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Original Research Paper

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SYNTHESIS OF 6- GINGEROL GOLD NANOPARTICLES AND THEIR ANTI-CANCER ACTIVITY AGAINST THIOUREA INDUCED THYROID CANCER IN ALBINO RATS

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ABSTRACT Studies have indicated that 6-gingerol, a naturally occurring component of ginger, has been widely reported to possess anti-tumorigenic activities. Nanotechnology has been materialised as a proficient technology for the delivery of anti-cancer drugs. The present research was done to prepare and characterise 6-gingerol tagged gold nanoparticles and find their anti-cancer activity against Thiourea induced cancer in the Thyroid gland. Synthesis of gold nanoparticles was done by standard method. The 6-gingerol was tagged on the prepared gold nanoparticles. The 6-gingerol tagged gold nanoparticle (AuNPs) was possessed to find their anti-cancer activity against Thiourea induced thyroid cancer in experimental rats. Animal studies don't show a significant improvement in the thyroid level, but the histopathological evaluation shows an improvement in the 6- Gingerol coated Gold nanoparticles compared to all other groups. In conclusion, six gingerols coated gold nanoparticles significantly reduced the elevated expression of thyroid cancer in experimental rats.

KEYWORDS : Gold nanoparticles, 6 Gingerol, Thyroid cancer, Thiourea, Albino rats

INTRODUCTION

Cancer is a prominent cause of mortality in India. Cancer is expected to have a point prevalence of roughly 2-2.5 million in India. [1] According to the Government of India's National Cancer Registry Program, males are more likely to get cancer in the oral cavity, lungs, oesophagus, and stomach. At the same time, females are more likely to get cancer in the cervix, breast, and oral cavity. Thyroid cancer is a form of cancer that begins in the thyroid gland's tissues, and cells grow abnormally, potentially spreading to other regions of the body. Neck swelling or a bump are possible symptoms. Cancer may also arise in the thyroid due to metastasis from different places; in this scenario, it is not classed as thyroid cancer. Early radiation exposure, having an enlarged thyroid, and family history are all risk factors. Papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer are the four types of thyroid cancer. Thyroid cancer is the sixteenth most prevalent cancer globally, accounting for around 298,000 new cases in 2012. (2 per cent of the total). [2]

Plants have been utilised in traditional medicine to treat a range of diseases for millennia. 70–95 per cent of the population in underdeveloped nations is predicted to continue to use traditional medicines. [3] Ginger (Zingiber officinale) is a flowering plant whose rhizome, which is sometimes referred to as ginger root or just ginger, is widely used as a spice and folk cure. Ginger is anti-inflammatory, antioxidant, anti-cancer, anti-angiogenesis, and anti-artherosclerotic [4]. Ginger rhizomes are mainly composed of carbohydrates (50–70%), lipids (3–8%), terpenes, and phenolic compounds. Ginger includes terpenes such as zingiberene, bisabolene, farnesene, sesquiphellandrene, and curcumene, as well as phenolic compounds such gingerol, paradols, and shogaol. Additionally, amino acids, raw fibre, ash, and protein are present, including phytosterols, vitamins (such as nicotinic acid and vitamin A), and minerals. The most prevalent bioactive component in ginger was found as 6-gingerol, which has antioxidant, analgesic, anti-inflammatory, and antipyretic activities. While gingerol and its equivalents have a low toxicity profile, they are cytotoxic to various cancer cell types [5].

Traditional cancer therapies such as radiation and chemotherapy have significant side effects since they damage cancer tumours and healthy tissue throughout the body. The use of nanotechnology in cancer therapy has several attractive potential benefits, including the ability to eliminate cancer tumours while causing minimum harm to healthy tissue and organs, as well as the identification and eradication of cancer cells before their formation of tumours. Nanoscale devices are hundreds to thousands of times shorter than human cells yet are comparable in size to significant macromolecules such as enzymes and receptors. Additionally, they may be customised to deliver both medications and imaging probes concurrently and can be constructed to mainly target molecules found in diseased tissues. Gold nanoparticles in chemotherapy and radiation are colloidal gold particles used in therapeutic procedures, most often for cancer or rheumatoid arthritis [6]. Among the several nanomaterials being created for use in nanomedicine, gold nanoparticles (AuNPs) are gaining interest in various fields of study for various reasons. To begin, AuNPs are believed to be more physiologically inert and hence appropriate for in vivo applications in comparison to the very poisonous cadmium and silver NPs6, but the differences are considerable. Thus, the current work was designed to examine the potential applications of 6-gingerol-coated gold nanoparticles to treat cancer-induced endocrine tissue, most notably thyroid cancer.

MATERIALS AND METHODS

Synthesis of gold nanoparticles

An aqueous solution of gold (III) chloride hydrate (HAuCl4.3H2O) was prepared. 5ml of the extract was added to50 ml of 1.0×10-3M HAuCl4 solution at room temperature. Following that, the flask was placed in a shaker (120 rpm) set at 37°C for 48 hours. The extract was dried to powder using a dry vacuum evaporator. This powdered extract is preserved until for use.

Conjugation of 6- gingerol with gold nanoparticle:

Biosynthesized gold nanoparticles were conjugated with 6-gingerol. 4ml of an aqueous solution of gold nanoparticles with a diameter of 10 nm, OD 1, stabilised suspension in citrate buffer (sigma Aldrich product no. 741957) was bought and added to 2 mg of 6-gingerol at room temperature. Following that, the flask was placed in a shaker (120 rpm) set at 37°C. The reaction was carried out for 48 hours. After 48 hours of incubation, the content was transferred to the centrifuge tube for centrifugation at 5000 rpm for 20 min. The pellet was further utilised for studies.

Characterisation of 6- gingerol gold nanoparticle

In order to confirm, the tagged test sample was analysed for

UV- Vis spectroscopy, FTIR, SEM. The reduction of pure Au+ ions was determined by measuring the UV-Vis spectra of a tiny aliquot of the sample diluted in distilled water. UV-Vis spectral analysis was performed between 190 and 1100 nm using a UV-Vis spectrophotometer. The sample was FT-IR spectrophotometrically determined using a Shimadzu FT-IRspectrophotometer. Scanning Electron Microscopicotometer (SEM) examination was performed on the samples using Thermo scientific SEM equipment. Thin films of the selection were created on a carbon-coated copper grid by simply dropping a minimal quantity of the sample onto the grid, blotting away the excess solution with a blotting paper, and then drying the film on the SEM grid 5 minutes under a mercury lamp.

Anti-cancer activity of 6- gingerol gold nanoparticle
Experimental Design:

Albino Wistar rats weighing around 125-250 grams were used in this investigation. Two weeks were spent procuring and acclimating the rats to our laboratory surroundings. Experiments were done under the guidelines established by the Committee for the Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India, and the study was authorised by the Institutional Animal Ethics Committee. The animals were classified into seven distinct groups:

Group No	Group Name	Group description
Group I	Control Group	The rats received typical saline 1ml/100gm BW/day for 180 days and used as control.
Group II	Thiourea Group-	The animals were injected Thiourea 1.0mg/100g BW/day twice a week for 90 days intraperitoneally.
Group III	6-Gingerol Group -	The animal was injected 6-Gingerol alone 0.5mg/100g BW/ day, twice a week for 90 days intraperitoneally.
Group IV	Thiourea + 6-Gingerol -	Treatment of Thiourea induced rat using 6-gingerol 0.5mg/100g BW/day, twice a week for 90 days intraperitoneally.
Group V	Thiourea + Gold Nano-particles	Treatment of Thiourea induced rat using gold nanoparticles 0.1ml/100g BW/day, twice a week for 90 days intraperitoneally.
Group VI	Thiourea+ 6-Gingerol coated Gold nano-particles	Treatment of Thiourea induced rat using 6- gingerol coated gold nanoparticles 0.1ml/100g BW/day, twice a week for 90 days intraperitoneally.
Group VII	Thiourea + Anti-cancerous drug (5-Fluorouracil)	Treatment of Thiourea induced rat using 5-FU (Fluorouracil) 0.1ml/100g BW/day twice a week for 90 days intraperitoneally.

After therapy, animals were decapitated. A cardiac puncture was used to obtain blood. The serum was isolated and kept at -20 °c until analysis, at which point it was utilised for hormonal assay analysis. The animals were dissected, and the thyroid glands were removed and cleaned of adherent connective tissues and bloodstains, rinsed three times in cold physiological saline, blotted on filter paper, and weighed using an electronic scale, wrapped in aluminium foil, and kept at -20°C in airtight glass containers until biochemical parameters were determined. A small piece of the thyroid was fixed in formaldehyde for histological sections, and the histological method of Bancroft and Stevens [7] was followed. The slides were observed under a Leica microscope, and microphotography obtained.

RESULTS AND DISCUSSION

The study was to tag the bioactive component 6 gingerol with a gold nanoparticle. The tagging was made, and the pellet (tagged test sample) obtained was vacuum dried and further used for studies. To confirm, the tagged test sample was analysed for UV- Vis spectroscopy, FTIR, SEM.

UV-Vis spectroscopy shows the absorption of wavelength close to 278nm for six gingerol and band shifts to 510nm due to tagging of gold nanoparticle (fig 1). Usually, the SPR (Surface plasma resonance) bands centred between 500 – 600nm confirms the formation of GNPs in the solution. The FTIR spectrum of 6 gingerols tagged gold nanoparticles shows the characteristic absorption bands that occur close to 3451cm−1 corresponds to o-H; stretching vibrations of phenol and carboxylic acid indicates the tagging of gold nanoparticle to 6 gingerols (fig 2). According to the references, o-H stretch usually occurs at 3700cm-1for 6 gingerol. The presence of C=O stretching occurs to 1637.85 cm-1 indicates the presence of 6 gingerols in the combination. SEM analysis of the Tagged AuNPs revealed the formation of well-dispersed gold nanoparticle size from 100 nm to the maximum to 500nm (in figure no.3).

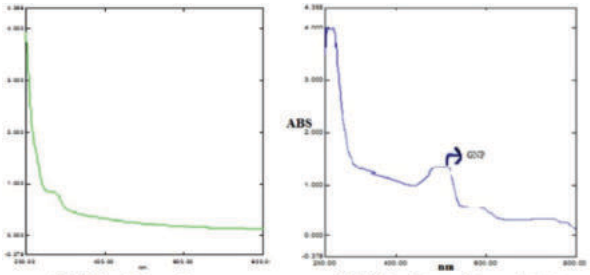

Fig 1: UV-Vis spectroscopy

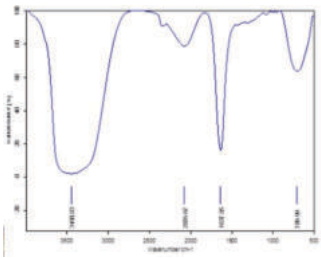

Fig 2:FTIR spectrum of 6 gingerol AuNPs

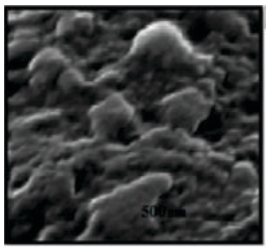

Fig 3: SEM analysis of 6-gingerol AuNPs

Table 2: Effect of 6-Gingerol and 6-Gingerol coated gold nanoparticle on Thiourea induced Thyroid hormonal assays

Group name	Group details	Thyroid function test		
		T3	T4	TSH
		ng/dl	ng/dl	ng/ml
G1	Normal	109	4.7	2.0
G2	Thiourea induced rat	67	2.2	3.6
G3	6-Gingerol alone	78	1.7	2.3
G4	Thiourea + 6-Gingerol	98	2.8	1.6
G5	Thiourea + gold Nano-particle	105	4.3	2.2
G6	Thiourea + 6-Gingerol coated gold nano- particle	91	1.5	3.6
G7	Thiourea + positive control	80	3.2	2.6

It is well established that certain compounds which are derivatives of either aniline or Thiourea will prevent the formation of thyroxine by the thyroid gland and, as a result, the thyroid hypertrophies due to the compensatory action of the thyrotropic hormone of the anterior pituitary gland [8]. Our study doesn't show a significant improvement in the thyroid level.

As the other studies indicate, administration of 6-Gingerol may lead to decreased thyroid hormone synthesis.

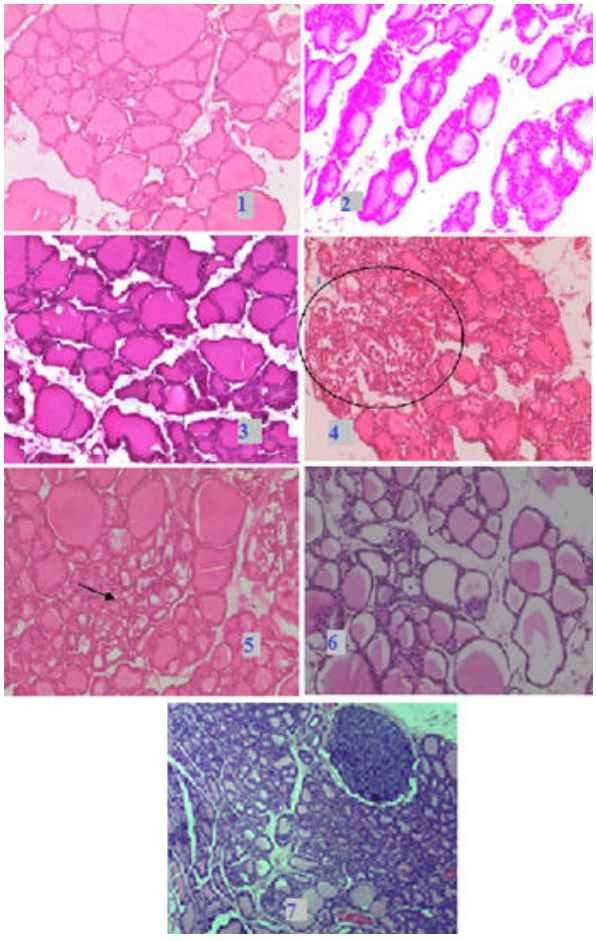

Fig 1: Histopathology of cancer-induced thyroid cells

Histopathology of the average rat shows a normal thyroid follicle with a normal colloid. No abnormality in follicular and parafollicular cells. But the Thiourea induced rat shows a loss of standard follicular shape, and many follicles are devoid of colloid formation. Multifocal areas of necrosis with focal inflammatory cell infiltration and total loss of common follicular form and loss of colloid. The 6-Gingerol alone given rat shows no significant pathological lesions found- Each follicle is lined with cuboidal epithelial cells enclosing an internal lumen occupied with homogeneous colloid. Thiourea induced 6-Gingerol treated rat shows a focal degeneration exhibited with colloid depletion in follicles, Partial loss of architecture and coalescence with adjacent follicles evident. Thiourea caused gold nanoparticle treated groups shows focal C cell hyperplasia and multifocal areas of degeneration, with some follicles showing scanty colloid observed many follicles expressing colloid filled appearance. Thiourea and 6-Gingerol coated Gold Nano-particle treated group has a regular follicle shape filled with insufficient colloid observed. No significant pathological lesions found in this group. Thiourea and positive control (5- Fluorouracil) treated groups shows several adenomatous nodules in the slide seen in the margin. Loss of architecture and coherence with adjacent follicles observed neoplasia is also evident.

Ginger and its bioactive molecules effectively control the extent of colorectal, gastric, ovarian, liver, and skin cancers [9]. Mechanisms of action of the major bioactive component [6]-gingerol for targeted cancer therapy include apoptotic potential, inhibition of NF-κB activation, inhibition of cell adhesion invasion motility and activities of MMP-2 and MMP-9, TRAIL-induced NF-κB activation, and inhibition of LTA (4) H activity [10]. Six -gingerol suppresses the transformation, hyper-proliferation, and inflammatory processes which are linked with the development of carcinogenesis, angiogenesis and metastasis.

CONCLUSION

The synthesis of gold nanoparticles was achieved and standardised by UV- Vis spectroscopy, FTIR, SEM analysis. The research work proves that the 6-Gingerol has an anti-cancer activity; it effectively manages thyroid cancer. The anti-cancer activity can be improved by delivering 6-Gingerol coated gold nanoparticle. This biosynthesis of 6-Gingerol coated gold nanoparticle was easy and eco-friendly; hence synthesised nanoparticles were more efficient in the biomedical applications in cancer treatment for their high anti-cancer activity.

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