Study on the anticancer activity of *Poria cocos* extract mediated gold nanoparticles in the treatment of pancreatic cancer

Miao Nie¹ and Peijun Sun²

¹ Department of Gastroenterology, Jiaozhou People’s Hospital, No.180 Huzhou Road, Jiaozhou City, Shandong Province, 266300, People’s Republic of China
² Department of Traditional Chinese Medicine, Qingdao Jiaozhou Central Hospital, 99 Yunxi Henan Road, Jiaozhou City, Qingdao 266300, People’s Republic of China

E-mail: miaonie@outlook.com and niemiao10322@163.com

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Abstract

*Poria cocos*, a fungus used extensively in the Chinese herbal medicine, has been known for myriad of pharmacological applications. There is a growing body of evidence on developing medications for antitumor therapies. The study is aimed to investigate the antitumor potential of gold nanoparticles synthesized from *P. cocos* extract against pancreatic cancer cells. Firstly, gold nanoparticles were generated from *P. cocos* extract and characterized through several techniques. The analysis unveiled the average size of nanomaterial as 24 nm. Remarkably, gold nanoparticles synthesized from *P. cocos* extract showed significant cytotoxic activities. Accumulation of ROS in pancreatic cancer cells is evidenced through the cell permeable probe. Furthermore, to substantiate the ROS-mediated apoptotic event, quantitative real-time PCR was carried out. The results revealed the upregulation of caspase-3, caspase-9 and Bax in gold nanoparticle treated PANC-1 cancer cells. These findings unravelled the ROS-mediated caspase-dependent apoptotic event in pancreatic cancer cells by gold nanoparticles synthesized from *P. cocos* extract. However, further research in preclinical work would shed light on therapeutic potential of this green-synthesized nanoparticles.

1. Introduction

*Poria cocos* belonging to the family Polyporaceae is an edible mushroom. It is known as ‘Fu ling’ in Chinese. Notably, it is being consumed in Chinese folk medicines and Japanese medicines for more than 2000 years. Triterpenes, polysaccharides, fatty acids, enzyme, and sterols are the major bioactive constituents from *P. cocos*. Nevertheless, several biochemical studies revealed that polysaccharide is the primary copious bioactive constituents in *P. cocos*. Literally, it accounts for 84% of the dried sclerotium. Exploration on therapeutic potential of triterpenoids and polysaccharides of *P. cocos* revealed the antibacterial, antitumor, anti-inflammatory, antioxidant, immunomodulating, anti-angiogenic, anti-hemorrhagic fever, antihypertitic, antinephritic, antidiabetic, and antihypertensive effect (Feng *et al* 2013, Li *et al* 2019, Nie *et al* 2020).

Glucose, fucose, xylose, arabinose, β-glucan, mannose, and galactose are the polysaccharides detected from *P. cocos*. Among these polysaccharides, β-glucan have been shown to possess anticancer activity against breast cancer. Different solvent extraction methods have been described for the isolation of different polysaccharide fractions, such as PCP0 (methanol), PCP-1 (0.9% sodium chloride), PCP-2 (hot water), PCP-3-I and -II (0.5 mol l⁻¹ sodium hydroxide), PCP-4-I and -II (88% formic acid). Polysaccharide of *P. cocos* is available as an over-the-counter herbal adjunct since 1970s. Importantly, it has been permitted to treat multiple cancer and hepatitis in 2015 by Chinese Food and Drug Administration (CFDA). A polysaccharide H11 from *P. cocos* was demonstrated to have anticancer property against murine sarcoma S180 cancer cell line. Several polysaccharides have been reported for antitumor property against different cancers such as lung, prostate, pancreatic, and breast cancer cells (Cheng *et al* 2013, Feng *et al* 2013, Li *et al* 2019, Jiang and Fan 2020, Nie *et al* 2020).
Though, the polysaccharide β-glucan from P. cocos has shown better anticancer activity, it has poor water solubility. Therefore, to improve the water-soluble property of β-glucan polysaccharide, derivatives such as pachymaran and carboxymethylated pachymaran are fabricated through chemical approaches. In general, bioavailability is the most common issue in drug development. It greatly limits the applications in various field. In fact, about 10% of drugs which is currently under investigation in the present scenario comprise bioavailability issues and it has been estimated to increase around 40% in the near future. About 60% of synthesized drugs have solubility below 0.1 mg ml$^{-1}$. Owing to the low bioavailability, these drugs fail to reach the market, though they exhibit excellent pharmacodynamic activities. To overcome this issue alternative approaches such as nanoparticle formulation was developed. Nanonization increase the disintegration rate as well as the saturation solubility of drug molecule according to the equation defined by Noyes-Whitney (Noyes and Whitney 1897, Jia 2005). A very few reports describe the nanoparticle production from P. cocos (Ansari et al 2019). For instance, gold nanoparticle generated with aqueous extract of P. cocos has been shown to modulate the anti-obesity factor in obese diabetes rat model, induced with high-fat diet and streptozotocin. Therefore, the current study is aimed to assess the therapeutic effect of P. cocos-mediated gold nanoparticles in the remedy of pancreatic cancers.

2. Methods

2.1. Chemical and media
Chemicals and media used in the research work were procured from Sigma-Aldrich, Shanghai.

2.2. Cell lines and culture conditions
Human pancreatic cancer cells, PANC-1 obtained from Shanghai Cell Bank, were deployed to assess the anticancer property of green synthesized gold nanoparticles. It was grown in high glucose DMEM containing FBS (10%) and antibiotics (gentamycin, 1%). Incubation of PANC-1 cell lines were carried out at humidified conditions (37°C & 5%CO$_2$). The cell lines were allowed to grow for 24 h unless otherwise stated and cells were monitored routinely on inverted microscope (Nikon Eclipse TS100, Zeiss)

2.3. Fabrication of gold nanoparticles using leaf extract solution
As mentioned above, various concentrations of gold solutions leaf extract were optimized. At first, formation of gold nanoparticles was indicated by colour change. By colour change and varying concentrations, high stable gold nanoparticles formation was confirmed. Thus, the colour change of clear ruby pink aqueous P. cocos leaf extract to violet was observed within a time period of 15 min after addition of gold solutions and this colour change indicated the fabrication of gold nanoparticles through green synthesis method. The pinkish violet colour intensity was increased with time period of incubation and this was because of Surface Plasmon Resonance (SPR) activation. Later, with the help of several physio-chemical characterizations like x-ray diffraction analysis (XRD), FT-IR, UV–visible spectroscopy. The confirmation of gold nanoparticles green synthesis was done.

2.4. Characterization
The gold nanoparticles crystallinity was attenuated by using x-ray diffractometer (Bruker, D8 discover) with $\lambda = 1.54$ Å Cu radiation in 2θ of 10°–80° range and was operated with 30 kv 20 mA voltage. For determining functional group and confirmation of biomolecule capping on gold nanoparticles surface, Bruker Fourier Transform Infrared (FT-IR) spectroscopy with 500–4000 cm$^{-1}$ range was performed. A pellet was prepared with potassium bromide (KBr).

The spectrum results from UV–Vis Spectroscopy was achieved through Perkin Elmer (LAMBDA 950) UV–VIS-NIR spectrophotometer, which confirmed the formation of gold nanoparticles by determining SPR of gold surface vibrations. With the help of JEOL GCMAZE II GC–MS spectrometer, GC–MS examination was done. Temperature of the injection port was made sure at 220°C and flow rate of helium at 1 ml min$^{-1}$. Ionization voltage of 70 ev was applied. Search was performed in NIST (National Institute of Standards and Technology, Ver.2.1) data library. Comparison of the spectrum attained through GC–MS examination with existing compound list of NIST library was carried out to confirm the synthesis of gold nanoparticles. GC eluted a varied range of semi-volatile and volatile mixtures. With the help of JEOL instrument (JEM2010), High-Resolution TEM (HRTEM) was utilized to measure the particles size and shape. The sample for HRTEM was attained by deposition of small quantity of gold (Au) with leaf colloids over copper grids that were coated with carbon and by evaporation of water at ambient temperature. By image analysis, gold nanoparticles particle size was identified.
2.5. Cell viability assay
To examine the anticancer property of gold nanoparticles synthesized from *P. cocos* extract, primarily the PANC-1 cancer cell (1 × 10⁴) was taken in a well-plate and incubated at the specified conditions for 24 h. To this, different doses from 1–100 μg ml⁻¹ of gold nanoparticles synthesized from *P. cocos* extract were mixed and incubated further. After the incubation period, the medium was exchanged with newly prepared DMEM (100 μl) and MTT dye solution (20 μl). The plates were set aside for 4 h, which allows the formation of water-insoluble purple formazan crystal due to the reduction of MTT by oxidoreductase enzymes (Berridge et al 2005). The crystals were then thoroughly dissolved in DMSO (200 μl). Absorbance was documented and the cell viability in percentage was calculated using the equation as follows

\[
\text{Cell viability (\%)} = \frac{\text{Absorbance of treated cells}}{\text{Absorbance of control cells}} \times 100
\]

In order to scrutinize the cytotoxic effect of *P. cocos* extract on PANC-1 cancer cells, the cells were treated with lower to higher doses of *P. cocos* extract (100 μg ml⁻¹–500 μg ml⁻¹) at specified conditions and the viability of cell were calculated as described above.

2.6. Effect of nanoparticles on ROS generation in cancer cells
The intracellular ROS levels in the control and nanoparticles treated PANC-1 cells were measured by using 2′,7′-dichlorodihydrofluorescein diacetate (H 2 DCFDA). In brief, PANC-1 (1 × 10⁶ cells pre ml) cells were cultivated in well-plate and mixed with 20 and 40 μg ml⁻¹ gold nanoparticles. After incubation for 24 h under specified conditions, 10 μl of H 2 DCFDA was added and the well-plates were allowed to set aside at RT for 30 min (Wang et al 2019a). Then the fluorescent intensities of the cells were measured through flow cytometer (excitation & emission wavelength −480 & 530 nm, respectively).

2.7. Assessment of apoptotic gene expressions
The expression of apoptotic regulatory genes (caspase-3, caspase-9 and Bax) were studied in pancreatic cancer cells (PANC-1). Cell lines were treated with 20 and 40 μg ml⁻¹ gold nanoparticles synthesized from *P. cocos* through qRT-PCR. Briefly, total RNA was isolated from control and gold nanoparticles treated PANC-1 cells (20 μg ml⁻¹ and 40 μg ml⁻¹) by using RNeasy kit (Qiagen). The extracted RNA was quantified through BioSpec-Nano (Shimadzu) and the quality was analysed through agarose gel electrophoresis. RNA was converted into cDNA through QuantiNova Reverse Transcription Kit (Qiagen) and SYBR Green Real-Time PCR Master Mixes (Thermo Fisher Scientific) was employed for real-time PCR, carried out in Applied Biosystems thermal cycler RT-PCR. GADPH was used as a reference gene. The relative change in the gene expression was calculated using 2−ΔΔCt formula.

2.8. Statistics
Experiments were performed in triplicates. Data are denoted as mean±SD. Statistical analysis was carried out through one-way ANOVA. Asterisk * denote significance, *p < .05: significant.

3. Results and discussion
Measurement of FT-IR spectroscopy was performed for the identification of functional groups in biomolecules that were liable for capping and reduction of bio-reduced gold nanoparticles fabricated by the extract of *P. cocos* plant. The distinctive FT-IR spectrum of *P. cocos* leaf was shown in figure 1. The presence of peaks at 2923 and 3266 cm⁻¹, obtained using FT-IR spectrum corresponds to the C–H and OH broad bands and the presence of large quantity of OH functional group represents the plants extract. The presence of IR bands at 1367, 1997, 2111 and 2333 cm⁻¹ correspond to the carbonyl and alkynes groups like COOH, C=O groups accordingly. At peak positions, these IR peaks adsorptions exhibited sharp nature. The peak observed at 1047 cm⁻¹ was developed due to C−OH vibration (Ahmad et al 2016). In addition, the existence of peak at 620 cm⁻¹ could be associated with C−H vibrations of carbon chain. On the other hand, the FT-IR spectrum of plant extract exhibited the similar peaks which further indicated the capping of plant extract bioconstituents on the surface of prepared NPs. In addition, the peak locations were subsequently corroborated with GC–MS findings attributing carbonyl acid, aldehyde and alcohol classes of all forms. As illustrated in the previous reports (Ramesh et al 2019a, Ramesh et al 2019b), free carbonyl and amine groups can be utilized to reduce Au³⁺ to Au⁰ state which can be confirmed by the change in color (Ramesh et al 2019a, Ramesh et al 2019b). The reducing group existence at 1743 cm⁻¹ was showed by low intense bands presence and the moderate intense bands present at 1367 cm⁻¹ indicates that gold nanoparticles were bound possibly to the carbonyl compounds existed in extract of *P. cocos* plant (Ramesh et al 2019a). XRD analysis confirms the gold nanoparticles purity and crystalline nature. XRD
pattern of gold nanoparticles Capping with extract of *P. cocos* leaves was displayed in figure 2. The five diffraction peaks from XRD pattern at 2θ angles 78°, 64.68°, 44.36° and 38.5° with characteristic planes (311), (220), (200) and (111) were indexed based on gold nanoparticles face centered cubic (fcc) structure as displayed in figure 2. On the other hand, the existence of broad amorphous peak at 2θ = 15° – 35° may be due to existence of adsorbed bioconstituents onto the surface of AuNPs. The XRD diffraction of AuNPs with JCPDS (card no. 04-0784) was matched with results reported previously (Ramesh et al 2019a). The Au was reduced completely with high purity by extract of *P. cocos* leaves. These results indicate that the biofabrication of Au NPs can be achieved with an extremely stable form of gold. Further, the average crystalline size for the prepared NPs was calculated using the Scherrer equation from the obtained XRD data, which was found to be 45 nm. The following Scherrer equation was used for crystalline size calculations

\[ D_p = \frac{0.94\lambda}{\beta \cos \theta} \]

where \( \theta \) = Bragg angle, \( \lambda \) = x-ray wavelength \( D_p \) = average crystallite size, \( \beta \) = line broadening in radians

UV–vis spectrum of gold nanoparticles was displayed in figure 3. In this procedure, the extract of *P. cocos* leaves served as both reducing as well as capping agents. Confirmation of gold nanoparticles formation was primarily performed through UV–Vis spectrum, which was confirmed to quite sensitive to size, shape and nature of the formed materials. An analysis of absorption peak displayed the band at 530 nm (exhibiting SPR).
The absorption peak of gold nanoparticles was present at 530 nm. The fabricated gold nanoparticles had morphology that was spherical in nature.

In figure 4, the images of HR-TEM analysis exposed the new approaches for gold nanoparticles green synthesis. The shape and size of the generated nanomaterial range were identified to be susceptible to concentration of leaf extracts. It was displayed in figures 4(A)–(C) that the various morphology of gold nanoparticles presents in a combination of spherical and triangular like particles. Additionally, the SAED pattern of AuNPs indicated the polycrystalline nature of the prepared NPs (shown in figure 4(D)). The elemental composition of the synthesized AuNPs was studied by using EDS analysis (figure 4(E)). Figure 4(E) showed the
existence of elemental peaks corresponding to gold, carbon and oxygen, which indicated the formation of AuNPs. On the other hand, no impurity peaks were found in the EDS spectrum further indicating the high purity of prepared NPs. The pale-yellow color development in sample was because of gold nanoparticles reduction. When the plant extract was exposed to HAuCl4, the active compounds present in extract of plant involved to reduce Au ions that can be identified visually by change in color (Ramesh et al. 2019a).

3.1. Cell viability
The gold nanoparticles synthesized from P. cocos were evaluated for cytotoxicity on PANC-1 cell. Different concentrations used in the analysis revealed the cytotoxic effect of gold nanoparticles synthesized from P. cocos on PANC-1 human cancer cells. As from figure 5(A), the cell proliferation rates progressively decreased with raise in gold nanoparticle concentrations. Our findings are in harmony with previous report of gold nanoparticles (fabricated through green method) on PANC-1 pancreatic cancers, in which the nanoparticles synthesized from Panax notoginseng and Scutellaria barbata exhibited cytotoxicity at higher concentrations (Wang et al. 2019a, Wang et al. 2019b). Sibuyi et al. (2021) reported that gold nanoparticles synthesized from Acai berry and Elderberry extracts had significant antiproliferative effect on PANC-1 cells. Similarly, report from Emanzadeh and Pasparakis (2021) revealed the cytotoxic effect with increasing concentrations of gold nanoshells on MIA PaCa-2 pancreatic cancer cells. Evaluation of P. cocos extract on PANC-1 cancer cell unveiled the cytotoxic effect at higher concentrations (figure 5(B)). It has been reported that bioactives extracted from P. cocos has cytotoxic and antitumor property (Zhou et al. 2008, Kikuchi et al. 2011, Rios 2011, Rios et al. 2012). The ethanolic extract obtained from sclerotia of P. cocos have been shown to exert considerable cytotoxic action on human lung adenocarcinoma, H1264, H1299, A549, and Calu-6 cells (Lee et al. 2018). The ethanol extract of P. cocos have been shown to demonstrate mitochondria-mediated caspase triggering mechanism in A549 lung cancer cells (Chu et al. 2016). Bioconstituents such as triterpenoids and polysaccharides of P. cocos, have been documented to trigger apoptosis in multiple human cancer cells (Kaminaga et al. 1996, Gapter et al. 2005, Zhang et al. 2006). Therefore, it is not surprising that P. cocos exhibiting antitumor potential against pancreatic cancer cells.

Nitrocellulose’s size plays a critical role in cytotoxicity. Gold nanoparticles with very small dimensions (1–2 nm) have been found to exert cytotoxicity in both malignant and healthy cells. However, nanoparticles in the size range of 5 to 12 nm have been selectively shown to exhibit cytotoxicity on malignant cells while rendering the normal cells with meagre cytotoxic effect. Intriguingly, nanoparticles greater than 15 nm were found to be non-toxic (Tomşa et al. 2021). On the other hand, gold nanoparticles stabilized and conjugated with drug molecules have been shown to display dose-dependent cytotoxicity effect on cancer cells (Steckiewicz et al. 2020).

It is reported that negatively charged gold nanoparticles makes an ionic interaction with positively charged biomolecules. Hydrophobic interaction between proteins and gold nanoparticles were reported. In addition, conjugation with amine and carboxyl group have also been reported from gold nanoparticles (Singh et al. 2013, Jazayeri et al. 2016, Devi et al. 2020). Therefore, the bioactives (triterpenes, polysaccharides, fatty acids, and enzyme) from P. cocos have the potential to serve as a stabilizing and reducing agent. This stabilizing and conjugating properties might have resulted in the enhanced cytotoxic property.

3.2. Estimation of ROS
ROS generation in control and green-synthesized gold nanoparticles were measured using fluorescent probe H2DCFDA. Two different concentrations (20 and 40 μg ml−1) of gold nanoparticles synthesised from P. cocos was assessed for ROS generation. In both the tested concentration, the ROS levels were found to be in higher amount in comparison to untreated or control cells (Wang et al. 2019b). Among them, 40 μg ml−1 displayed highest ROS generation than 20 μg ml−1 treated PANC-1 cells (figure 6). These results are suggestive that gold nanoparticles synthesized from P. cocos induces ROS production in PANC-1 cancer cells. Increased ROS levels in tumor cell are reported to inhibit the tumor growth and thereby it can enhance the cancer therapy (Brenneisen and Reichert 2018).

3.3. Assessment of apoptotic gene expressions by qRT-PCR
Evaluation of green-synthesized nanoparticles unveiled the accumulation of ROS in PANC-1 cells. This in turn may results in oxidative stress-mediated apoptosis in cancer cells. Therefore, to substantiate the ROS-induced apoptosis in PANC-1 cancer cells, apoptotic regulatory genes were quantified in the presence of gold nanoparticles. Expression of apoptotic-related genes (caspase-3, caspase-9 and Bax) in control i.e., untreated and gold nanoparticles (synthesized from P. cocos) treated PANC-1 cells were examined through qRT-PCR. The expressions of apoptotic genes were found to be upregulated in gold nanoparticle treated cells when compared to control cells (figure 7). In comparison to 20 μg ml−1 treated cells, 40 μg ml−1 treated cells displayed significant
upregulation in the gene expression of apoptotic-related proteins. These results indicate the caspase-mediated apoptotic pathway in PANC-1 cancer cells in the presence of gold nanoparticles synthesized from \textit{P. cocos}.

Generation of ROS and caspase-dependent apoptosis is the fundamental mechanism in nanoparticles-mediated cancer therapy. Several studies have reported the increased production of ROS and activation of cell death through apoptosis (Thayyullathil \textit{et al} 2008, Kim \textit{et al} 2018, Guerrero-Florez \textit{et al} 2020, Piktel \textit{et al} 2021).

4. Conclusion

The study describes the easy method of eco-friendly fabrication of gold nanoparticles from \textit{P. cocos} extract and its antitumor potential in PANC-1 cancer cells. Gold nanoparticles that are highly stable were fabricated using

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**Figure 5.** Cell viability assay (A) Effect of gold nanoparticles synthesized from \textit{P. cocos} extract on cell viability of PANC-1 cancer cells. Cell proliferation rate was measured at various concentrations of gold nanoparticles (from 1–100 $\mu$g ml$^{-1}$) by MTT assay. (B) Effect of \textit{P. cocos} extract on cell viability of PANC-1 cancer cells. A sequence of concentrations varying from 100 $\mu$g ml$^{-1}$ to 500 $\mu$g ml$^{-1}$ were evaluated. Error bars in the graph signifies SD of the mean.

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various concentrations of leaf extract from *P. cocos* plant in the present study. By several physio-chemicals methods, the produced gold nanoparticles were characterized. Intriguingly, the extract obtained from *P. cocos* exhibited antitumor property in pancreatic cancer cell. Despite, it augmented the antitumor property by enhancing the cytotoxic activity. In addition, the gold nanoparticles increased the ROS production and apoptotic regulator proteins (caspase-3, caspase-9 and *Bax*). This result signifies the ROS-induced apoptosis event in pancreatic cancer cells.

**Data availability statement**

The data that support the findings of this study are available upon reasonable request from the authors.

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**Figure 6.** Effect of gold nanoparticles generated from *P. cocos* extract on ROS production in PANC-1 cancer cells. Intracellular ROS generation was measured by H$_2$DCFDA at 20 and 40 μg ml$^{-1}$ concentration gold nanoparticles. Error bars in the graph signifies SD of the mean.

**Figure 7.** Assessment of gold nanoparticles synthesized from *P. cocos* extract on gene expression of apoptotic-related protein. Caspase-3, caspase-9 and *Bax* expressions in pancreatic cancer cells were analysed in the presence (20 and 40 μg ml$^{-1}$) and absence of the gold nanoparticles through qRT-PCR. Error bars in the graph signifies SD of the mean.
Author’s contribution

Miao Nie. Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Writing—original draft; Writing—review & editing; Supervision; Peijun Sun: Methodology; Project administration; Resources; Software; Validation; Visualization; Writing—original draft; Writing—review & editing.

ORCID iDs

Miao Nie https://orcid.org/0000-0002-2482-7825

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