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RESEARCH PAPER

Therapeutic Potential of Green Tea Extract in Counteracting Gold Nanoparticle Damage on Ovarian Tissues of Adult Sprague Dawley Rats

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ABSTRACT

This study aimed to elucidate the effects of gold nanoparticles (AuNPs) on ovarian tissue and assess the protective role of green tea extract in adult female Sprague Dawley (SD) rats. A total of 32 subjects were divided into four experimental groups: a control group with no treatment, an AuNPs group receiving 200 mg/kg/day, a green tea extract group with a daily dosage of 10 ml/kg, and a combined treatment group receiving both AuNPs and green tea extract. Post a 28-day treatment period, the AuNPs group demonstrated a stark reduction in ovarian volume metrics compared to control, with the total ovarian volume dropping to 1.32 ± 0.14 μm^3, cortical volume to 0.99 ± 0.10 μm^3, and corpus luteum volume to 0.08 ± 0.04 μm^3. In contrast, the combined treatment group displayed a pronounced compensatory effect with increased total ovarian volume (2.83 ± 0.44 μm^3), cortical volume (2.26 ± 0.41 μm^3), and corpus luteum volume (0.67 ± 0.09 μm^3). The combined therapy also led to a significant increase in mean oocyte volume across various follicular stages, mirroring the control group's metrics. Furthermore, the green tea extract group alone showed elevated oocyte volume, suggesting its stimulatory impact on follicular development. The findings underscore green tea extract's mitigating response to the deleterious effects of AuNPs on ovarian morphology, highlighted by statistical significance ($p<0.01$) across numerous parameters including volumes of the ovary, cortex, medulla, and corpus luteum, as well as oocyte and nucleus volumes. The study presents strong evidence of green tea extract's potential as an ovario-protective agent against nanoparticle-induced toxicity, suggesting its value for future clinical applications in reproductive health.

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INTRODUCTION

The swift advancement of nanotechnology has led to the proliferation of materials with nano dimensions across a vast array of applications. Among the myriad of nanoparticles, gold nanoparticles (AuNPs) have emerged as particularly prominent, owing to their unique properties such as high surface-to-volume ratio, optical characteristics, and chemical stability [1–3]. These characteristics make AuNPs exceptionally versatile and valuable in a multitude of fields, including biomedicine, electronics, catalysis, and materials science.

For instance, in therapeutics, AuNPs have shown promise in enhancing wound healing and burn treatment through their incorporation into dressings, promoting faster tissue repair and regeneration [4]. In the domain of oncology, AuNPs are used to improve the efficacy of cancer therapies [5]. They can be engineered to target tumor cells specifically, allowing for precise drug delivery or enhancing the effectiveness of radiation therapy by localizing energy deposition within malignant tissues, thereby minimizing damage to healthy surrounding cells [6]. Dental applications also benefit from AuNPs. They are utilized in the formulation of coatings for dental implants, contributing to better biocompatibility and reduced risk of infection. Moreover, AuNPs are used in dental restorative materials due to their antibacterial properties and aesthetic advantage, as they can be designed to mimic the natural color of teeth [7,8].

In diagnostics, AuNPs are a cornerstone in the development of advanced biosensors, enabling the sensitive and rapid detection of biomarkers for various diseases. These biosensors can greatly improve early diagnosis, which is critical for effective treatment outcomes [9–11]. Additionally, because of their biocompatibility and non-toxic nature, AuNPs offer a promising alternative for drug delivery systems. They can be tailored to carry therapeutic agents, including small molecules, peptides, or nucleic acids, directly to specific sites within the body, thereby reducing systemic side effects and improving treatment efficacy [12–14].

The AuNPs, while considered relatively biocompatible, can also have potential cytotoxic effects, and their interactions with biological systems are a focus of ongoing research [15–17]. The AuNPs can induce the production of reactive oxygen species (ROS), leading to oxidative stress within cellular environments. The generation of ROS can result in a variety of cellular damages, such as DNA fragmentation, disruption of cellular signaling pathways, alterations in gene expression, and overall cellular dysfunction [18].

Furthermore, AuNPs can influence cell viability by affecting cell proliferation, potentially leading to cell cycle arrest, apoptosis (programmed cell death), or necrosis (uncontrolled cell death), depending on concentration, size, shape, and surface chemistry of the nanoparticles [19]. The cytotoxicity of AuNPs can have systemic implications, potentially impacting vital organs such as the liver and kidneys, which are instrumental in metabolizing and excreting foreign substances, including nanoparticles [20]. Exposure to AuNPs may lead to a buildup in these organs, causing inflammation and cellular damage. Respiratory exposure to AuNPs is also a concern, as inhalation can lead to accumulation in the lungs, causing pulmonary inflammation or fibrosis [21]. Considering that the ovary, akin to other organs, is vulnerable to harm from the toxicity of AuNPs, numerous studies have been undertaken to understand the accumulation of these particles in the ovary and the subsequent insufficiency it may cause [22–24].

Green tea, derived from the *Camellia sinensis* plant, is a widely consumed beverage with an array of health benefits attributed to its rich content of bioactive compounds [25]. An evergreen shrub or small tree from the family *Theaceae*, green tea leaves contain a diverse composition of phytochemicals including catechins (such as *epigallocatechin-3-gallate* [EGCG], *epicatechin*, *epicatechin-3-gallate*, and *epigallocatechin*), flavonoids, phenolic acids, amino acids (such as *theanine*), caffeine, and a variety of vitamins, minerals, and trace elements like manganese, potassium, calcium, magnesium, and fluoride [26].

EGCG is considered the most significant and abundant active compound in green tea extract and has been extensively studied for its pharmacological properties. Green tea extract and its constituents, particularly catechins, demonstrate a wide spectrum of therapeutic qualities, encompassing antioxidant activity, immunomodulatory effects, antiviral and antimicrobial properties, anti-cancer potential, hepatic protection, cardiovascular benefits including blood pressure reduction, anti-asthmatic effects, anti-diabetic functions, anti-inflammatory properties, and neuroprotective impacts [27].

Additionally, green tea has been associated with various metabolic benefits, such as aiding in weight management, improving digestion, and offering protective effects against neurodegenerative diseases. The high level of antioxidants in green tea can also contribute to overall well-being, promoting skin health and possibly delaying signs of aging due to its anti-aging properties [28,29]. This study aims to determine the effect of green tea extract on the effects of AuNPs on the ovarian tissue of Sprague Dawley (SD) rats.

MATERIALS AND METHODS

This study was carried out in full accordance with the ethical guidelines set by the Animal Care Committee, ensuring the highest standards of animal experimentation ethics were upheld. The experiment involved 32 adult female Sprague Dawley (SD) rats, which were accommodated in the specialized Animal House Unit at the Iraqi Center for Genetics and Cancer Research. The rats were provided with an environment that was optimized for their well-being, with a stable temperature of 23 ± 1°C and a balanced light-dark cycle of 12 hours each. The SD rats had unrestricted access to food and water throughout the study.

Before the experimental procedures began, a two-week acclimation period was observed to allow the rats to adjust to their new environment and minimize stress. The SD rats were carefully divided into four distinct groups, each consisting of five rats (n=8). The groups were allocated as follows [30–32], the first group served as the control and did not receive any treatment. The second group was treated with AuNPs, receiving a daily dose of 200 mg/kg administered via gavage. The third group was given a daily dosage of 10 ml/kg of green tea extract, also administered via gavage. The final group received a combined treatment of both AuNPs and green tea extract, with the dosages and administration method consistent with the individual treatment groups.

The SD rats underwent a treatment regimen spanning 28 days, with treatments administered at 24-hour intervals. Following the completion of this phase, the rats were first anesthetized using diethyl ether to ensure a painless procedure. A careful dissection was then carried out, during which the left ovaries were extracted with precision. The extracted ovaries were weighed to document their mass, providing crucial data for the study. To preserve their structural integrity for subsequent analysis, the ovaries were immediately placed in Bouin solution.

After a fixation period of 18 hours, the tissue samples were subjected to a series of meticulous processing steps. This included the transition of tissue through various stages and the creation of paraffin blocks using cylindrical molds. These procedures were executed in strict accordance with the principles of Independent Uniform Random (IUR) sectioning [33]. This method, renowned for its capacity to produce sections that are random across all three planes, is particularly invaluable in the realm of stereological studies.

This involved a two-step randomization process using ϕ and θ coordinates. Each ovary was placed on the ϕ coordinate system, represented as a clock face. A random number between 0 and 9 was selected from a numerical table to determine the cutting angle. Based on this number, the ovary was bisected, resulting in two separate pieces. The first piece of each ovary was then aligned on the θ clock, ensuring the cut surface was parallel to the 0-0 axis of this coordinate system. Another random number was chosen, and the tissue was sliced again along this second number. The tissues were then sectioned using a microtome into slices of 5- and 20-microns thickness. These sections were placed on slides and subsequently

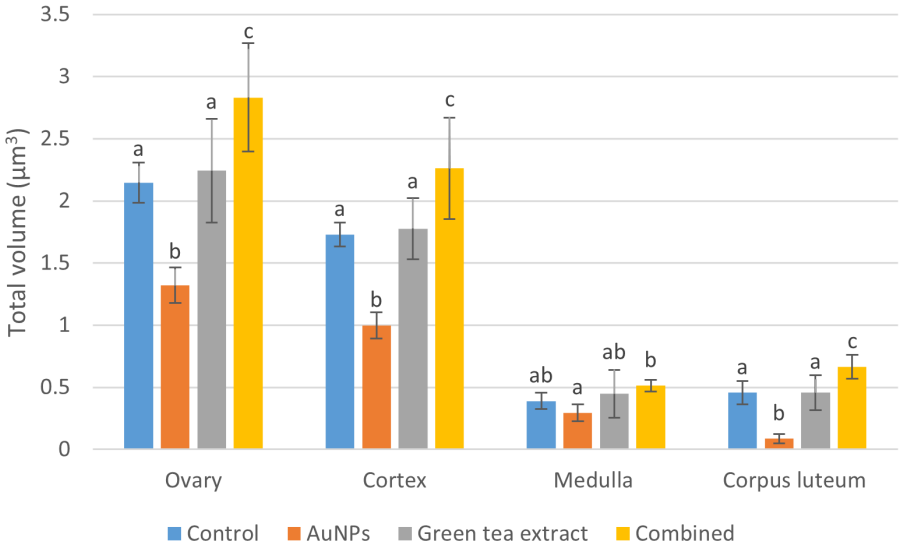

Fig. 1. Comparison of the mean volumes of the total ovary, cortex, medulla, and corpus luteum (µm3) across different SD rat groups, 28 days post-treatment with AuNPs (200 mg/kg/day) and green tea extract (10 ml/kg/day).

underwent staining using Hematoxylin and Eosin (H&E) method, which involved placing the slides in special staining baskets for coloration.

Several key measurements were taken from the ovarian samples. The total volume of the ovary, as well as the volumes of the cortex and medulla, were calculated using the Cavalieri method [34]. In addition, the volume of the corpus luteum was also determined using the same method. The volume of the oocyte and its nucleus in various types of ovarian follicles were measured using the nucleator method. Lastly, the number of different types of ovarian follicles was determined using the disector method [35]. This method is a stereological technique that provides unbiased estimates of cell numbers within a defined volume.

The data obtained from the study were rigorously analyzed using SPSS 23.0 software. The statistical tests employed included one-way ANOVA and the Tukey Test. These tests were used to compare the means of the different groups and identify any significant differences. A p-value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

The study revealed a significant reduction in the mean total volume of the ovary, the volume of the cortex, and the volume of the corpus luteum in mice treated with AuNPs compared to the control group ($p<0.01$). Interestingly, when comparing the simultaneous treatment group (those treated with both AuNPs and green tea extract) to the group treated solely with AuNPs, there was a notable increase in the average total ovarian volume, cortical volume, and corpus luteum volume ($p<0.01$). This indicates that the combination of AuNPs and green tea extract may counteract some of the effects of AuNPs alone, leading to an enhancement in these specific ovarian parameters (Fig. 1).

The study observed a significant decrease in the average number of primordial, primary, secondary, and tertiary follicles in the group treated with AuNPs when compared to the control group ($p<0.01$). However, in the group that received simultaneous treatment with AuNPs and green tea extract, this reduction in follicle numbers was significantly compensated ($p<0.01$). The follicle count in this group was comparable to that of the control group, indicating that the combined treatment may counteract the inhibitory effects of AuNPs on follicular development.

Furthermore, the group treated with green tea extract alone exhibited a significant increase in the average number of primordial, primary, secondary, and tertiary follicles compared to the control group ($p<0.01$). This suggests that green tea extract may have a stimulatory effect on follicular development (Fig. 2).

The mean oocyte volume in primordial, primary, secondary, and tertiary follicles in the group treated with AuNPs was significantly reduced compared to all other groups ($p<0.01$). In the group that received simultaneous treatment with AuNPs and green tea extract, this reduction was significantly compensated, bringing the mean oocyte volume back to the level observed in the

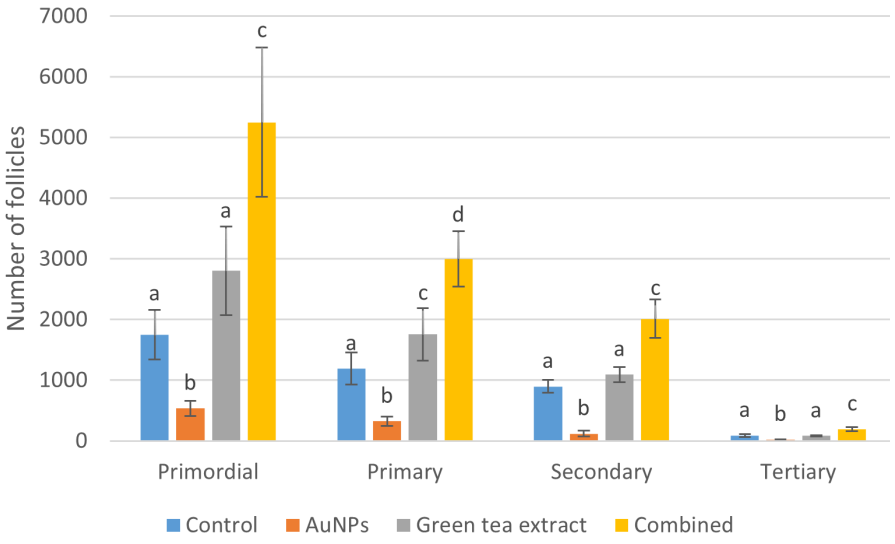

Fig. 2. Comparison of the mean number of primordial, primary, secondary and tertiary follicles across different SD rat groups, 28 days post-treatment with AuNPs (200 mg/kg/day) and green tea extract (10 ml/kg/day).

control group ($p<0.01$)). Furthermore, the mean oocyte volume of the aforementioned types of follicles increased significantly in the group treated solely with green tea extract, compared to the control group ($p<0.01$) (Table 1).

The mean volume of the oocyte nucleus in primordial, primary, and secondary follicles in the group treated with AuNPs was significantly reduced compared to the control group ($p<0.01$). In contrast, a significant increase was observed in the average volume of oocytes nucleus in the green tea extract group compared to the control group ($p<0.01$). In the group that received simultaneous treatment with AuNPs and green tea extract, the decrease in the volume of the oocyte nucleus in primordial, primary, and secondary follicles observed in the AuNPs group was significantly compensated, returning to the levels observed in the control group ($p<0.01$) (Table 2).

The results of this study provide compelling evidence that green tea extract can help mitigate AuNPs-induced damage to ovarian tissue in adult female SD rats. Specifically, the data demonstrates that administering green tea extract concurrently with AuNPs significantly preserves ovarian morphological parameters including total ovarian volume, cortical volume, medullary volume, and corpus luteum volume compared to treatment with AuNPs alone (Fig. 1). These findings align with previous research which has established the antioxidant and protective capacities of green tea extract against nanoparticle toxicity. For example, a study found that green tea extract alleviated testicular tissue impairment triggered by silver nanoparticles in Wistar rats, indicated by improved sperm parameters [18]. The researchers attributed these beneficial impacts to the free radical scavenging abilities of green tea extract catechins including EGCG.

In the current study, morphological analysis further revealed a drastic decline in the number of ovarian follicles across all developmental stages, primordial, primary, secondary and graafian upon AuNPs treatment relative to control animals (Fig. 2). This aligns with earlier reports demonstrating the suppressive effect of nanoparticles like silver and titanium dioxide on folliculogenesis [25,28,31]. However, green tea extract co-administration was notably effective in recovering follicular abundance, restoring it to levels comparable to the control group. Green tea extract supplementation alone also elicited significant improvement beyond the control baseline. The oocyte and nuclear volumes within follicles exhibited similar patterns among groups (Table 1 and 2).

These enhancements in morphological and quantitative traits could be attributed to the

Table 1. Comparison of the mean volume of oocytes (μm^3) in primordial, primary, secondary and tertiary follicles across different SD rat groups, 28 days post-treatment with AuNPs (200 mg/kg/day) and green tea extract (10 ml/kg/day).

Groups	Primordial	Primary	Secondary	Tertiary
Control	1771.23 ± 145.11a	62529.48 ± 481.27a	92725.13 ± 3600.93a	187217.98 ± 8311.55a
AuNPs	1375.47 ± 85.18b	4346.04 ± 340.48b	72990.07 ± 4705.97b	137169.04 ± 37088.95b
Green tea extract	1757.28 ± 84.06a	6010.98 ± 631.88a	85876.88 ± 5991.07ab	167242.42 ± 7852.99ab
Combined	2098.26 ± 279.90c	7893.07 ± 1707.64c	133621.92 ± 22883.60c	227244.33 ± 14744.00c

Table 2. Comparison of the mean volume of oocytes nucleus (μm^3) in primordial, primary, secondary and tertiary follicles across different SD rat groups, 28 days post-treatment with AuNPs (200 mg/kg/day) and green tea extract (10 ml/kg/day).

Groups	Primordial	Primary	Secondary	Tertiary
Control	433.11 ± 29.22a	892.95 ± 40.30a	4366.68 ± 239.05a	6429.93 ± 352.98a
AuNPs	301.14 ± 3.76b	753.01 ± 27.98b	3568.52 ± 151.22b	5534.63 ± 279.96b
Green tea extract	422.01 ± 17.92a	865.40 ± 78.79a	4065.27 ± 426.87a	7242.24 ± 411.54c
Combined	515.49 ± 36.78c	1143.27 ± 100.56c	6204.59 ± 679.83c	9797.65 ± 746.62d

antioxidant and free radical quenching properties of green tea extract polyphenols like EGCG [32]. By mitigating nanoparticle-mediated oxidative damage, green tea enables preservation of ovarian tissue architecture. The stimulatory effect of green tea extract on follicular development observed here corroborates past studies which have suggested green tea supports female reproductive parameters through multiple mechanisms, enhancing ovarian angiogenesis, blocking pathways triggering follicular atresia, stimulating granulosa cell proliferation etc. [15].

Thus, this study provides robust evidence that green tea extract holds immense promise as a protective agent against ovarian perturbations induced by AuNPs specifically, and potentially nanomaterials in general. The ability of green tea extract supplementation to rescue morphological, histological and quantitative ovarian traits from AuNPs-mediated toxicity bears noteworthy clinical relevance. These findings merit further investigation to enable translational applications promoting female reproductive health against increasing nanoparticle exposures.

CONCLUSION

This study provides compelling evidence supporting the promise of green tea extract as an ovario-protective agent capable of mitigating AuNPs-induced toxicity. Co-supplementation with green tea extract was notably effective in recovering morphological traits like ovarian, cortical, medullary and corpus luteum volumes along with quantitative parameters such as follicle counts and oocyte/nuclear volumes compared to standalone AuNPs treatment. The antioxidative and free radical scavenging properties of green tea extract, mediated by bioactive polyphenols, seem to promote ovarian health by alleviating nanoparticle-triggered oxidative damage. These impacts could mitigate downstream effects including impaired folliculogenesis, suppressed steroidogenesis and reduced fertility. The present findings align with and substantially build upon previous preliminary research demonstrating reproductive benefits of green tea extract.

While further studies are warranted exploring translational applications, this investigation substantiates the promising potential of green tea extract to promote female reproductive health amidst increasing environmental nanoparticle exposures. From a clinical perspective, incorporating green tea extract as a dietary supplement could provide a safe, economical and readily accessible solution to attenuate ovarian perturbations induced by inadvertent nanoparticle toxicities. Going forward, high-throughput transcriptomic and metabolomic profiling could uncover the precise biomolecular mechanisms governing these protective synergies between green tea extract and gold nanoparticles within ovarian microenvironments.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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