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REVIEW PAPER

# Recent advances in biological mediated cancer research using silver nanoparticles as a promising strategy for hepatic cancer therapeutics: a systematic review

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## ABSTRACT

Nanoparticles are of highlighted interest in scientific research for a wide range of applications as they bridge the gap between atomic structures and bulk materials with unique physicochemical properties. This systematic review was aimed to study the current trends in biological mediated cancer research using biogenic silver nanoparticles (AgNPs) against hepatic cancer cell lines. For this purpose, the electronic databases including Cochrane Library, PubMed, Scopus, Science Direct, ProQuest, Embase, and Web of Science were searched. Forty-six studies passed the eligibility assessments and entered into the current study. All of the studies stated the size distribution of biosynthesized AgNPs below 100 nm with different shapes. Whereas, most studies stated spherical morphology for biogenic AgNPs. Most of the studies (91.30%) represented significant anticancer activity of biogenic AgNPs toward hepatic cancer cell lines. The molecular mechanisms also showed the induction of intracellular Reactive Oxygen Species (ROS) and apoptosis through the biogenic AgNPs-treated hepatic cancer cells. The AgNPs-mediated induction of intracellular ROS overgeneration and ATP synthesis interruption disturb the mitochondria respiratory chain function resulting in the induction of mitochondrial pathway apoptosis. Overall, this systematic review provided strong preliminary evidence representing the efficacy of biogenic AgNPs to combat hepatic cancer cells through in vitro models.

***Keywords:*** *Anticancer Activity,Hepatic Cancer, Nanotoxicity, Silver Nanoparticles*

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## INTRODUCTION

### *Hepatic cancer: An insight*

Hepatic cancer is a global leading lethal malignancy. The predominant form of primary hepatic cancer is hepatocellular carcinoma (HCC) [1, 2]. The 4th most common cancer related-mortality is attributed to HCC in the world [3]. The global burden of HCC may reach an annual incidence of one million patients during next decades [4]. The American Cancer Society anticipated that in 2019, more than 43,000 new cases of hepatic and intrahepatic bile duct cancer will be diagnosed in the United State (US). Besides, an estimated 31,780 hepatic and intrahepatic bile duct cancer deaths will occur in the US during 2019 including 21,600 deaths in males and 10,180 deaths in females [5]. The risk factors that may cause HCC contain hepatitis B virus (HCV), hepatitis C virus (HCV), cirrhosis, fungal toxins, metabolic liver disease, poor diet and inactivity, etc [2, 3, 6].

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The HCC has been observed in less than 10% of patients with healthy liver, whereas most cases may have an underlying chronic hepatic disease [7]. Hepatocarcinogenesis is a multistep process and different genetic and epigenetic alterations are engaged in this process. Unfortunately, a number of patients are identified at advanced stages of hepatic cancer and the current therapeutic options are not effective [1]. HCC is highly resistant to current therapies and exploring novel strategies to combat HCC remains an urgent medical need [4]. The anticancer drugs such as doxorubicin, fluoropyrimidines and platinum salts showed no definitive proof on their effectiveness for hepatic cancer therapeutics [8].

### *Nanotechnology as a novel approach to combat cancer*

In recent years, nanotechnology has been emerging as a rapidly growing field with effective influence on human life [9, 10]. Nanotechnology is the science that deals with the materials at the range of 1 to 100 nm that results in enhanced utility and/or new applications [11]. Even though both nanomaterials and bulk materials are made of the same atoms, the physicochemical properties of materials at nanoscale differ from their bulk [12]. Out of all types of nanomaterials, metallic NPs and in particular silver nanoparticles (AgNPs) have shown significant promise in terms of wide biomedical applications such as antibacterial [13-16], antifungal [17], anticancer activity [18, 19], photocatalytic activity [20, 21], and drug delivery system [22]. Because of the large surface to volume ratio in AgNPs, their physicochemical and biological properties differ from their bulk [23]. The efficacy of AgNPs as nanocarriers for drug delivery of anticancer medicines have been reported [24, 25]. Moreover, the surface of AgNPs can be functionalized with diagnostic and therapeutic agents to build smart multifunctional NPs [26]. Traditionally, the AgNPs were synthesized using different physical, chemical methods. These methods had some drawbacks due to the use of hazardous chemicals in chemical methods or high amount of energy consumption through physical methods [27, 28]. Tremendous growth in nanoscience and exceeding need to produce large amounts of NPs have opened the biosynthetic approach as an ecofriendly and nontoxic route for NPs preparation [29]. Biosynthesis of metal NPs like AgNPs is the most innovative and highly specialized field exploring novel natural sources to form NPs with special morphologies and size distributions [30]. It is quite interesting that metal NPs can be synthesized from simple microorganisms [31, 32] up to evolved plants [33-37], and even animals [38]. The biological activity of AgNPs depends on different parameters such as size, shape, composition, surface composition, surface charge, surface area, and ion release [30, 39].

### *Objective of the study*

Recently, biosynthesized AgNPs have been investigated extensively for their anticancer activity toward hepatic cancer cells through in vitro models [40-49]. The studies stated different efficacy of biogenic AgNPs against hepatic cancer cells. Because of the lack of comprehensive review in the literature, this study was aimed to systematically review the published articles to evaluate the anticancer activity of biogenic AgNPs against hepatic cancer cells. Another purpose of this study was to discuss the molecular mechanisms of biogenic AgNPs-induced cytotoxicity against hepatic cancer cells.

### *Methods*

Published literature was reviewed systematically for any extractable information about the anticancer activity of biogenic AgNPs against hepatic cancer cells.

### *Data source and search strategy*

In the present study, the electronic search was performed on Web of Science, Science Direct, ProQuest, PubMed, Scopus, Cochrane, and Embase for the articles published up to 25 September 2019. The search was done in English language using keywords including "Ag", "silver", and "fabrication", "synthesis","microbial","biofabrication", "biosynthesis","plant*","biological","herbal", "alga*","phyto*","bioreduction","biomimetic", "fungal","biogenic","bacterial","myco*", "green", and "nanoparticle*","nano-silver", "colloidal","nanomaterial*","nanostructure*", and "antineoplastic","tumor*","antitumor*", "anticancer*","cytotoxicity", "cancer*", "cytotoxic", "cell line*", "hepatic", "liver".

### *Inclusion criteria*

The articles that satisfied the following criteria were included: i) English language study; ii) experimental study design; iii) in vitro study; iv) articles that evaluated the cytotoxicity of biogenic AgNPs toward hepatic cancer cells.

Table 1. The results of anticancer activity of biosynthesized AgNPs against hepatic cancer cells

| Author/Year | Biological source/ Scientific name | characterization techniques | Size (nm)/ Morphology | Hepatic cancer cell line[a] | Dose | Exposure time (h) | Method | Major outcome | Ref |
|---|---|---|---|---|---|---|---|---|---|
| Rajkumar et al. 2019 | Plant/*Zea mays* L. | UV-vis, SEM, XRD, EDX, FT-IR | 100</Aggregated spherical | HepG2 | 125-1000 µg/mL | 24 | Trypan blue exclusion assay | At 125 and 1000 µg/mL, around 40 and 80% cell inhibition were found, respectively. | [40] |
| Qasim Nasar et al. 2019 | Plant/*Seripheidium quettense* | UV-vis, SEM, XRD, FT-IR | 48.40-55.35/Spherical | HepG2 | 7.8-500 µg/mL | 24 | MTT | $IC_{50}$: 62.5 µg/mL | [41] |
| Patra et al. 2019 | Plant/*Pisum sativum* L. | UV-vis, SEM, XRD, EDX, FT-IR | 10-25/Spherical | HepG2 | 0.01-1000 µg/mL | 24 | Trypan blue exclusion assay | $IC_{50}$: 4.0 µg/mL | [42] |
| Pathak et al. 2019 | Plant/*Phyllanthus fraternus* | UV-vis, SEM, XRD, TEM, FT-IR | <50/Spherical | HepG2 | 0.97-250 µg/mL | 48 | MTT | $IC_{50}$: 62.5 µg/mL | [43] |
| Nasar et al. 2019 | Plant/*Ephedra procera* | UV-vis, SEM, XRD, FT-IR | Average: 20.4/Spherical | HepG2 | 7.8-500 µg/mL | 24 | MTT | $IC_{50}$: 61.3 µg/mL | [44] |
| Ibrahim et al. 2019 | a) Plant/*Rhus coriaria* L.<br>b) Plant/*Carthamus tinctorius* L. | UV-vis, TEM | a) 22.41-37.58/Spherical<br>b) 14.52–35.77/Spherical | HepG2 | 100-500 µg/mL | 48 | Sulforhodamine B (SRB) | a) $IC_{50}$: 720.49±9.89 µg/mL<br>b) $IC_{50}$: 18.24±0.80 µg/mL | [45] |
| Bhatnagar et al. 2019 | Plant/*Talaromyces purpurogenus* | TEM, DLS, FT-IR, EPMA, Zeta potential | 4-60/Spherical | HepG2 | 25-200 µg/mL | 24 | Cell counting kit-8 (CCK-8) assay | $IC_{50}$: 11.1 µg/mL | [47] |
| Aziz et al. 2019 | Fungus/*Piriformospora indica* | UV-vis, SEM, TEM, EDX, XRD, FT-IR | 6-15/Spherical | HepG2 | 0.5-250 µg/mL | 48 | MTT | $IC_{50}$: 2.45±0.62 µg/mL | [48] |
| Abbasi et al. 2019 | Plant/*Ocimum basilicum* L. var. *purpurascens*<br>a) callus extract<br>b) anthocyanin extract | UV-vis, XRD, FT-IR, SEM, EDX | a) 50.97±0.10/ Spherical<br>b) 42.73±1.24/ Spherical | HepG2 | 200 µg/mL | 24 | Sulforhodamine B (SRB) | a) 72.49±5.8% viability was found.<br>b) 24.70±4.5% cell inhibition was found. | [49] |
| Singh et al. 2018 | Plant/*Carissa carandas* | UV-vis, XRD, FT-IR, FE-SEM, EDX, TEM, TG ( Thermogravimetric) | 28-60/ Spherical | HUH-7 | 10-50 µg/mL | 24 | MTT | $IC_{50}$: 10.29 µg/mL | [51] |
| Singh et al. 2018 | Plant/*Morus alba* | UV-vis, TEM, SEM, XRD, FT-IR, Zeta potential | 10-50/ Spherical | HepG2 | 1-80 µg/mL | 24 | MTT | $IC_{50}$: 20 µg/mL | [52] |
| Saratale et al. 2018 | Plant/*Punica granatum* | UV-vis, XRD, FT-IR, HR-TEM, FE-SEM, EDX, XPS | 35-60/ Spherical | HepG2 | 5-200 µg/mL | 24 | MTT | $IC_{50}$: 70 µg/mL | [53] |
| Saratale et al. 2018 | Plant/*Taraxacum officinale* | UV-vis, XRD, FT-IR, HR-TEM | 5-30/Spherical | HepG2 | 10-200 µg/mL | 48 | MTT | $IC_{50}$: 60 µg/mL | [54] |
| Raghuwanshi et al. 2018 | Plant/*Pterospermum acerifolium* | UV-vis, HR-TEM, FT-IR, XRD | 10-20/ Spherical | HepG2 | 7.8-250 µg/mL | 24, 48 | MTT | $IC_{50}$ values were found at 24.5±1.3 and 4.76±1.1 µg/mL after 24 and 48 h of treatment, respectively. | [55] |
| Paul Das et al. 2018 | Plant/*Wedelia chinensis* | UV-vis, XRD, TEM, EDX, XPS, FT-IR | 18-68.76/ Spherical | HepG2 | 6.12-200 µg/mL | 24 | MTT | $IC_{50}$: 25 µg/mL | [56] |
| Patra et al. 2018 | Plant/*Physalis peruviana* L. | UV-vis, SEM, EDX, FT-IR, XRD | 30-55/Nearly quasi-spherical | HepG2 | 0.01-1000 µg/mL | 24 | Trypan blue exclusion assay | No cell inhibition was found up to 10 µg/mL. Besides, at 100 and 1000 µg/mL, around 60 and 20% cell viability were found, respectively. | [57] |
| Padinjarathil et al. 2018 | Plant/*Punica granatum* | UV-vis, TEM, SAED, DLS, Zeta potential, FT-IR | Average: 30/ Spherical | HepG2 | 0.01-200 µg/mL | 24, 48, 72 | MTT | $IC_{50}$ values were found at 80 and 64 µg/mL after 48 and 72 h of treatment, respectively. However, No $IC_{50}$ was found after 24 h of treatment. | [58] |
| Ovais et al. 2018 | Plant/*Olax nana* Wall. ex Benth. | UV-vis, XRD, FTIR, SEM, TEM, DLS, EDX, SAED | Average: 26/ Mostly spherical | HepG2 | 3.9-500 µg/mL | 48 | MTT | $IC_{50}$: 14.93 µg/mL | [59] |
| Khan et al. 2018 | Plant/*Albizia chevalier* | UV-vis, TEM, FE-SEM, XRD, EDX, FT-IR | Average: 30/ Spherical | HepG2 | 10-200 µg/mL | 48 | MTT | $IC_{50}$: 23.66 µg/mL | [60] |
| Kahsay et al. 2018 | Plant/*Dolichos lablab* | UV-vis, FT-IR, XRD, FE-SEM, EDX, SAED, TEM | Average: 9/ Spherical | HepG2 | 0-320 µg/mL | 24 | MTT | $IC_{50}$: 59.60 µg/mL | [61] |
| Jadhav et al. 2018 | Plant/*Salacia chinensis* | UV-vis, TEM, zeta potential | 40-80/ Primarily spherical with few rods, triangular and hexagonal | HepG2 | 2.45-78.62 µg/mL | 24 | MTT | $IC_{50}$: 6.31 µg/mL | [62] |
| Dhayalan et al. 2018 | Plant/*Coleus forskohlii* | UV-vis, HR-TEM, XRD, FT-IR | 5-35/Elliptical | HepG2 | 0.01-100 µg/mL | 48 | MTT | At 100 µg/mL, around 60% cell viability was found. | [63] |
| Yassin et al. 2017 | Plant/*Balanites aegyptiaca* | SEM, XRD, FT-IR | 20-47/ Aggregated spherical | HepG2 | 630 µg/mL | 24 | BrdU assay | 84.5% cell inhibition was found. | [64] |
| Sri Ramkumar et al. 2017 | Plant/*Garcinia imberti* | UV-vis, SEM, XRD, EDX, FT-IR | Average: 27/ Spherical | HepG2 | 25-75 µg/mL | 24 | MTT | More than 70% cell viability was found at 75 µg/mL. | [65] |
| Sheet et al. 2017 | Fungus/*Penicillium chrysogenum* | UV-vis, FT-IR, XRD, TEM | 10-15/ Spherical | HepG2 | 25-80 µg/mL | 24 | MTT | $IC_{50}$: 52.071 µg/mL | [66] |
| Shanmugasundaram et al. 2017 | Bacterium/*Streptomyces* sp. | TEM, XRD, FT-IR, SAED, XPS | <100/ Spherical | HepG2 | 6.25-100 µg/mL | 24 | MTT | $IC_{50}$: 38.42 µg/mL | [67] |
| Prasannaraj et al. 2017 | Plant/ *Aegle marmelos, Alstonia scholaris, Andrographis* | UV-vis, SEM, EDX, XRD, FT-IR | 36-97/ Predominantly spherical, fibres, | HepG2 | 5-50 µg/mL | 48 | MTT | The $IC_{50}$ values were 75.68, 27.01, 43.76 and 40.32 µg/mL for *A. marmelos* AgNPs, *A.* | [68] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *paniculata,* and *Centella asiatica* | | rectangle | | | | | *paniculata* AgNPs, *A. scholaris* AgNPs and *C. asiatica* AgNPs, respectively. | |
| Prasannaraj et al. 2017 | Plant/ *Eclipta prostrata, Moringa oleifera* and *Thespesia populnea* | SEM, EDX, FT-IR, XRD | 44-97/ Spherical | HepG2 | 5-50 µg/mL | 48 | MTT | The $IC_{50}$ values were 42.16, 28.16, and 26.81 µg/mL for *E. prostrata* AgNPs, *M. oleifera* AgNPs and *T. populnea* AgNPs, respectively. | [69] |
| Khalid et al. 2017 | Microalga/ *Dictyosphaerium* sp. strain HM1 (DHM1), *Dictyosphaerium* sp. strain HM2 (DHM2) and *Pectinodesmus* sp. strain HM3 (PHM3) | TEM, FT-IR, XRD | The DHM1-AgNPs (size: 15-30 nm) and DHM2-AgNPs (size: 40-50 nm) were predominately spherical. However, the PHM3-AgNPs (size: 50-65 nm) appeared spherical to mostly ovoid. | HepG2 | 10-50 µg/mL | 24 | MTT | The $IC_{50}$ values for DHM1-AgNPs, and DHM2-AgNPs were 0.30 and 0.289 µg/mL, respectively. However, for PHM3-AgNPs, no $IC_{50}$ was found up to 50 µg/mL. | [70] |
| Karunagaran et al. 2017 | Bacterium/*Bacillus thuringiensis* SSV1 | UV-vis, SEM, TEM, XRD, FT-IR, EDX | Average: 30/ Spherical | HepG2 | 0.05-1 µg/mL | 48 | MTT | $IC_{50}$: 0.47 µg/mL | [71] |
| He et al. 2017 | Plant/*Cornus officinalis* | UV-vis, FE-TEM, EDX, SAED, XRD, FT-IR, DLS | Average: 11.7/ Quasi-spherical | HepG2 | 5-50 µg/mL | 48 | MTT | $IC_{50}$: 21.46 µg/mL | [72] |
| Gowri Shankar et al. 2017 | Plant/*Trainthema portulacastrum* | UV-vis, XRD, EDX, SEM, TEM, DLS, FT-IR | 11.5-29.2/ Spherical and hexagonal | HepG2 | 50-450 µg/mL | 24 | MTT | $IC_{50}$: 173.8±0.84 µg/mL | [73] |
| Gomaa 2017 | Plant/*Allium cepa* | UV-vis, XRD, FT-IR, TEM, EDX | 10-23/ Spherical | HepG2 | 1.56-50 µg/mL | 48 | MTT | $IC_{50}$: 2.3 µg/mL | [74] |
| El-Hela et al. 2017 | Plant/*Crataegus sinaica* | UV-vis, SEM, TEM, FT-IR | Average: 30/ Spherical | HepG2 | 0.78-100 µg/mL | 48 | Sulforhodamine B (SRB) | $IC_{50}$: 10.2 µg/mL | [75] |
| Bello et al. 2017 | Plant/*Guiera senegalensis* | UV-vis, TEM, FE-SEM, XRD, FT-IR, EDX | Average: 50/ Spherical | HepG2 | 10-200 µg/mL | 48 | MTT | $IC_{50}$: 33.25 µg/mL | [76] |
| Xia et al. 2016 | Plant/*Taxus yunnanensis* | TEM, XRD, FT-IR, Zeta potential | 6.4-27.2/ Spherical | human hepatoma SMMC-7721 | 25-125 µg/mL | 24 | MTT | $IC_{50}$: 27.75 µg/mL | [77] |
| Supraja et al. 2016 | Alga/*Gracilaria corticata* | UV-vis, XRD, SEM, FT-IR, DLS, Zeta potential | 20-55/ Spherical and hexagonal | HepG2 | 0.25-100 µg/mL | 48 | MTT | At 100 µg/mL, 77.4% cell viability was found. | [78] |
| Rajeshkumar et al. 2016 | Bacterium/*Enterococcus* sp. | UV-vis, XRD, SAED, EDX, TEM, FT-IR | 10-80/ Spherical | HepG2 | 1-100 µg/mL | 24 | MTT | $IC_{50}$: 25 µg/mL | [79] |
| Kumar et al. 2016 | Plant/*Rubus glaucus* Benth. | UV-vis, XRD, TEM, DLS, FT-IR | 12-50/Nearly quasi-spherical | HepG2 | 0.01-1 µM | 2 | Cell density change assessment | No cytotoxicity | [80] |
| Jaganathan et al. 2016 | Animal/*Eudrilus eugeniae* (earthworm) | UV-vis, FT-IR, FE-SEM | 4-10/ Predominantly spherical | HepG2 | 1.88-30 µg/mL | 48 | MTT | $IC_{50}$: 25.96 µg/mL | [81] |
| Ebrahiminezhad et al. 2016 | Microalga/*Chlorella vulgaris* | UV-vis, XRD, TEM, FT-IR, TEM, DLS, Zeta potential | Average: 7/ Spherical | HepG2 | 2.35-300 µg/mL | 24, 48 | MTT | A dose- and time-dependent cytotoxicity was found against HepG2 cells. At 4.7 µg/mL, the cell viability was found to be 61 and 37% after 24 and 48 h of incubation, respectively. Besides, a significant cytotoxicity was found at 9.4 µg/mL after 24 and 48 h of incubation. | [82] |
| Castro-Aceituno et al. 2016 | Plant/*Panax ginseng* | UV-vis, FE-TEM, EDX, XRD, SAED, DLS | 5-15/Spherical | HepG2 | 1-40 µg/mL | 48 | MTT | No cytotoxicity was found up to 5 µg/mL. At 40 µg/mL, less than 25% cell viability was found. | [83] |
| Abd-Elnaby et al. 2016 | Bacterium/*Streptomyces rochei* MHM13 | UV-vis, SEM, XRD, FT-IR | 22-85/ Spherical | HepG2 | 1.56-50 µg/Well | 24 | MTT | $IC_{50}$: 32.9 µg/Well | [84] |
| Rathi Sre et al. 2015 | Plant/*Erythrina indica* | UV-vis, FT-IR, XRD, DLS, HR-TEM, EDX | 20-118/ Spherical | HepG2 | 0.625-25 µg/mL | 24 | MTT | A dose-dependent cytotoxicity was found. Besides, at 25 µg/mL, 13.86±0.95% cell viability was found. | [85] |
| Abdel-Fattah et al. 2015 | Plant/<br>a) *Prunus amygdalus* (Almond nut)<br>b) Egyptian blackberry fruit (the scientific name of plant was not mentioned in the article) | TEM, XRD, FT-IR | <100/Nearly spherical, with some non-spherical ones. | HepG2 | 0.78-100 µg/mL | 48 | MTT | Significant dose-dependent cytotoxicity was found. | [86] |
| Inbathamizh et al. 2013 | Plant/*Morinda pubescens* | UV-vis, TEM, XRD, SEM, FT-IR | 20-40/ Spherical | HepG2 | 1.953-1000 µg/mL | 48 | MTT | $IC_{50}$: 93.75 µg/mL | [87] |

### *Exclusion criteria*

The articles that satisfied the following criteria were excluded: i) review articles; ii) editorials; iii) letters; iv) case reports; v) congress abstracts; vi) articles that evaluated the cytotoxicity of chemically or physically prepared AgNPs toward hepatic cancer cells; vii) articles that evaluated the cytotoxicity of biogenic AgNPs toward other cancer cells except hepatic cancer cells.

### *Eligibility assessment*

The assessment of the articles was primarily performed based on their title or abstract according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [50]. The articles which met the eligibility criteria were selected for further second screening by reviewing the articles' full text. Finally, the irrelevant articles were excluded and the articles that satisfied all inclusion characteristics were included into the current study. The eligibility assessments were conducted by two independent researchers to avoid bias. Moreover, the references

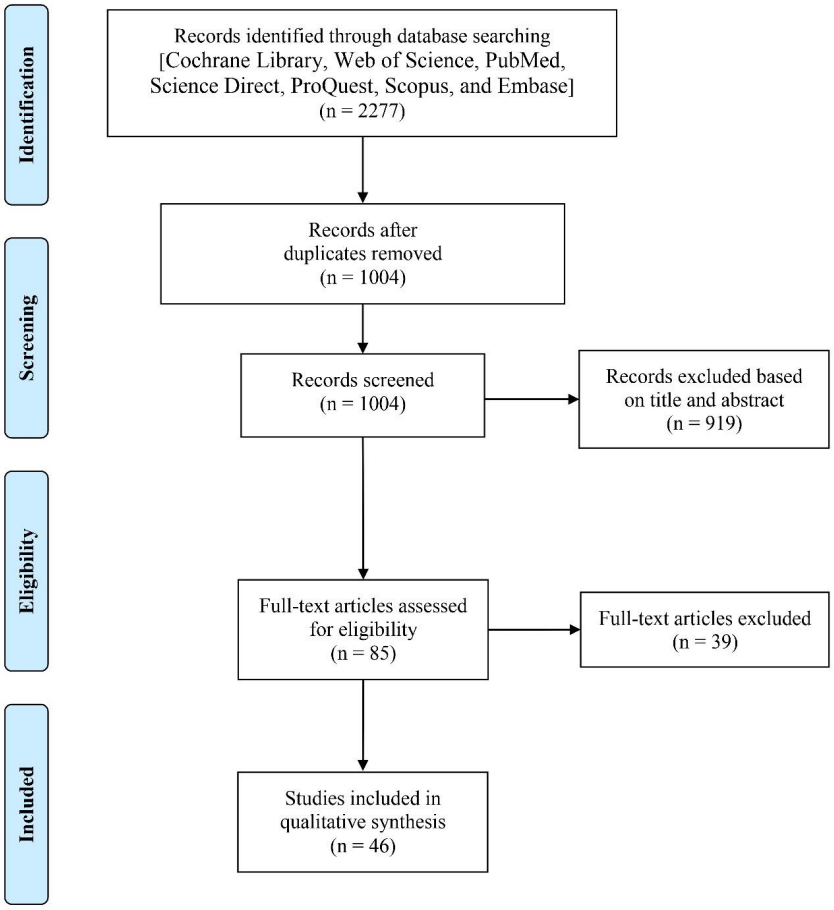


Fig 1. Flowchart describing the study design process

of the final eligible articles were checked for more relevant articles.

### *Data extraction and tabulation*

A data extraction form was designed to collect the desired information from the selected articles. Table 1 represented the data extraction form containing first author, year of publication, a biological source with scientific name, characterization techniques, size (nm), morphology, hepatic cancer cell line, dose, exposure time, cytotoxicity method, and major outcome (Table 1).

## RESULTS

### *Search Results*

In the current study, of 2277 primarily identified records, 1273 records were found to be duplicate. In the first screening, 919 articles were excluded. Besides, in the second screening, 39 articles were excluded. Eventually, 46 articles passed the eligibility assessments and entered into the current study. Fig 1 depicts a flow diagram of the study selection process.

### *Characteristics of included studies*

Various biological sources were used for green synthesis of AgNPs including plants (n=36), algae (n=3), fungi (n=2), bacteria (n=4), and even animals (n=1). However, the general approach referred to herbal-mediated fabrication of AgNPs (78.26% of studies). Besides, all of the studies stated the size distribution of biosynthesized AgNPs below 100 nm with different shapes. Whereas, most studies stated spherical morphology for biogenic AgNPs.

The anticancer studies were performed using different anticancer tests including MTT(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay (n=37), trypan blue exclusion assay (n=3), SRB (Sulforhodamine B) assay (n=3), cell counting kit-8 (CCK-8) assay (n=1), BrdU assay (n=1), and cell density change assessment (n=1). 80.43% of the studies applied MTT assay for AgNPs anticancer assessments.

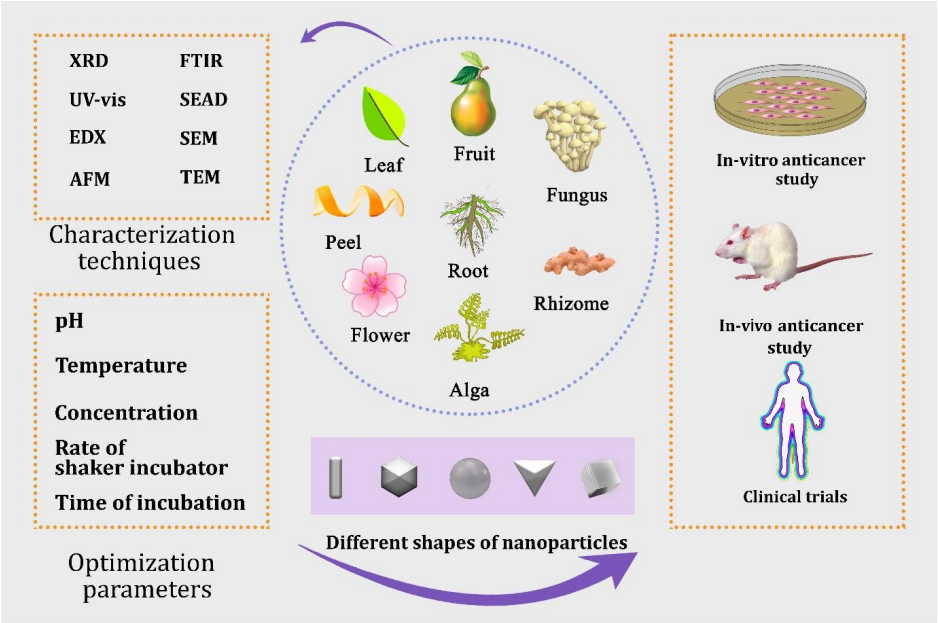


Fig 2. The interface of nature, nanotechnology and hepatic cancer

Moreover, four human hepatic cancer cell lines were used for cytotoxicity evaluations including HepG2 (n=44), HUH-7 (n=1), and SMMC-7721 (n=1). Majority of the studies (91.30%) stated considerable anticancer activity of biogenic AgNPs toward hepatic cancer cell lines. However, 8.7% of the studies stated less or no AuNPs-induced cytotoxicity toward hepatic cancer cell line.

## DISCUSSION

### *Emerging nano-biomaterials: a biosynthetic approach*

Over the last decade, research in the field of nanobiotechnology has been growing significantly. The development of nano-biomaterials and in particular exploring novel routes for biosynthesis of metallic NPs with controlling shape and size for their biological potentials is the major activity [88]. Biological sources have offered an eco-friendly, feasible and reliable alternative to traditional physicochemical procedures for metallic NPs synthesis [89]. In this systematic review, a wide range of natural sources were used for fabrication of AgNPs with different sizes and morphologies. From the pharmaceutical and biomedical aspects, biosynthetic approach for preparation of AgNPs is an ever-growing need owing to the use of biocompatible materials in their synthesis process [30, 90]. Plant-mediated synthesized AgNPs were prepared using Seripheidium quettense aqueous extract in the range of 49.96 to 54.36 nm and spherical morphology [41]. Besides, fungus-mediated synthesized AgNPs were prepared using Piriformospora indica in the range of 6 to 15 nm with spherical shape [48]. Likewise, bacterial-mediated synthesized AgNPs were prepared using Streptomyces sp. with spherical shape and size distribution of less than 100 nm [67]. Moreover, different microalgae including Dictyosphaerium sp., Dictyosphaerium sp. and Pectinodesmus sp. [70] and Chlorella vulgaris [82] as well as a macroalga (Gracilaria corticata) [78] were used as reducing and stabilizing agents for reliable fabrication of AgNPs. Furthermore, AgNPs were fabricated using Eudrilus eugeniae earthworms in the range of 4 to 10 nm with predominantly spherical morphology [81]. In addition to above mentioned plants, microorganisms, and algae, naturally biodegradable components like vitamins and isolated phytochemicals represented sustainable resources for preparation of AgNPs [89, 91, 92]. Fig 2 depicts the interface of nature, nanotechnology and liver cancer.

### *Anti-cancer silver nano-biomaterials to combat hepatic cancer cells*

A wide range of activities were listed in the literature for AgNPs such as anti-bacterial, anti-fungal, anti-inflammatory, anti-viral, and anti-cancer activities [93]. Recently, the anti-cancer

potential of biogenic AgNPs has been highlighted to combat hepatic cancer. In this systematic review, the efficacy of biogenic AgNPs were evaluated toward hepatic cancer cells through in vitro models. Of forty-six articles, forty-two articles stated significant AgNPs-induced cytotoxicity against hepatic cancer cells. Three articles depicted less cytotoxicity and only one article reported no cytotoxic influence against hepatic cancer cells. In a study, the AgNPs were synthesized using two plant extracts Rhus coriaria L. and Carthamus tinctorius L., separately. The AgNPs were fabricated in spherical shape in the range of 22.41 to 37.58 and 14.52 to 35.77 nm with the IC50 values of 720.49±9.89 and 18.24±0.80 µg/mL, respectively. The IC50 values of R. coriaria L. and C. tinctorius L. extracts were found to be 1093.46 ± 11.37 and 202.29 ± 5.35 µg/mL. This finding indicated that the AgNPs synthesized from C. tinctorius L. was highly more cytotoxic than the AgNPs synthesized from R. coriaria L. toward hepatic cancer cells [45]. Besides, the studies showed the time-dependent AgNPs-induced cytotoxicity. In a study, the anti-cancer activity of phytosynthesized AgNPs were evaluated toward HepG2 cells after 24 and 48 h of treatment using MTT assay. The IC50 values were found at 24.5±1.3 and 4.76±1.1 µg/mL after 24 and 48 h of treatment, respectively. This finding shows that the IC50 value dramatically dropped after 48 of treatment [55]. Likewise, in a study, the anticancer activity of herbal-mediated fabricated AgNPs were evaluated against HepG2 cells after 24, 48, and 72 h of treatment. No IC50 was found after 24 h of treatment. However, IC50 values were found at 80 and 64 µg/mL after 48 and 72 h of treatment, respectively indicating time-dependent AgNPs-induced cytotoxicity. The isolated galactomannan did not show any cytotoxicity at the same situation toward HepG2 cells [58]. Furthermore, the studies also reported dose-dependent AgNPs-induced cytotoxicity toward hepatic cancer cells. In a study, the phytosynthesized AgNPs were fabricated in the range of 5 to 15 nm with spherical morphology. The results of cytotoxicity of AgNPs showed no cytotoxicity up to 5 µg/mL after 48 h of treatment using MTT assay. Whereas, more than 75% cytotoxicity was found at 40 µg/mL at the same situation [83]. The anticancer activity of biogenic AgNPs were evaluated against HepG2 cells after 24 h of treatment using trypan blue exclusion assay in the concentrations of ranging from 125 to 1000 µg/mL. At 125 and 1000 µg/mL, around 40 and 80% cell inhibition were found, respectively indicating dose-dependent AgNPs-induced cytotoxicity [40]. In a study, the anticancer activity of chemically and biologically synthesized AgNPs were compared against HepG2 cells. The IC50 values were found at 2.09±1.21 and 2.45±0.62 µg/mL for chemically and biologically synthesized AgNPs, respectively [48]. The AgNPs can be conjugated to other anti-cancer drugs to combat hepatic cancer cells. In a study, epirubicin-capped AgNPs were synthesized using epirubicin as a reducing and capping agent with size distribution ranging from 30 to 40 nm. The epirubicin-capped AgNPs showed significant anticancer activity toward HepG2 cells [94]. Although the current systematic review showed considerable anticancer activity of AgNPs toward hepatic cancer cells, further studies are required to evaluate their efficacy through animal models.

### *Mechanistic approach to anti-cancer activity of silver nano-biomaterials toward hepatic cancer cells*

The exact molecular mechanisms of anti-cancer activity of biosynthesized AgNPs toward hepatic cancer cells have not yet been revealed. It is believed that oxidative stress is the most probable mechanism of AgNPs-induced cytotoxicity [95]. However, it was stated that AgNPs-mediated induction of intracellular ROS overgeneration and ATP synthesis interruption disturb the mitochondrial respiratory chain function resulting in the induction of mitochondrial pathway apoptosis [96]. Moreover, the AgNPs have been shown to induce the inflammatory cytokines such as IL-1, IL-6 and TNF-α. The induction of inflammatory cytokines is directly linked with ROS that may lead to damage to DNA [97, 98]. Depending on the physicochemical properties of AgNPs, intracellular biomolecules interact with AgNPs which may result in different cellular alterations such as mutations, enzyme failure, induction of apoptotic signalling pathways, ionic exchange disorders, etc. [95]. In addition, it was stated that AgNPs cause membrane damage which results in an overload of calcium within the cell with a further ROS generation and apoptosis [99]. The membrane phospholipids contain thiol groups. On the other hand, AgNPs have shown a major affinity to thiol groups. This reason may elucidate the interaction of AgNPs with cell membranes and further membrane damage [100, 101]. Figure 3

illustrated the proposed mechanisms for biogenic AgNPs-induced cytotoxicity through hepatic cancer cells. Padinjarathil et al. studied the molecular mechanisms of anticancer activity of biogenic AgNPs toward HepG2 cells. The expression profile of caspases 2, 3, 8, and 9 assessed by fluorimetry. Caspases 3, 8, and 9 were overexpressed indicating the activation of both intrinsic and extrinsic apoptotic pathways. Because, the activation of caspases is the hallmark of apoptosis. Moreover, the progressive cell apoptotic features were confirmed using phase-contrast microscopy, acridine orange-ethidium bromide staining, and Hoechst 33,342 nuclear staining [58]. Yassin et al. reported that the intracellular Reactive Oxygen Species (ROS) elevated in the HepG2 cells treated with biogenic AgNPs [64]. DNA fragmentation analysis also confirmed the biogenic AgNPs-induced DNA damage in the treated HepG2 cells. In addition, nuclear morphology assay (Hoechst staining) and Rhodamine staining assay confirmed nuclear and mitochondrial fragmentation in the biogenic AgNPs-treated HepG2 cells [68]. In a similar study, the DNA fragmentation, Rhodamine, Hoechst, and AO/EtBr staining assays confirmed biologically synthesized AgNPs-induced apoptosis in HepG2 treated cells [69]. The studies stated that AgNPs-overgenerated ROS in the cells can cause oxidative DNA damage [70].

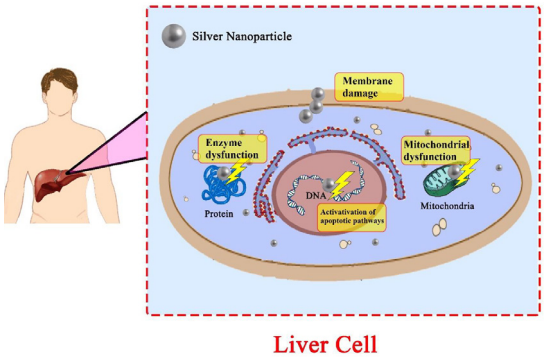


Fig 3. Schematic anticancer mechanisms of biogenic AgNPs

### *Silver nano-biomaterials as future cancer nanomedicine: hurdles and challenges*

The studies for biogenic AgNPs as an anticancer nanomedicine are still at a laboratory setting. In this study, we provided preliminary evidence representing biogenic AgNPs as a promising strategy for hepatic cancer therapeutics based on in vitro investigations. It is noted that in vitro studies are required to begin in vivo studies. However, in vivo studies may show different findings in the future. Because some of the in vivo situations may not be simulated through in vitro studies. For example, when NPs are entered into the biological medium such as blood vessels, the proteins are adsorbed on the surface of NPs called protein corona. The protein corona surrounds the NPs and has a major role in the interaction of NPs with biological moieties. For the case of AgNPs, protein corona may change the surface functionality. The protein corona composition can be changed gradually over time through the body [102, 103]. Hence, the protein corona is a challenge that should be simulated through in vitro studies. The fate of AgNPs in the body should be investigated in future studies. In this systematic review, we showed that different parameters have an influence on anticancer activity of biogenic AgNPs such as size, shape and capping agent. These parameters may also have an influence on the AgNPs-induced side effects through in vivo studies that should be considered in future animal model researches. Remarkably, future studies should reveal the characteristics of biomolecules bound to the outer surface of biogenic AgNPs and their exact role on the anticancer activity of these NPs. Significantly, the studies about the anticancer activity of biogenic AgNPs conjugated with other anticancer drugs may open a new avenue to reduce the required dose of anticancer drugs for therapeutic protocols. Moreover, the anticancer activity of biogenic AgNPs should be studied toward other cancer cells. In addition to AgNPs, gold NPs [104, 105], zinc oxide NPs [106], and selenium NPs [107] were shown as potential metal NPs for hepatic cancer therapeutics through in vitro investigations. Hence, evaluation of the anticancer activity of bimetal NPs through both in vitro and in vivo studies are suggested. Finally, although there are still fundamental issues such as acute and chronic toxicity of biogenic AgNPs that need to be addressed, biogenic AgNPs may emerge as potential hepatic cancer therapeutic agents alone or in combination with FDA-approved anticancer medicines in the future.

## CONCLUSION

The current review represented the significant anticancer activity of biogenic nano-silver particles against hepatic cancer cells. It was shown that the several biosynthesis approaches significantly

affect the cytotoxic activity of the achieved silver nanostructures. The findings revealed that the AgNPs were fabricated with different sizes and shapes and consequently represented different anticancer potentials toward hepatic cancer cells. Most studies stated the in vitro potential of AgNPs to combat hepatic cancers. The molecular studies suggested overgeneration of ROS and oxidative DNA damage as well as apoptosis through AgNPs-treated HepG2 cells. Remarkably, the in vitro anticancer studies are considered as the first step and future studies should be performed to evaluate the efficacy of these NPs through in vivo investigations. In addition, future studies should be conducted to evaluate the efficacy of silver nanostructures as nanocarriers for targeted drug delivery of FDA-approved anticancer drugs. Moreover, many challenges on clinical usages of AgNPs such as genotoxicity, immunogenicity, as well as their release into the environment other than scaling up production should be addressed before clinical trials.

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