-1} was obtained in Pt NPs which was obtained at 3400 cm^{-1} in AAE. There is a slight variation in the position and intensity of the peaks observed due to the complexation of Anbara with Pt to obtain the Pt NPs (Fig. 8).

3.3. Powder XRD analysis

The Powder pattern of the synthesized Pt NPs was recorded to determine the crystalline nature and the phase purity of the Pt NPs (Onizawa et al., 2009; Yoshida et al., 2008) (Fig. 9).

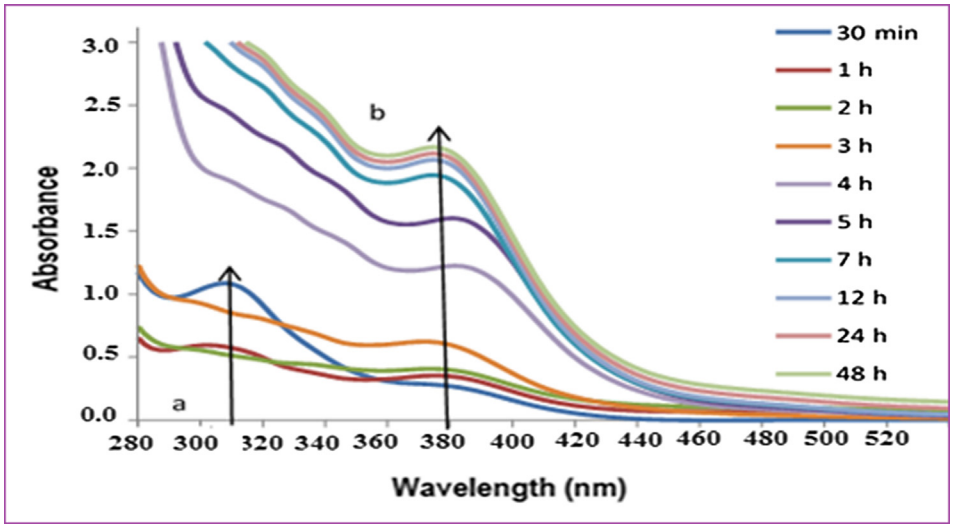


Fig. 5 UV–visible absorption spectra of Pt NPs obtained with 4 ml H_2PtCl_6 solution and 6 ml of Anbara extract as a function of time at 25 °C.

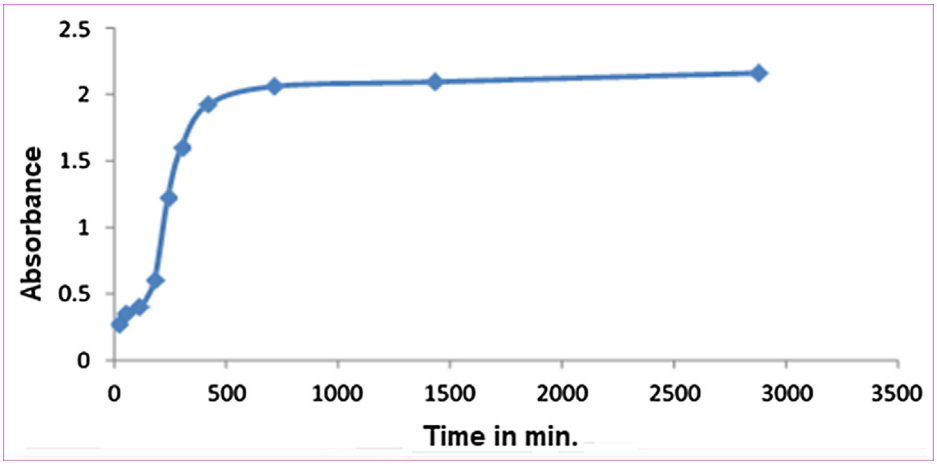


Fig. 6 Absorption intensity variation in the UV–visible absorption of Pt NPs obtained with 4 ml H_2PtCl_6 and 6 ml of Anbara extract as a function of time at 25 °C.

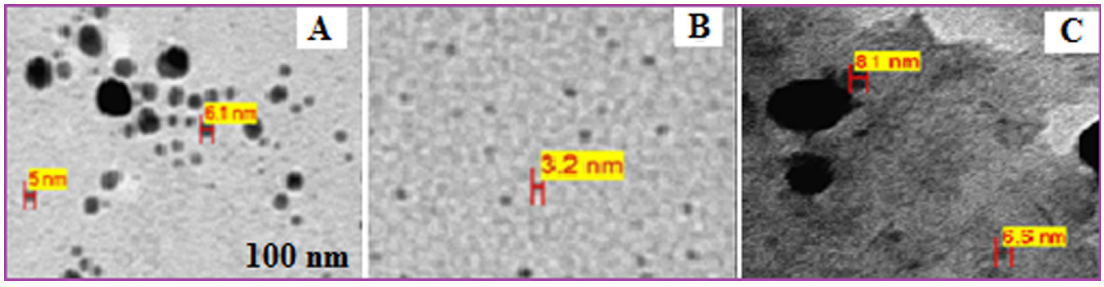


Fig. 7 TEM micrograph of Pt NPs (4 ml of H_2PtCl_6 solution and 6 ml of Anbara extract) at different time (A) 4 h (B) 7 h (C) 11 h at 25 °C.

3.4. Energy dispersive X-ray spectroscopy (EDX)

The EDX spectrum results of the synthesized Pt NPs showed a strong Pt signal that confirmed the presence and purity of Pt metal in the PtNPs. Whereas the presence of other elements were also identified (Gholami-Shabani et al., 2016) (Fig. 10).

3.5. Toxicity assessment

3.5.1. Growth changes

Oral doses of Pt NPs and AAE were given to 5 groups contain 6 rats in each group, and the change in body weight was observed after 7 days (Table 1). Body weight of all groups were

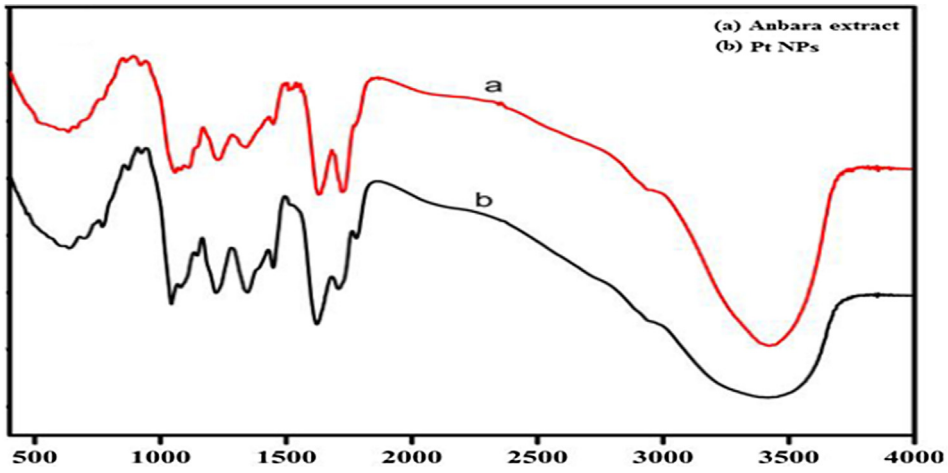


Fig. 8 FTIR spectra of AAE and Pt NPs.

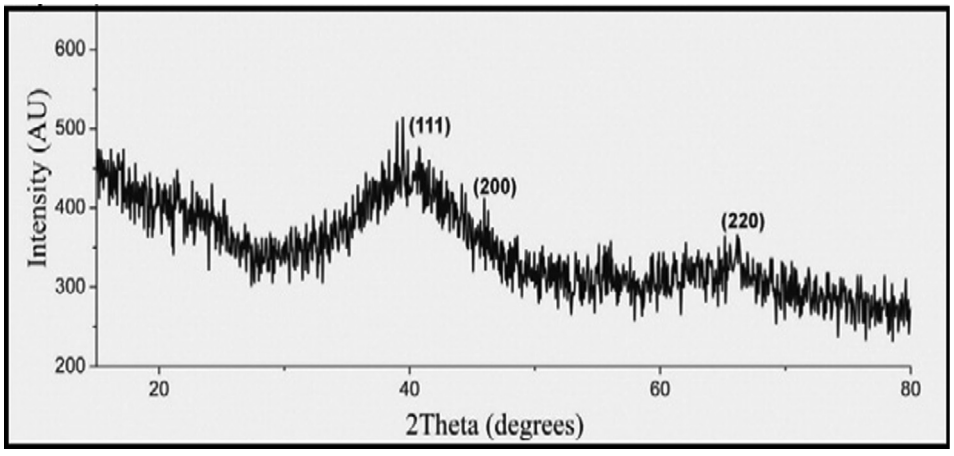


Fig. 9 Powder XRD of synthesized Pt NPs.

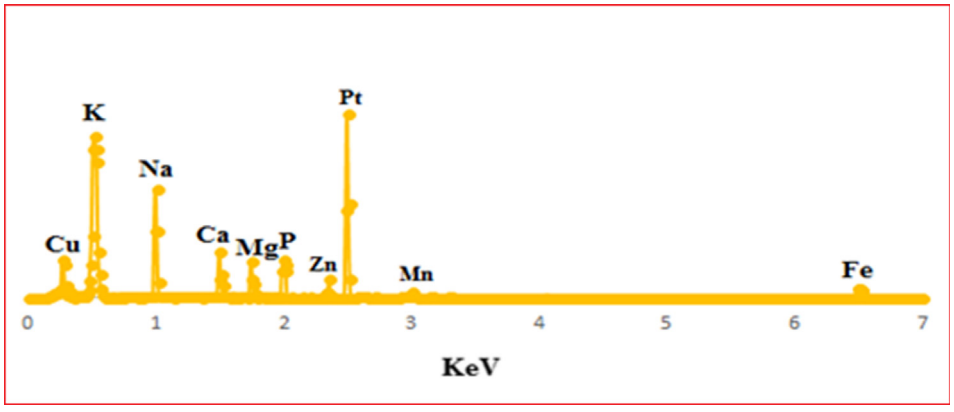


Fig. 10 The elemental composition analysis of Pt NPs using EDX spectroscopy.

decreased and group 3 showed significant decreased body weight ($P < 0.05$) when compared with control (Group 1). All rats were alive even after completion of the experiments.

3.6. Histopathological changes

Oral doses of Pt NPs and Anbara aqueous extract at different concentrations were given to 5 groups contain 6 rats in each

Table 1 Change in body weight of rats when the Pt NPs and aqueous Anbara extract given orally for 7 days.

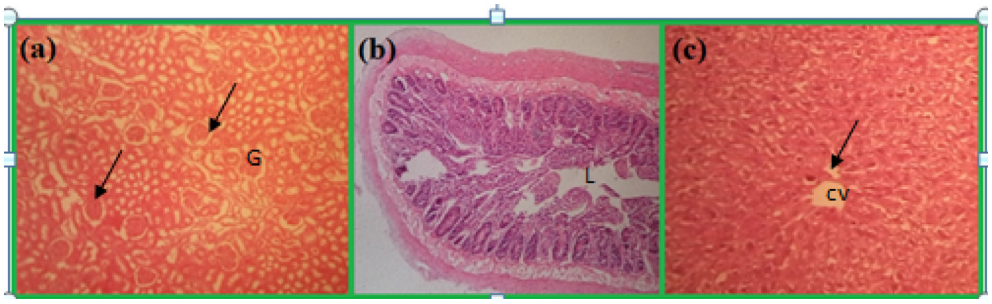
S.No.	Treatment groups	Experimental period	
		Body weight (g) 0 day	Body weight gain (g) After 7th days
1.	Control (normal diet)	122.0 ± 4.7	21.3 ± 6.3
2.	Anbara (0.78 g/kg/day)	124.3 ± 4.9	11.0 ± 5.9
3.	Anbara (1.56 g/kg/day)	123.5 ± 5.7	27.1 ± 4.8
4.	Pt NPs (5 μg/g/day)	122.7 ± 6.3	17.3 ± 6.4
5.	Pt NPs (10 μg/g/day)	123.5 ± 8.7	12.5 ± 7.7

group as in Table 1. After one week of the treatment, there were no lesions or alterations appeared on all the treated groups and other vital organs of control rats (group 1). The microscopic analysis showed no change in the sectioned small intestine, kidney and liver organs (Fig. 11).

3.7. Hepatoprotective activity

3.7.1. Clinical findings and growth changes

Details of oral doses of Pt NPs and AAE at various concentrations were given to 7 groups contain 6 rats in each group as in Table 2. CCl_4 induced in ratson 7th day and the treatment continued for 21 days. Depression, huddling together, reluctance to move, locomotors disturbances, erection of hair, weakness in limbs and emaciation are prominent manifestations which appeared on 7, 8 and 9 days after CCl_4 induction. These symptoms were moderate in groups 4 and 6, where severe in group 2. Ingroups 6 and 7 rats which received5 and 10 μg/g/day of Pt NPs and group 5 rats which received 1.56 g/kg of AAE. Mild symptoms aroused and no deaths occurred except in group 2. The kidney and liver postmortem report of the groups 2–7 explained moderate to severe fatty change, congestion and/or necrosis. The groups 2, 4 and 6 rats showed severe necrosis of kidneys and liver whereas group 1 had no clinical signs.



G= glomerular tufts, **L**= lamina propria, **CV** = central vein

Fig. 11 Microscopic images of tissues of rats taken after oral doses of PtNPs at 5 and 10 μg/g/day for one week: Glomerular in kidney (a) no changes observed in the intestine (b) and hepatocytes in liver.

Table 2 Details of oral dose concentration of Pt NPs and Anbara aqueous extract given to rats for 3 weeks and their clinical findings.

S. No.	Treatment groups	After 7 days		
		No. of rats/group	No of rats died	Mortality (%)
1	Control (normal diet)	6	0	0
2	Anbara (0.78 g/kg/day)	6	0	0
3	Anbara (1.56 g/kg/day)	6	0	0
4	PtNPs (5 μg/g/day)	6	0	0
5	PtNPs (10 μg/g/day)	6	0	0
		After 21 days + CCl_4 induction on 7th day		
1	Control (normal diet)	6	0	0
2	CCl_4 control	6	1	16.6
3	Silymarine control	6	0	0
4	Anbara (0.78 g/kg/day)	6	0	0
5	Anbara (1.56 g/kg/day)	6	0	0
6	PtNPs (5 μg/g/day)	6	0	0
7	PtNPs (10 μg/g/day)	6	0	0

The observed changes in the body weight of rats were presented in Table 3 where the groups 4, 5 and 7 showed increased body weight significantly ($P < 0.05$) and group 6 exhibits significant decrease in body weight when compared to group 1 (control).

3.8. Hematological analysis

The hematological data after 3 weeks of treatment with Pt NPs and AAE after CCl_4 induction on 7th day are presented in Table 4. Hematological changes of treated rats with low dose and high dose showed significant decrease in mean concentration of Hb and RBCs and the P-value ($P < 0.05$) was compared with untreated group. There was a significant increase mean concentration of WBCs and lymphocytes of low and high dose treated rats when compared with untreated group ($P < 0.05$). Except in group 5, other hematological parameters showed no significant change. The correlated concentrations of HB, RBC and WBC for all the groups after the treatment of rats with PtNPs and AAE for 3 weeks were shown in (Fig. 12).

3.9. Serobiochemical analysis

The results of Serobiochemical changes for the given pre and post-treated rats with Pt NPs, and AAE for 21 days with a dose of CCl_4 (3 ml/kg body weight) on day 7, are presented in Table 5. After 21 days of treatment, significant decrease in activity of AST and increase in ALP in treated groups than in CCl_4 control (group 2). ALT increase in group 4 and decrease in group 7 (Fig. 13). The concentrations of total protein and creatinine in group 6 and 7 were significantly decreased than in CCl_4 control. While the concentration of urea showed no significant change when compared with CCl_4 control (Fig. 14).

3.10. Histopathological changes

Microscopic examinations after 3 weeks of treatment with Pt NPs and AAE under CCl_4 induction on 7th day are summarized in Table 6 and presented in Figs. 11, 15–19. The results from various treatment groups revealed that the hepatocytes and the cells of the renal proximal convoluted tubules contained fatty vacuoles, showed hepatocellular degeneration, cytoplasmic vacuolar diffusion (Fig. 15), vacuolar degeneration of the glomerular tufts and necrosis of CCl4 (Fig. 16), and showed less damage of hepatocytes and low index of changes in treated groups including mild catarrhal enteritis with infiltration of lymphocytes in the lamina propria, fatty cytoplasmic vacuolation of hepatocytes and epithelial cells of the renal tubules with varying degrees of cellular infiltration in groups 4 and 6 (Fig. 17). These changes were less marked in groups 5 and 7 (Figs. 18 and 19). No significant lesions appeared in Control rats (Group1) and no death occurred among the rats recorded along with the treatment.

Table 3 Details of body weight changes in rats after 21 days of treatment with orally given Pt NPs and Anbara aqueous extract (CCl_4 induced on 7th day).

S.No.	Treatment groups	Body weight (g) 0 day	Body weight (g) 7 day	Body weight (g) 14 day	Body weight (g) 21 day	Body weight gain (g) After 21 days
1	Control (normal diet)	135.0 ± 6.1	143.0 ± 5.9	146.3 ± 5.2	154.3 ± 9.9	19.3 ± 5.1
2	CCl_4 control	133.0 ± 8.0	140.0 ± 6.9	144.7 ± 7.3	148.7 ± 13.4	15.7 ± 7.2*
3	Silymarine control	130.2 ± 3.0	141.0 ± 5.8	143.5 ± 5.7	147.53 ± 5.9	17.3 ± 2.8 ^{NS}
4	Anbara (0.78 g/kg/day)	134.0 ± 9.4	135.3 ± 8.8	140.7 ± 6.9	149.9 ± 9.8	15.9 ± 8.4 *
5	Anbara (1.56 g/kg/day)	134.7 ± 9.3	144.0 ± 9.3	152.3 ± 8.9	160.75 ± 10.0	26.0 ± 5.2*
6	PtNPs (5 μg/g/day)	130.0 ± 4.0	135.0 ± 5.0	139.5 ± 1.0	142.5 ± 0.0	12.5 ± 3.0*
7	PtNPs (10 μg/g/day)	135.3 ± 10.4	142.0 ± 6.9	145.7 ± 4.8	152.7 ± 4.8	17.4 ± 7.2 ^{NS}

NS = not significant. *Significant ($P < 0.05$).

Table 4 Heamatological analysis of rats which has given Pt NPs and AAE orally for 21 days and the CCl_4 induced on 7th day.

Parameters	Groups						
	1. Control (normal diet)	2. CCl_4 Control	3. Silymarin Control	4. Anbara (0.78 g/kg/day)	5. Anbara (1.56 g/kg/day)	6. PtNPs (5 μg/g/day) (low dose)	7. PtNPs (10 μg/g/day) (high dose)
Hb (g/dl)	15.3 ± 0.4	13.0 ± 2.6*	15.3 ± 1.4^{NS}	13.8 ± 0.3*	13.0 ± 0.6*	14.4 ± 0.6^{NS}	13.6 ± 0.1*
RBC ($\times 10^6$ mm^3)	8.6 ± 0.3	7.3 ± 1.4*	7.8 ± 1.4^{NS}	8.1 ± 0.2^{NS}	7.7 ± 0.7^{NS}	8.1 ± 0.4^{NS}	7.7 ± 0.1*
PCV (%)	48.0 ± 1.3	41.0 ± 3.1^{NS}	49.0 ± 1.6^{NS}	43.9 ± 1.1 ^{NS}	41.1 ± 4.5 ^{NS}	45.6 ± 1.8^{NS}	43.0 ± 0.5*
MCV (m^3)	55.6 ± 0.4	55.6 ± 1.0^{NS}	54.2 ± 0.2^{NS}	54.0 ± 0.9^{NS}	53.5 ± 1.3^{NS}	56.3 ± 0.4^{NS}	55.2 ± 0.9^{NS}
MCH (pg)	17.6 ± 0.3	17.4 ± 0.4 ^{NS}	17.2 ± 0.6^{NS}	16.9 ± 0.2^{NS}	16.8 ± 0.6^{NS}	17.7 ± 0.1^{NS}	17.4 ± 0.3 ^{NS}
MCHC (%)	31.8 ± 0.3	31.4 ± 0.4 ^{NS}	31.7 ± 1.0^{NS}	31.4 ± 0.1^{NS}	31.5 ± 0.4^{NS}	31.5 ± 0.2^{NS}	31.6 ± 0.1^{NS}
WBC ($\times 10^6$ mm^3)	11.5 ± 0.8	9.7 ± 2.3*	11.3 ± 1.8^{NS}	11.0 ± 1.1^{NS}	7.8 ± 0.4*	14.8 ± 3.3*	15.3 ± 2.8*
Lymphocytes (%)	53.9 ± 0.7	58.3 ± 0.5*	50.9 ± 0.6 ^{NS}	68.9 ± 2.0*	58.8 ± 3.4*	55.1 ± 4.5^{NS}	66.6 ± 0.3*
Granulocytes (%)	46.1 ± 0.7	41.7.7 ± 0.5*	49.1 ± 6.0^{NS}	32.1 ± 2.0*	41.2 ± 0.3^{NS}	44.9 ± 4.5^{NS}	33.4 ± 0.3 *

Values are expressed as mean ± S.E; NS = not significant; *Significant = ($P < 0.05$); n = 6 rats per group.

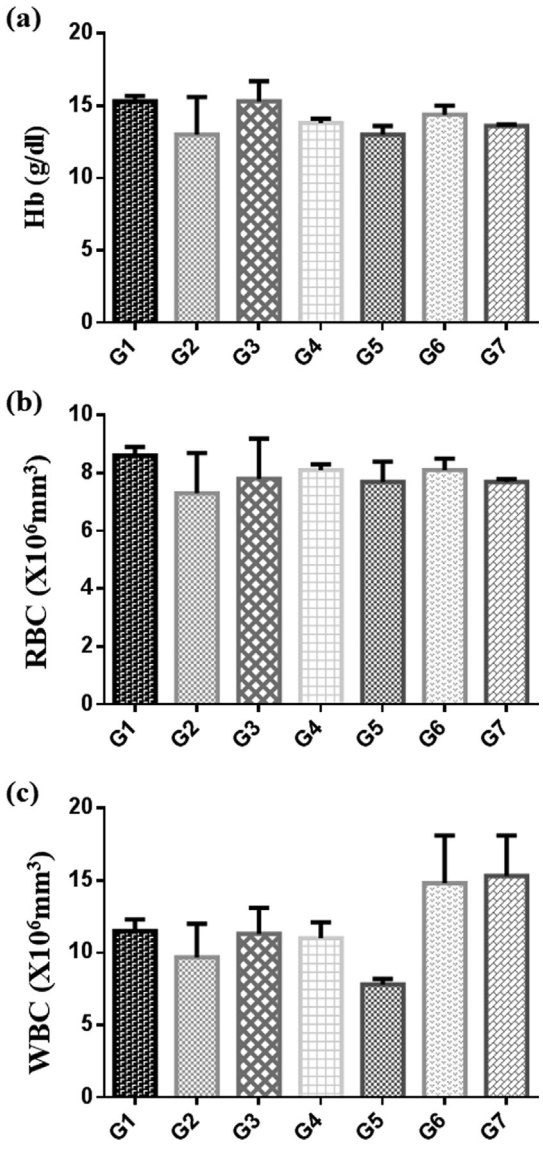


Fig. 12 Graphs of concentrations of HB (a), RBC (b) and WBC (c), after treatment of rats with Pt NPs and Anbara aqueous extract for 3 weeks as shown in Table 4. Groups expressed as mean ± SR.

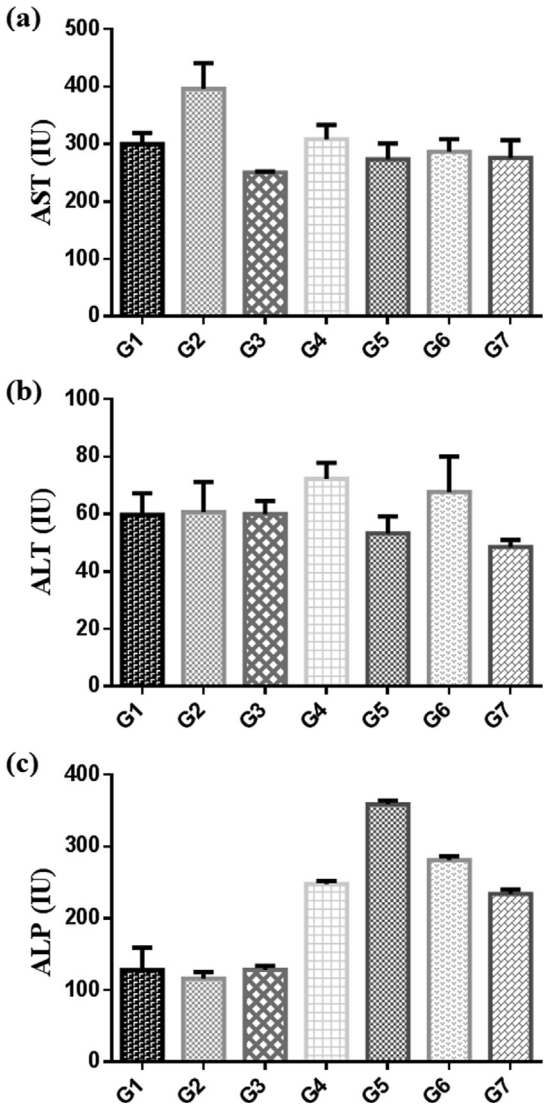


Fig. 13 Comparitive activity of enzymes (a) AST, (b) ALT and (c) ALP, after treatment for 3 weeks with Pt NPs and aqueous Anbara extract in control group (G1), CCl_4 (G2), Silymarin control (G3), low does Anbara 0.78 g/kg (G4), high dose Anbara 1.56 g /kg (G5), low does Pt NPs 5 μg/g (G6) and high dose Pt NPs 10 μg/g (G7).

Table 5 Blood biochemical parameters in rats after oral administration of Pt NPs and AAE for 21 days where CCl_4 induced on 7th day.

Parameters	Groups						
	1. Control (normal diet)	2. CCl_4 Control	3. Silymarin Control	4. Anbara (0.78 g/kg/day)	5. Anbara (1.56 g/kg/day)	6. Pt NPs (5 μg/g/day) (low dose)	7. Pt NPs (10 μg/g/day) (high dose)
AST (IU)	300.3 ± 18.9	396.3 ± 44.7*	250.7 ± 0.4*	308.7 ± 24.9	273.7 ± 27.3*	286.7 ± 21.9*	276.0 ± 31.0*
ALT (IU)	59.7 ± 7.5	60.7 ± 10.5 ^{NS}	60.0 ± 4.5 ^{NS}	72.3 ± 5.6*	53.3 ± 5.9*	67.7 ± 12.3*	48.5 ± 2.5*
ALP (IU)	127.7 ± 31.3	216.0 ± 9.1 *	128.0 ± 5.9*	247.7 ± 4.5*	358.8 ± 5.5*	281.0 ± 5.5*	234.3 ± 5.9*
Total protein (g/dl)	8.1 ± 0.3	7.5 ± 0.1^{NS}	8.2 ± 0.4^{NS}	7.5 ± 0.1^{NS}	7.7 ± 0.4^{NS}	6.7 ± 0.3*	7.0 ± 0.1*
Albumin (g/dl)	3.7 ± 0.1	3.3 ± 0.0 ^{NS}	3.6 ± 0.2^{NS}	3.3 ± 0.1 ^{NS}	3.2 ± 0.2^{NS}	3.2 ± 0.1*	3.1 ± 0.0*
Globulin (g/dl)	4.4 ± 0.3	4.2 ± 0.1^{NS}	4.3 ± 0.3 ^{NS}	4.2 ± 0.2 ^{NS}	4.5 ± 0.2 ^{NS}	3.5 ± 0.2 *	3.9 ± 0.1 ^{NS}
Bilirubin (mg/dl)	0.7 ± 0.7	1.9 ± 0.3*	1.5 ± 0.3*	1.7 ± 0.9*	1.4 ± 0.2 *	1.6 ± 0.3*	1.3 ± 0.2*
Creatinine (mg/dl)	0.3 ± 0.1	0.6 ± 0.1 ^{NS}	0.6 ± 0.1 ^{NS}	0.6 ± 0.0 ^{NS}	0.7 ± 0.1 ^{NS}	0.3 ± 0.1*	0.3 ± 0.0*
Urea (mg/dl)	29.7 ± 3.0	39.7 ± 2.3*	32.3 ± 4.1 ^{NS}	29.0 ± 1.7 ^{NS}	36.7 ± 7.0*	29.7 ± 4.4 ^{NS}	32.5 ± 1.5 ^{NS}

Values are expressed as mean ± S.E; NS = not significant; *Significant = ($P < 0.05$); n = 6 rats per group.

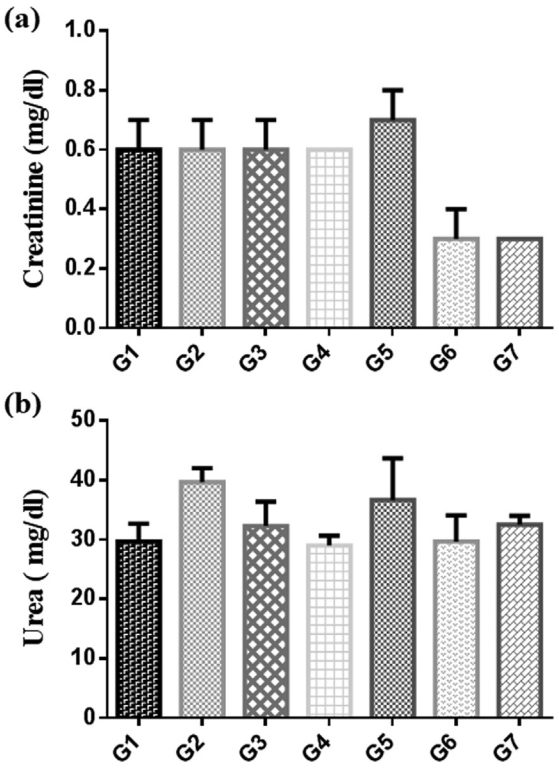
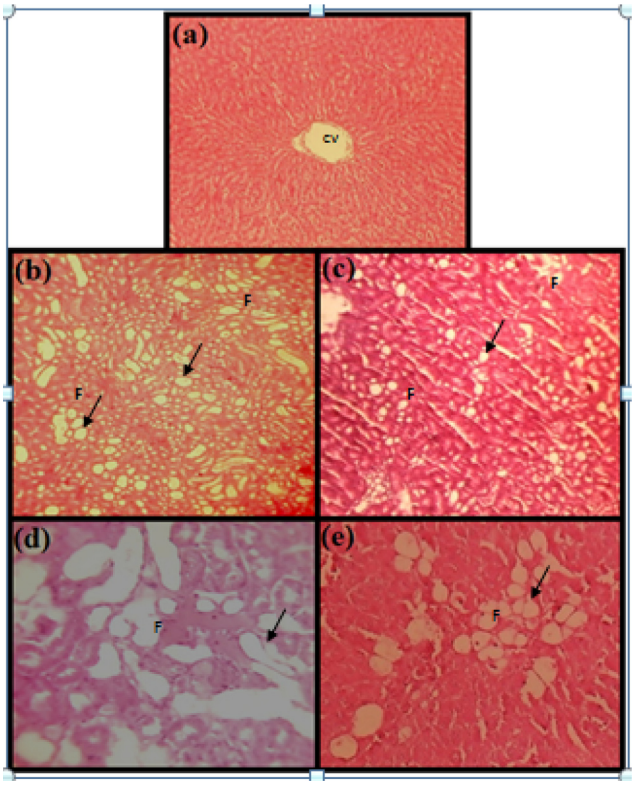


Fig. 14 Concentrations of (a) urea and (b) creatinine, after treatment for 3 weeks with Pt NPs and AAE in control (G1), CCl_4 (G2), Silymarin control (G3), low does AAE 0.78 g/kg (G4), high dose AAE 1.56 g/kg (G5), low does Pt NPs 5 μg/g (G6) and high dose Pt NPs 10 μg/g (G7). Groups expressed as mean ± SR.



CV = central vein, **F**= fatty changes

Fig. 15 Liver damage comparison in normal control and CCl_4 induction single dose 3 ml/kg subcutaneous (s.c), (a) liver of normal rat (b, c) CCl_4 control × 100, (d, e) CCl_4 control × 200 showing fatty cytoplasmic vacuolation of entrilobularhepatocytes. (H & E) × 100.

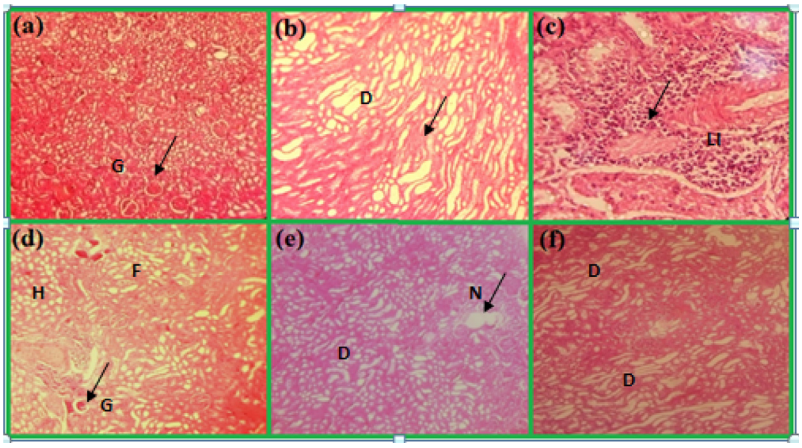
4. Discussion

Date palm fruits are rich source of different nutritional compounds like proteins, minerals, lipids, carbohydrates and polyphenolic compounds (Behija et al., 2011; El et al., 2014; Park et al., 2010). Consumption of these fruits naturallyare beneficial due to its carbohydrates content and great potential as a medicinal food (Al-orf et al., 2012; Bankar et al., 2010; Meena and Chouhan, 2015) contains antioxidants (El et al., 2014; Taylor et al., 2012), and protective towards human health. The beneficial roles of Pt NPs in green synthesis attributed for its antioxidant, anticancer, antimicrobial activity, and protective effect on reactive oxygen species (Ahmed and Hasona, 2008; Arem et al., 2013; Aswathy Aromal and Philip, 2012; Bouhlali et al., 2017; Fang et al., 2009; Hamad et al., 2015; Kostova, 2006; Shrinath et al., 2011). But lack of toxicity information and no research reports till yet leads

Table 6 Histopathological results.

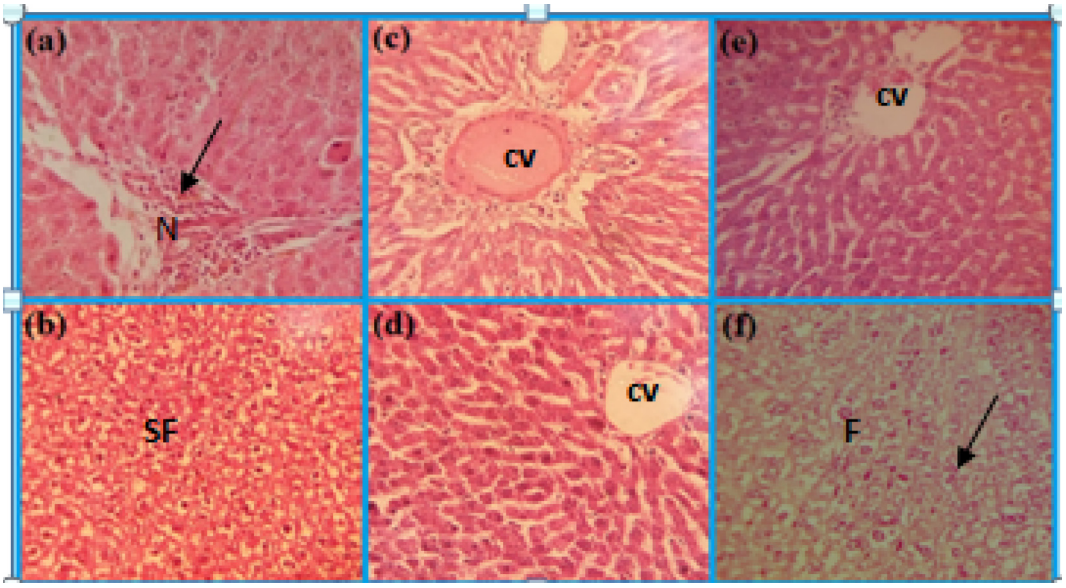
Treatment groups	Histopathological results			
	Experiment	liver	kidney	intestine
1. Control (normal diet)	Not given any thing (not effected)	Normal	Normal	Normal
2. CCL4 control	Given Carbon tetra chloride (CCl_4) after 7th day	Severe damage	Severe damage	Abnormal
3. Silymarine control	Given sylimarine after 7th day	Better than CCl_4	Semi normal	Semi normal
4. Anbara 0.78 g/kg/day)	This group given Low dose Anbara from day 1 to day 7 before given CCl_4	Abnormal liver better than CCl_4	No treated (but better than CCl_4)	Better than CCl_4
5. PtNPs (5 μg/g/day)	This group given low dose platinum nanoparticles (PtNPs) from day 1 to day 7 before given CCl_4	Abnormal	Abnormal	Semi normal
6. Anbara 1.56 g/kg/day)	This group given high dose Anbarabefore and after CCl_4	Semi normal	Medium effect	Semi normal
7. PtNPs (10 μg/g/day)	Given platinum nanoparticles before and after CCl_4	Semi normal	Semi normal	Abnormal

*Cytoplasmic fatty change in low and high dose dates; Semi normal = Semi similar to the control group.



G= glomerular tufts, **D**= dilatation of renal tubules, **LI**= lymphocytic infiltration, **F**= fatty changes, **N**= necrosis, **H**=hydropic degeneration

Fig. 16 Comparison of kidneys of rats after 3 weeks of oral doses of Pt NPs and AAE, (a) kidney of normal rats (no change), (b) CCl_4 control × 100, (Sever cytoplasmic fatty vaculation and dilatation of renal tubules in cortex), (c) represents CCl_4 control × 200, (severe lymphacytic infiltration),(d) 0.78 g/kg AAE- (cytoplasmic fatty vacuolation change), (e) 1.56 g/kg AAE, (f) PtNPs (high dose degeneration of glomeruli and dilatation of renal tubules in cortex) (H & E) × 100.

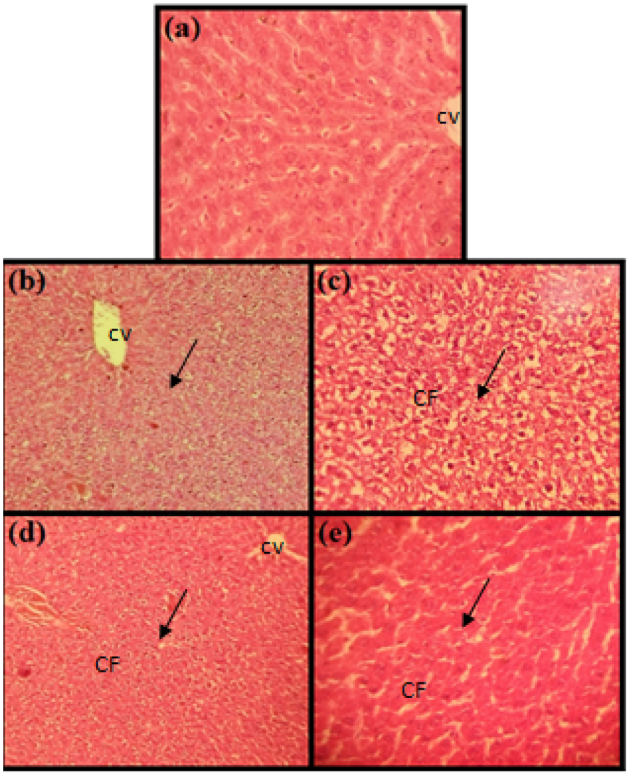


CV = central vein, **CF**= cytoplasmic fatty changes, **N**= necrosis

Fig. 17 Comparison of liver damage in rats after providing daily high oral dose of PtNPs (10 μg/g) for 3 weeks, (a, b) CCl_4 control single dose (shows fatty changes, necrosis and lymphocytic infiltration) (c, d) PtNPs, before and after CCl_4induction (shows view cytoplasmic vacuolation of entrilobularhepatocytes and necrosis of the central vein) (e, f) represents PtNPs (shows semi similar to the control group) (H & E) × 100.

us to investigate the safety and possible side effects of Pt NPs. The present work was carried out to investigate the toxic and protective effects and histopathological studies of Pt NPs and aqueous Anbara Fruit extract at different doses on CCl_4-induced liver damage in Wistar rats.

Hepatic damage due to CCl_4 intoxication was assessed by employing hematological and biochemical parameters. In addition, CCl_4-induced pathological changes in liver and kidneys were evaluated by histopathological studies. Significant changes in mean body weight of treated groups were observed when compared with control. After 3 weeks of administration of the Pt NPs and aqueous Anbara extract, the body weight significantly decreased ($P < 0.05$) in groups 4, 6 and 7, when compare to group 1 and 2. Where the higher dosed group 5 gain weight when compared to group 1 (Table 3). The decrease in body weight may be due to decrease of total protein or



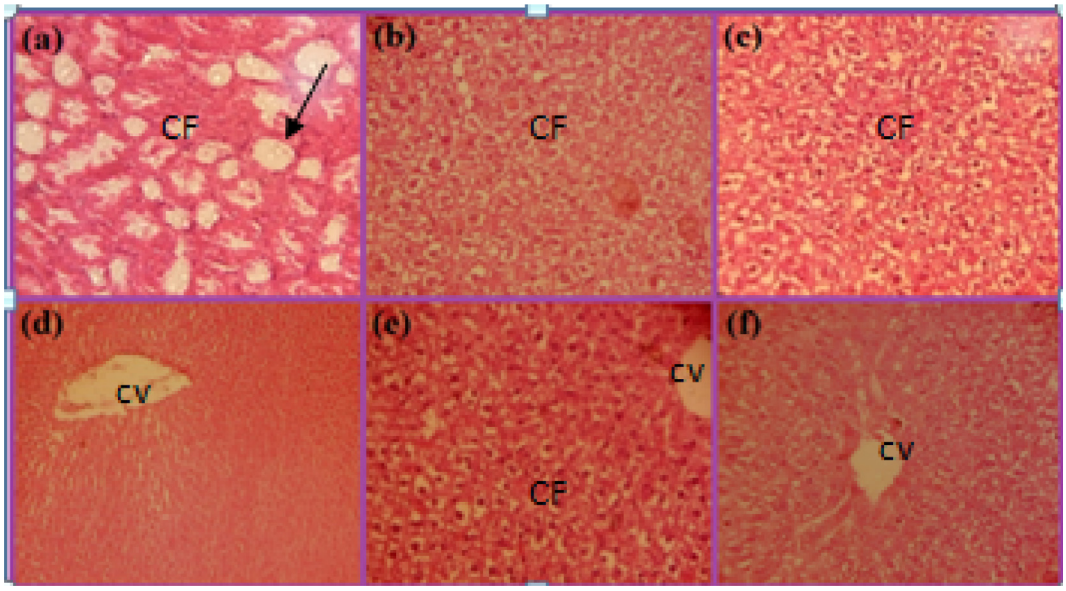
CV = central vein, **CF**= cytoplasmic fatty changes

Fig. 18 Liver images of rats receiveda daily oral low dose of PtNPs (5 μg/g) for 3 weeks and CCl_4induced on 7th day. (a) No lesions were observed in hepatocytes, (b, c) and Cytoplasmic fatty vaculation of the interlobular hepatocytes, (d, e) Semi normal H & E (×100).

attributed to gastroenteritis but actual mechanism for the loss of weight is not clear.

The serum alanine transferase (ALT), aspartate amino transferase (AST) and alkaline phosphatase (ALP) enzymes of liver exhibits enhanced activity after exposed with a single dose of CCl_4 which indicated the liver toxicity with CCl_4 (Kim et al., 2012; Martins et al., 2012; Salim et al., 2018; Xiao et al., 2018). These enzymes ALT, AST and ALP activity in rats significantly decreased ($p \leq 0.05$) when pretreated and post-treated with Pt NPs than in CCl_4 treated rats. Decrease in the concentration of serum creatinine and bilirubin also observed in rats with pre and post treated Pt NPs than in CCl_4 treated rats. This indicates the hepatocytic cell membrane structural integrity protection or damaged liver cells regeneration and restoration of the normal functioning of the poisoned liver, which further protect against CCl_4 hepatotoxicity (Nadaroglu et al., 2017). The administration of Pt NPs in all treated groups enhanced the kidney tissue and concentration of creatinine and bilirubin compared to CCl_4 group. No significant effect occurred in blood biochemical parameters (Kim et al., 2012). Histopathological examinations showed necrosis of central vein, fatty cytoplasmic vacuolation of entrilobular hepatocytes, hepatocellular degeneration, renal tubular necrosis and fatty degeneration in rats treated with CCl_4 (Fig. 15).

The histological examination of rats pretreated with the PtNPs, exhibited good liver protection against the toxicant rats. But with pretreated AAE exhibited no significant liver protection against the CCl_4. Pretreated and post-treated with PtNPs and aqueous Anbara extract, were exhibited excellent protective effect in the kidney and liver in all the groups as evidenced by the normal hepatocytes, absence of necrosis and less cytoplasmic fatty vaculation (Figs. 16–19). Our findings demonstrate that PtNPs, has a potent hepato-protective effect on CCl_4 induced liver injury by improving the change in



CV = central vein, **CF**= cytoplasmic fatty vaculation

Fig. 19 Liver images of rats received a daily oral low dose of AAE (0.78 g/kg) for 7 days and CCl_4induced on 7th day showing, Cytoplasmic fatty vaculation(a, b, c) and high dose (1.56 g/kg) for 21 days and CCl_4 on 7th day showing less cytoplasmic fatty vaculation (d, e, f) (H & E) × 100.

histopathological structure and enhancing liver enzyme activity in rats. The mechanism for hepatoprotective activity by PtNPs is not assured. Oral administration of AAE at a dose of 1.56 g/kg/day attenuate the elevated level of enzymes (AST and ALT) produced by CCl_4, caused subsequent recovery towards normalization like silymarin. The rats pretreated with AAE (0.78 g/kg/day), showed a good recovery. All the obtained values were evaluated with control animals (Table 5).

The decrease levels of serum marker enzymes and serum bilirubin concentration in pre and post-treated rats with AAE (1.56 g/kg/day) indicates the liver protective effect of Anbara against CCl_4 poisoning. The AAE administration reinstate physiological integrity of hepatocytes, thus normalize the values of transaminases in serum. This suggests that the free radical and antioxidant properties of aqueous Anbara extract palliate the liver injuriespossibly by antioxidative effect. Hence the CCl_4induced harmful effects of toxic metabolites were eliminated. These findings indicate the protective effect of AAE against CCl_4 induced liver damage in rats (Kim et al., 2012; Nadaroglu et al., 2017; Salim et al., 2018).

From the *in vivo* study the significant decrease in body weight in all the groups when administered the Pt NPs and Anbara extract in various doses (low and high doses) orally for 7 days in Wistar rats indicate the decrease in total protein compared to control (group-1). In group-3, increase in the body weight-gain (Table 5) indicates the interference of Anbara in growth processes. There is no significant change occurred in biological parameters, toxic effects or damage on the vital organs, liver and kidney (Schmid et al., 2007).

It is assumed that the secondary metabolites of Anbara fruits are non toxic or they might be low molecular weight components that can be easy to pass through and excrete by kidneys. Hence Anbara fruits showed non toxic effects on Wistar rats. Even at higher concentrations the Anbara extract doesn't affected the vital organs and there is no significant changes in parameters occurred upon administration.

All the results in the present study explained that the Pt NPs and Anbara fruits extract are non-toxic to rats and protects the liver against CCl_4 toxicity.

5. Conclusion

In summary, the best types of Saudi Anbara dates contained higher antioxidants were used for the biosynthesis of Pt NPs and aqueous Anbara extract. The flavonoids, amino acids, phenols, vitamins and minerals present in the aqueous extract act as both reducing and capping/stabilizing agents supports the synthesis of Pt NPs. These synthesized Pt NPs and aqueous Anbara extract were characterized using UV–visible, FTIR, TEM, XRD and EDX spectroscopic analytical techniques. The histopathological and biochemical examinations concluded that the Pt NPs have considerable potential in healing and regeneration of liver cells. Thus, it can be used as not toxic, potent liver tonic and efficient to utilizein the treatment of diseases. The aqueous Anbara extract obtained its protective nature on rat liver from CCl_4induced injury. By observing the results, we recommend Pt NPs and aqueous Anbara extractfor potential therapeutic use. Further studies can be used to develop possible mechanisms and the hepatoprotective activity can be used to compose standard therapeutic doses.

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