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Original article

Antiviral and cytotoxic effects of a traditional drug *KanthaRasaVillai* with a cocktail of metallic nanoparticles

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ABSTRACT

Objective: Alternative medicine plays an important role today in searching for therapeutics for cancer and viral infection. So, a scientific validation to characterize constituents in the alternative medicines and therapeutic testing is warranted using modern instrumentation.

Methods: In the present study, an old herbomineral formulation, KanthaRasavillai [KRV], was characterized using UV–vis spectrometry, FT-IR, XRD, SEM, and TEM study. Also, In vitro and in vivo studies were done to evaluate their antiviral and anticancer activity. FT-IR and XRD studies revealed a cocktail of nanoparticles of mercury, magnetic oxide, cinnabar, and arsenic.

Results.

Based on SEM, TEM, and XRD report, KRV contains nanoparticles in the size range of 9.1 nm to 25.0 nm. FT-IR analysis exposed the presence of several anti-cancerous bioactive compounds.

Further in vitro testing against HCV virus proved KRV to inhibit HCV virus a close relative to SARS-CoV-2. MTT assay confirmed the anticancer effect of KRV against Huh-7 and MCF-7 cell lines.

Conclusion: The anticancer and antiviral properties in the ancient herbomineral drug with a cocktail of metal nanoparticles acknowledge the traditional medical practice as a pioneering approach for present-day ailments. However, the study concludes that the use of KRV depends on safety dosage and genuine preparation as described by ancient saints.

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1. Introduction

Virus infections and cancer inflictions have become a major threat to humanity globally. Though virus infections can lead to cancer development, other etiological agents of unknown origin induce cancer. After the emergence of the Ebola virus, Influenza A virus (H1N1), MERS-CoV, and SARS-CoV and its mutants' threat, intensive search is accelerated to find solutions from different medical systems including alternative, complementary medicine.

The prevailing COVID-19 infection is threatening the lives of several million people globally. Nearly ten million cancer-related deaths are reported in 2020 worldwide (Sung et al., 2021). In the current corona viral pandemic since 2019 December, millions of people have lost their lives. In addition to the chemical intervention, alternative medicine/complementary medical treatments are given importance (Jayashree et al., 2020; Ho et al., 2021). Also, solutions from alternate and complementary medicines are highlighted (Al-Ansari et al., 2021). In searching for alternative medicine for cancer and viral infections, herbomineral/metal preparations proved effective (Sheikh et al., 2012). The herbomineral formulations are products developed using the protocol given by ancient Saints (Kumar et al., 2006). The herbominerals are the adjunct formulation of herbal products and minerals/metals. The toxic mercury, lead, arsenic, and other metals are converted into therapeutically effective formulations. The formulations include Bhasma (Purified incinerated metals/minerals), Churna (Powders), Ghrita (medicated clarified butter), Guggulu (Resins), and Kwath/

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Kashaya (Decoctions), etc. (Janadri et al., 2015; Saper et al. 2008). Several studies, including *in silico* analysis, proved the efficacy of herbomineral preparations against viral infections (Rajput, 2021). Nagabhasma, a herbomineral preparation containing lead in PbO (plumbous oxide), is very effective against many ailments (Garg et al., 2012). The preparation and conversion of metal compounds into herbomineral formulation with nanosized constituents is well explained (Devanesan et al., 2020). Though mercury is a potent neurotoxin, the herbal mineral formulation using mercury is proven to be safe and free from toxicity (Tian et al., 2019). Hua-Feng-Dan (HFD), Chinese medicine with cinnabar (HgS) and realgar (As₄S₄), cured neurodegenerative diseases (Chen et al., 2020). Tamra Bhasma, prepared using copper intended for some human disorders, proved safe and nongenotoxic (Hu et al., 2020). In reality, it is essential to understand how the toxic metals get converted into a therapeutic compound. Ethnobotanical data shows that proven ancient technology transformed the toxic elements into traditional drugs (Alfuraydi et al., 2019). Recent scientific evaluation using advanced instrumentation and pharmacological studies confirmed that the herbominerals prepared from metals are safe if the preparation protocol strictly adheres to the ancient technology (Nirmala and Sridevi, 2021). In the preparation process, plant compounds convert the metals into herbominerals/metals with nanosized particles. Green synthesized metal nanoparticles exhibit antitumor and antiviral activities (Devanesan et al., 2020). Antimicrobial and anticancer properties of *Carica papaya* leaves derived di-methyl flubendazole mediated silver nanoparticles were reported (AlSalhi et al., 2019).

Another herbomineral preparation, Linga chenduram contained nano-form mercury was reported for antiviral effect (Al-Ansari et al., 2021). So, converting metals into nanoparticles with healing action and formulating as herbomineral drugs according to ancient scripts, and evaluating their characteristics for pharmaceutical action could open an avenue for the synthesis of several therapeutic products. With a curiosity to validate the biomedical use of an ancient herbomineral drug preparation, Kantha Rasavillai [KRV], the present study is planned. KRV is a product of mercury [Rasam], cinnabar (Saathilingam), white arsenic (Vellai pashanam), Camphor (Soodan), magnetic oxide of iron (Kaantham), and several other plant compounds.

2. Material and methods

The drug, Kantharasavillai [KRV] in the form of a pill was purchased from an Indian medicine drug store, Gopala Asan drug store, Nagercoil, South India. This druggist prepares the KRV for four generations following the procedure written in ancient palm scripts from the fifth century.

For the preparation of KRV, the druggist uses several metallic contents according to traditional methodology. KRV contains a purified form of Mercury, Cinnabar, Magnetic oxide of iron, and plant products *Piper longum*, *Rubia cordifolia*, *Psoralea corylifolia*, *Embelia Ribes*, and *Piper cubeba*. After detoxifying the metals and purifying the above components were mixed with White arsenic and Camphor. All these ingredients were put together and grounded for four days continuously with little water as required. Using the ground paste, made small balls of KRV [5 g] called KRV villai [pill] are prepared manually and incubated the pills inside paddy grains taken in an earthen pot for four days. After that, the prepared KRV is stored in a clean, air-tight glass container. For the present study, one of our authors collected the drug and brought it to the King Saud University laboratory for further eval-

uation. The drug KRV was subjected to different physicochemical and biomedical evaluations using standard procedures.

2.1. UV-vis spectral analysis

Using UV-vis Spectrum (Hitachi UV-1700 Spectrophotometer, Japan), the elements present in KRV were analysed at the wavelength range from 190 to 600 nm with a bandwidth of 1.0 nm and at a speed of 120 nm/min.

2.2. XRD (X-Ray Diffraction) analysis

To characterize the KRV, X-ray diffractometer [Philips 1710 x-ray diffractometer] operating at 30 kV and 20 mA was used. The pattern was recorded for the angle (2 θ) ranging from 5 to 80° at 3° / second scanning rate.

2.3. SEM with EDAX analysis

Using Scanning Electron Microscope (JEOL-JSM 6390, Japan) and EDX (Energy Dispersive X-ray) by X'Pert Pro X-ray diffractometer (PAN analytical BV), studied the size of the components in KRV.

2.4. FTIR analysis of KRV

The Infrared spectroscopic analysis using a PerkinElmer FTIR with resolution 4 cm⁻¹ in the range of 400–4000 cm⁻¹ was used to identify the chemical components in KRV.

2.5. TEM (Transmission Electron Microscope) analysis

The nature of active particles in KRV was studied using TEM [Tecnai G2 Spirit TEM Thermo Fisher Scientific].

2.6. Anticancer study of KRV

To find out the anticancer potential of KRV, *in vitro* studies were carried out using two human cancer cell lines, human hepatoma cell line (Huh-7) and breast cancer cell lines (MCF-7). The cell lines obtained from Sigma-Aldrich, USA, were inoculated into Dulbecco's modified Eagle's medium [DMEM] with 10% fetal bovine serum and 1% penicillin-streptomycin. The cell lines were sub-cultured in a CO₂ incubator with 5% CO₂, and the cell viability of the cells was checked by trypan blue staining using a hemocytometer. The Cultured cells were seeded onto a 96-well plate [1 × 10⁵ cell/well] and incubated for 24 h at 37 °C. To the cells in the plate, six different concentrations of KRV [(1–100 µg /ml in DMSO (0.2%))] were added and incubated for 24 h. After incubation, the cells were observed under a microscope to analyze the changes in the cells. The experiment was conducted in triplicate, keeping DMSO as a control (0.2%). After incubating the cells with KRV for 24 h, the media was removed from the wells and washed with one × PBS. Then, 20 µL of MTT (5 mg/mL in 1 × PBS) was added to each well and covered the plates with aluminum foil. The plates were incubated at 37 °C with 5% CO₂ for 3–4 h until cells were lysed and purple crystals were dissolved. [MTT is a tetrazolium dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide that gives purple color when insoluble formazan formed]. After removing MTT carefully, the formazan formed was dissolved with the addition of 100 µL DMSO in each well and measured the absorbance spectrum of formazan with purple color at 570 nm. The cell viability was calculated

$$\% \text{ viable cells} = \frac{(abs_{\text{sample}} - abs_{\text{blank}})}{abs_{\text{control}} - abs_{\text{blank}}} \times 100$$

2.7. Antiviral study of KRV

The antiviral evaluation of KRV was carried out using the human hepatitis C viral stain JFH-1, a genotype 2a HCV strain, obtained from the lab of Arumugaswami (Arumugaswami et al., 2008). For the propagation of the HCV virus human hepatoma (Huh) cell line obtained from ATCC was used. According to the previous protocols, HCV was infected with the human hepatoma (Huh) cell line (Arumugaswami et al., 2008; Loutfy et al., 2020). After treating the infected Huh cells with various doses of the KRV [1–100 µg /ml] for an hour *Renilla luciferase*, a reporter of HCV was added. The infected cells with drugs were incubated for an additional 48 h in 96 well tissue culture plates. And the *Renilla luciferase* activity was measured using a *Renilla Luciferase Assay System* kit (Promega). Clean DMSO (drug vehicle) was the control. MTT assay assessed the percent infectivity by calculating the HCV replication ratio between drug-treated and DMSO.

2.8. Statistical analysis

The results were expressed as mean ± standard deviation of three experiments.

3. Results

UV–vis spectroscopy is one of the essential techniques to ascertain the formation and stability of metal nanoparticles in an aqueous solution. The UV–vis spectrum of KRV in the wavelength 190 and 600 nm and the absorption spectra [around 400 nm] confirmed the presence of elemental nanoparticles [Fig. 1].

Powder X-Ray Diffraction (PXRD) study showed that the grain size of particles in KRV ranged from 18.0 nm to 25.0 nm, with an average size of 25.0 nm [Fig. 2]. The XRD pattern of KRV analysed using the JCPDS database showed four major peaks (2θ) to indicate the presence of crystalline elemental cinnabar [26.6], mercury [28.1], arsenic [18.12] and iron oxide [35.5], and low-intensity peaks for other metals.

The elemental composition in KRV identified by EDAX is presented in Table 1. In KRV Carbon [42.86%], nitrogen [12.43%], oxygen [32.79%], iron [3.76%], arsenic [2.08%] and mercury [1.76%] were seen in good proportion and elements like sulphur (S), copper (Cu), iron (Fe), calcium (Ca), chlorine (Cl), silver (Ag) and barium (Ba) were present in a lesser concentration.

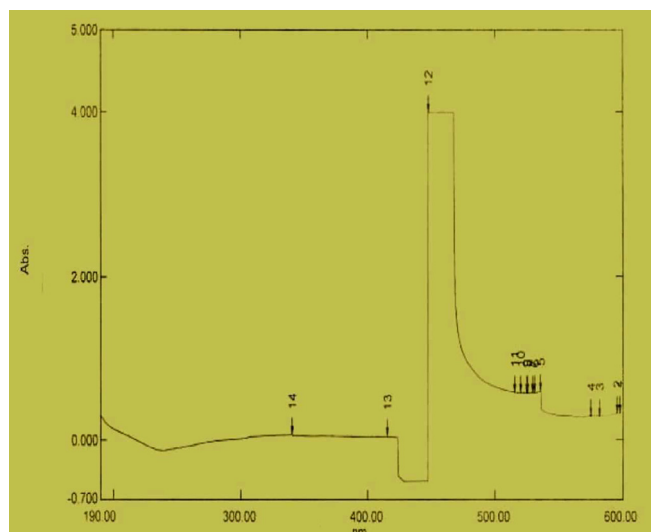


Fig. 1. UV. Vis spectrum of Kantha Rasavillai.

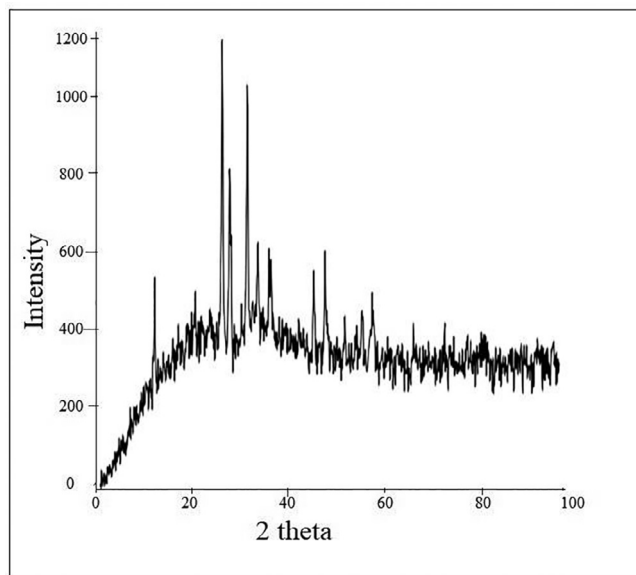


Fig. 2. XRD pattern of Kantha Rasavillai.

Table 1
EDAX data showing the presence of different elements in Kantha Rasavillai.

| Elements Present | KRV | |
|------------------|--------|--------|
| | wt (%) | At (%) |
| C | 42.86 | 53.10 |
| N | 12.43 | 13.21 |
| O | 32.79 | 30.50 |
| Mg | 0.20 | 0.12 |
| Al | 0.28 | 0.15 |
| Si | 0.68 | 0.36 |
| P | – | – |
| S | 0.28 | 0.13 |
| Cl | 0.04 | 0.02 |
| K | 1.11 | 0.42 |
| Ca | 0.49 | 0.18 |
| Fe | 3.76 | 1.00 |
| Cu | 0.94 | 0.22 |
| As | 2.08 | 0.41 |
| Mo | – | – |
| Ag | 0.09 | 0.01 |
| Ba | 0.20 | 0.02 |
| Hg | 1.76 | 0.13 |

The Fourier transform infrared spectrum for KRV [Fig. 3] showed 14 peaks of absorption with different wavenumbers (cm⁻¹). The absorbed frequency (cm⁻¹) and the respective probable functional group were tabulated (Table 2). The main functional groups present in the KRV are alkynes, carboxylic acids, Alkanes, Alkenes, 1° amines, Aromatics Alkanes, Aromatics, Nitro compounds, Aromatic amines, 1° 2° amines, and Alkyl halides.

The SEM image of the KRV showed the predominance of spherical-shaped particles [Fig. 4]. As per the TEM image, the nanoparticles present in KRV were in size range of 9.1 nm to 25.0 nm in [Fig. 5 (a-b)]. The presence of nanosized metal particles in KRV can play a good role in antiviral activity. The metal-based nano theranostics agents are effective antiviral tools against SARS-CoV. As KRV is also a metal-based drug, it can be tried against the present pandemic situation. The recent information about green NPs in carrying the biomedical compounds to the targeted site known to the ancient healers is appreciable. They might have used the metal nanoparticles to carry the plant-based compounds to the targeted sites. However, further study is needed.

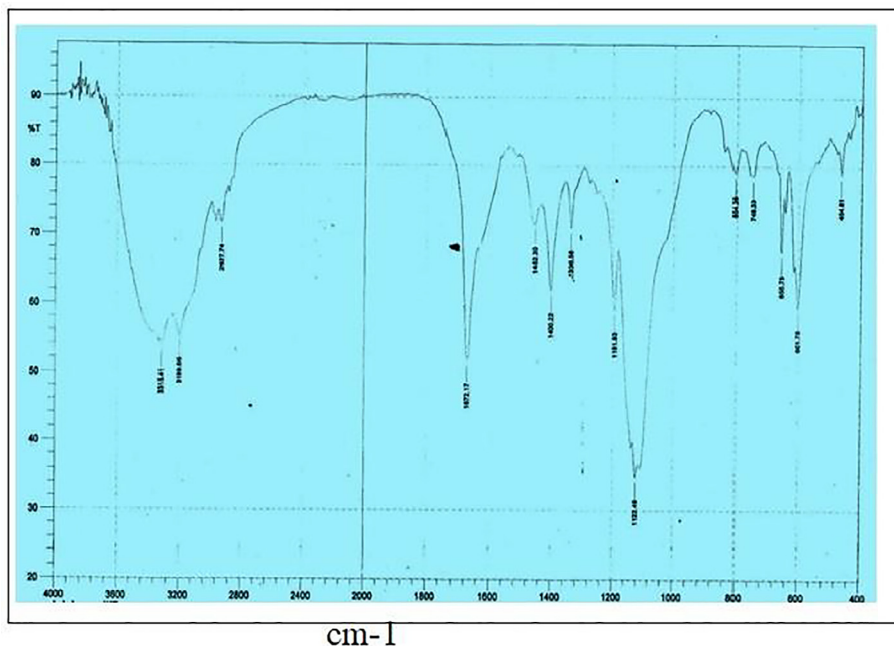


Fig. 3. FTIR image of Kantha Rasavillai showing the different functional groups.

Table 2

FTIR Analysis showing Absorption, Probable Bond and Probable Functional group of Kantha Rasavillai.

| S.N | Absorption cm ⁻¹ (KRV) | Probable Bond | Functional group |
|-----|-----------------------------------|-----------------------|--------------------|
| 1. | 3315.41 | —C≡C—H; C—H stretch | alkynes |
| 2. | 3199.69 | O—H stretch | carboxylic acids |
| 3. | 2927.74 | O—H stretch | carboxylic acids |
| | | C—H stretch | Alkanes |
| 4. | 1672.17 | —C=C— stretch | Alkenes |
| | | N—H stretch | 1° amines |
| 5. | 1452.30 | C—C stretch | Aromatics |
| | | C—H bond | Alkanes |
| 6. | 1400.22 | C—C stretch | Aromatics |
| 7. | 1336.58 | N—O symmetric stretch | Nitro compounds |
| | | C—N stretch | Aromatic amines |
| 8. | 1191.93 | C—N stretch | Aromatic amines |
| 9. | 1122.49 | C—N stretch | Aromatic amines |
| 10. | 804.26 | =C—H bend | Alkenes |
| | | N—H Wag | 1,00 , 2 amines |
| 11. | 748.33 | C—Cl stretch | Alkyl halides |
| 12. | 655.75 | —C≡C—H; C—H bend | alkynes |
| 13. | 601.81 | C—Br Stretch | Alkyl halides |

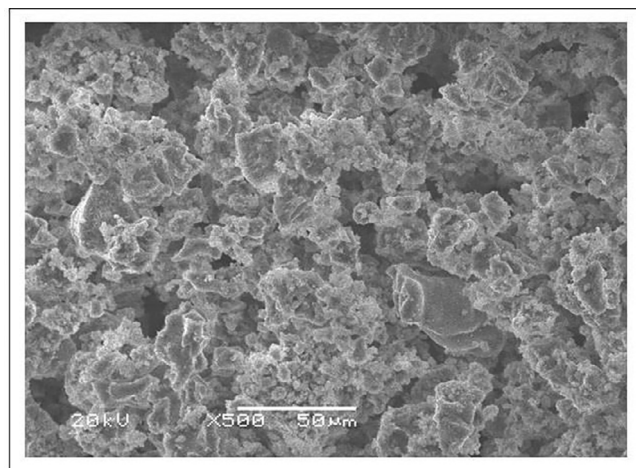


Fig. 4. SEM image of Kantha Rasavillai showing the shape of N.P.s formed.

In the present study, the antiviral potential of KRV was tested using a viral strain, HCV [JFH-1, a genotype 2a HCV strain, based on intra-genotype 2a chimeric HCV]. Hepatitis C Virus (HCV) is an enveloped RNA virus, belongs to the family of Flaviviridae, causing hepatitis C, a harmful liver disease prevalent globally. The KRV showed [Fig. 6] a good antiviral activity in a dose-dependent manner. The percent proliferation of the HCV was $6.2 \pm 0.65\%$ at the high concentration, 10 µg/ml. But at a minimum concentration [1 µg/ml], the proliferation of HCV was $70.5 \pm 0.5\%$. KRV at higher concentrations exhibited a many-fold increase in the inhibition activity.

The cytotoxic effects of different concentrations of KRV on human hepatoma cells (Huh-7) and breast cancer cell lines [MCF-7] determined by the MTT assay show that KRV is a good cytotoxic

agent [Fig. 7]. The cytotoxic effect of KRV on cell viability was concentrations dependent in action. The viability of the Huh-7 tumor cell line was $2.0 \pm 0.5\%$ at 100 µg/ml concentration of the KRV, indicating the inhibition of viability of Huh-7 cells by 98%. In the lowest test concentration, [1 µg/ml], the viability of Huh-7 cells was $60.0 \pm 0.75\%$ indicating a forty percent inhibition compared to control. The anticancer activity of the drug KRV is higher for Huh-7 cell lines than MCF-7 cells. In the lowest [1 µg/ml] concentration of the drug, the inhibition of MCF-cell lines was less, indicating a high survival rate of the MCF-7 cells [64.5 ± 1.0%]. It inhibited 35.5% of the cells. In the same tested concentration [1 µg/ml], the inhibition of Huh-7 cells was $59.9 \pm 0.5\%$ indicating 40.1% inhibition. Similarly, in the concentration, 100 µg/ml of KRV, the viability of MCF-7 cells was $4.5 \pm 0.5\%$ and it was $2.0 \pm 0.0\%$ for Huh-7 cell lines. The observation indicates that the inhibition of Huh-7 cells is more than the MCF-7 cells.

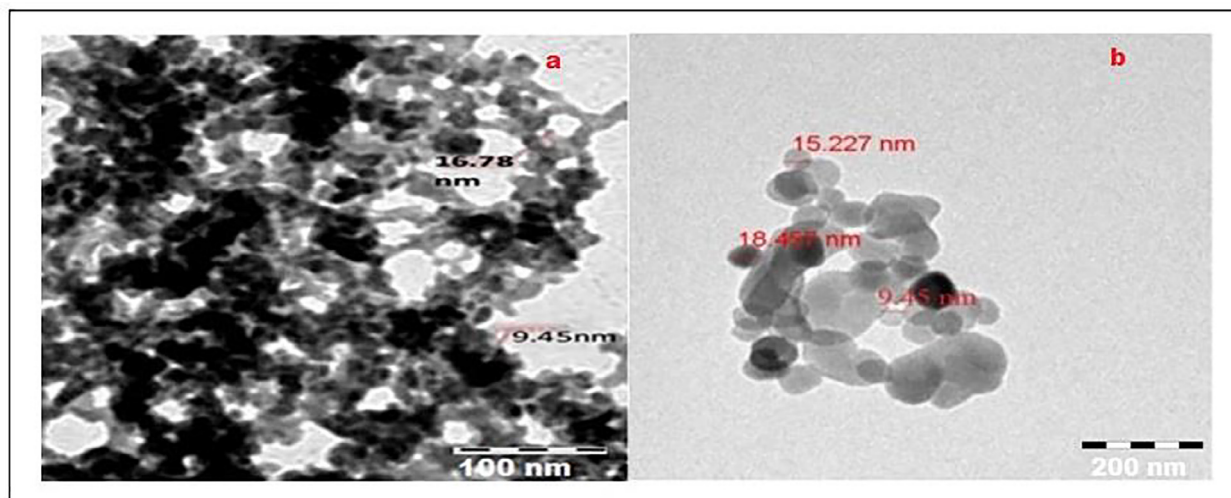


Fig. 5. TEM image of *Kantha Rasavillai* showing the size of nanoparticles.

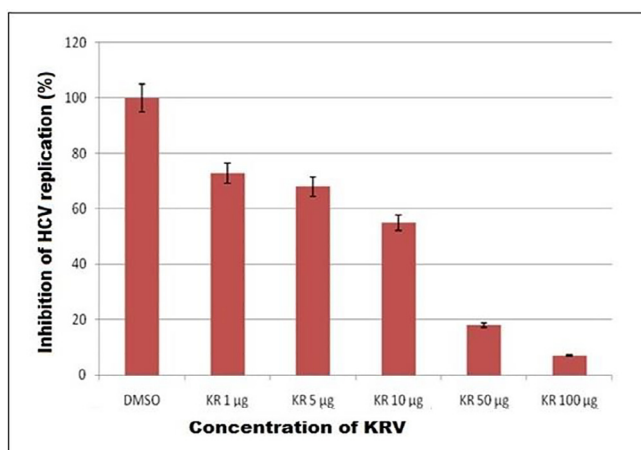


Fig. 6. Anti-HCV activity of *Kantha Rasavillai* showing the dose-dependent inhibition of HCV replication.

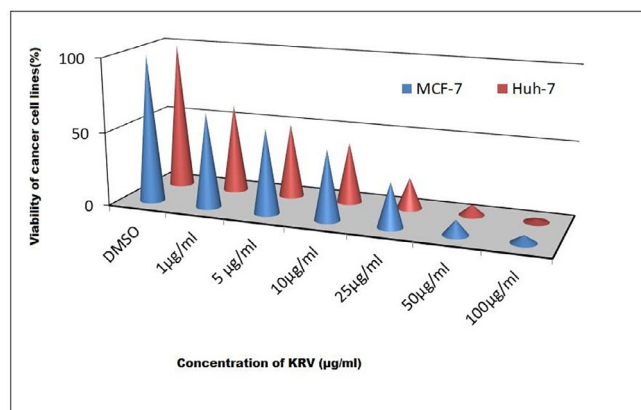


Fig. 7. Cytotoxic effects of *Kantha Rasavillai* on human hepatoma cells (Huh-7) and breast cancer cell lines (MCF-7).

4. Discussion

To prepare KRV, metals like mercury, cinnabar, magnetic oxide, arsenic, and mercuric perchloride were used in nanoform. Using

the technology used by the traditional healers, who lived several thousand years ago, the drug was prepared. According to the ancient protocol, the conversion of toxic mercury into a safe therapeutic drug-using plant extracts is proved in several previous studies (Kiefer et al., 2019). Mukhi et al. prepared a mercury-based drug, Rasasindur, based on the traditional knowledge and found it effective (Mukhi et al., 2017). Gokarn et al. also validated the efficiency of the age-old procedure of converting the toxic element mercury into a drug with antioxidant activities (Arunachalam, 2015). The efficiency of traditional medical formulation to convert metallic compounds into safe herbomineral drugs by removing the toxicity is well proved (Al-Ansari et al., 2021; Sujatha Pushpakanthi Hewageegana et al., 2021).

The absorption band range observed for KRV is similar to previous reports indicating the presence of nanosized particles (Al-Ansari et al., 2021; Srikanth et al., 2014). In an X-ray diffraction study on a herbomineral formulation, Rajat bhasma showed no signature of Rajat bhasma in the spectra because of the non-crystalline nature of the particles in Rajat bhasma. In the present study, the XRD spectrum of KRV showed the presence of their metallic components as reported in other studies (Devanesan and AlSalhi, 2021; AlSalhi et al., 2019).

EDAX provides useful information on the distribution and the chemical form of the elements constituting the sample. The heavy presence of carbon was due to repeated cycles of calcinations in the presence of plant juices, as reported (Al-Ansari et al., 2021; Devanesan and AlSalhi, 2021). The presence of carbon would be responsible for the passivity of the oxide to decrease the toxicity and impart therapeutic value to the iron, arsenic, and mercury present in KRV.

FTIR showed the presence of alkyne compounds [Absorption cm^{-1} 3315.41]. The presence of several bio-organic compounds enhances the stabilization of the nanoparticles in herbomineral KRV and promotes the formation of surface capping in nanoparticles, as reported (Bommagani et al., 2017). Several studies show that alkyne is a macromolecule exhibiting a good anticancer activity (Qi, et al., 2020). Carboxylic acid [$3199.69 \text{ Absorption } \text{cm}^{-1}$] with O–H stretch is also present as per the FTIR report. Carboxylic acid is also an excellent anticancer agent (Kaps et al., 2021). Alkanes reported in the FTIR are organic compounds with single-bonded carbon and hydrogen atoms. The anticancer activity of alkanes is well proved (Shahram et al., 2020). The presence of an alkene moiety between C12 and C13 in Oleanane-Type Triterpenoids nanoformulation is an anticancer compound to activate

apoptosis (Behzadi et al., 2017). The presence of organic compounds like amines, alkenes, alcohols, and phenols, as per FTIR, confirms their roles in fixing the nanoparticles in KRV and exhibiting anticancer activity (Behzadi et al., 2017). The FTIR also showed nitro compounds [N-O symmetric stretch] reported with an excellent anticancer activity (Lopes et al., 2015). The FTIR analysis of KRV also indicates the presence of several organic compounds with proven anticancer activity.

The size and shape of nanoparticles enhance the absorption in the human system to combat cancer. (Kannan et al., 2017; Devanesan et al., 2020). Metal-based nanoparticles are carriers for active antiviral drugs and a diagnostic tool (Mosselhy et al., 2021; Ibrahim Fouad, 2021). As per earlier report reports, the spherical shape and small-sized nanoparticles present in KRV influence anticancer activity (Kannan et al., 2017). The uptake of spherical NPs by cancer cell lines and their trafficking is fivefold higher than rod-shaped NPs (Lee et al., 2019). The predominance of spherical nanoparticles as per SEM image of KRV thereby validates the efficiency of absorption of KRV during treatment. Earlier studies proved that the less sized NPs enhance cellular uptake and cytotoxic action (Lee et al., 2019). In the present study, this has been seen in the TEM image of KRV, showing the size range 9.45–16.78 nm.

The anticancer and antiviral potential of KRV is well proved in the present study. Of the two cancer cell lines tested, the cytotoxic action of KRV was more pronounced in Huh-7 cell lines than MCF-7 cells. The results indicate that the tested drug is a good anti cancerous agent. For both cell lines, a dose-dependent inhibition was found. The output of the present study appreciates the medical knowledge of traditional healers lived several thousand years ago who have formulated nanosized metal particles remedy for many chronic ailments. The herbomineral formulation, Linga chenduram with few elements adjunct with phytochemicals and several other traditional nano formulated herbomineral drugs, shows antiviral and anticancer properties as seen in KRV (Al-Ansari et al., 2021; Ahmadi et al., 2020; Rajput, 2021).

The action of the drug, KRV on the RNA virus, HCV showed a dose-dependent action. At the highest dose, [100 µg/ml] the percentage of HCV inhibition was 98%. The results confirms the antiviral effect of KRV. HCV and SARS-CoV-2 are genetically close because both are positive single-stranded RNA viruses (Jain et al., 2020). Protease inhibitor drugs used for HCV were found effective against SARS-CoV-2 also (Allothaid et al., 2020). So the outcome of the present study opens the avenue for further study to control coronavirus.

Today viral infection is a significant challenge to human health. Hence alternative medicines may be tested to encounter pandemic viral infections. Although many herbomineral formulations like Linga chenduram is reported with an excellent antiviral action (Al-Ansari et al., 2021), it remains unused further to develop antiviral drugs. The phytochemicals resveratrol, and curcumin incorporated in the synthesis of tin oxide nanoparticles [TiO₂NP], functioned as capping and stabilizing agents during synthesis. Such modifications gave a protective effect against DNA damage by TiO₂-NPs (Ahmad et al., 2021a; Ahmad et al., 2021b). The phytochemicals stimulated encapsulation act as capping and stabilizing agents to influence their antiviral effect (Ashutosh et al., 2020). The encapsulation or conjugation of phytochemicals with nanocarriers enhances the drug's bio-efficacy. It also influences gastrointestinal stability, absorption rate, and dispersion (Al-Sheddi et al., 2018). The green synthesized metal NPs are good anticancer agents due to the conjugation of phytochemicals with NPs during synthesis. During green synthesis, the phytochemicals act as a reducing agent to form NPs from metals and get conjugated with NPs for target site delivery. However, the best use of herbomineral as a therapeutic drug depends on the exact formulation protocols and adminis-

tration dose (Sharma et al., 2020a; Sharma et al., 2020b). The present study on KRV, a herbomineral formulation, confirms the composition of metallic NPs and phytochemicals to execute anticancer and antiviral effects.

5. Conclusion

In the present study, experimentations were conducted to evaluate the antiviral and anticancer activity of an ancient drug, KRV, with the combination of metal nanoparticles and plant bioactive compounds. The Kaantharasvillai [KRV] is a cocktail of several metal nanoparticles encapsulated with phytochemicals derived from several plants. The formulated KRV, a herbomineral pill, contained the nanoparticles of mercury, arsenic, magnetic oxides, cinnabar, and mercuric perchloride in a combined form along with plant compounds. *In vitro* testing of the KRV with liver cancer cell lines and HCV virus confirmed their anticancer and antiviral action. The findings conclude that KRV contains a cocktail of metal nanoparticles adjunct with bioactive compounds of plants to execute anticancer and antitumor properties. However, the best use of KRV as a therapeutic drug depends on the exact formulation protocols of ancient healers and the dose of administration. Hence further research is needed in molecular pharmacokinetics and pharmacodynamics.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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