Original Article

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In-vitro Assessment of Cytotoxicity, Antioxidant Potential and Anti-inflammatory Activity of a Novel Ginseng Gel Formulation

Dentistry Section

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ABSTRACT

Introduction: Plant-derived bioactive compounds, particularly *Panax ginseng*, have attracted considerable interest owing to their antioxidant, anti-inflammatory, and cytoprotective properties relevant to human wellbeing and health. Such phytoconstituents are increasingly explored in medicine for addressing inflammation-associated disease and oxidative stress-related illness. Incorporation of these compounds into biocompatible gel formulations may enhance localised therapeutic efficacy when applied to oral mucosal or periodontal tissues while minimising systemic adverse effects, thereby supporting human wellbeing and broader public health outcomes.

Aim: To formulate a novel ginseng-based gel and evaluate its cytotoxicity, antioxidant potential, and anti-inflammatory activity using standardised in-vitro assays.

Materials and Methods: The present in-vitro experimental study was conducted at the Department of Periodontics, Saveetha Dental College and Hospitals, Chennai, Tamil Nadu, India, between July 2025 and October 2025. A 2% ginseng gel was prepared using a carbopol-based matrix. Cytotoxicity was assessed using the brine shrimp lethality assay. Antioxidant activity was evaluated using 2,2-Diphenyl-1-Picrylhydrazyl (DPPH) radical scavenging and Ferric Reducing Antioxidant Power (FRAP) assays. Anti-inflammatory activity was determined through Human Red Blood Cell (HRBC) membrane stabilisation and Bovine Serum Albumin (BSA) protein denaturation assays. All experiments were performed in triplicate. Statistical analysis was carried out using one-way Analysis of Variance (ANOVA) and independent samples t-tests, with significance set at $p<0.05$.

Results: The ginseng gel demonstrated a concentration-dependent response in the brine shrimp lethality assay ($p<0.001$); however, mortality values remained within acceptable limits and did not differ significantly from the standard control ($p>0.05$). Antioxidant activity increased significantly with concentration in both DPPH and FRAP assays ($p<0.001$), with activity comparable to reference antioxidants ($p>0.05$). The formulation also exhibited significant, dose-dependent inhibition of protein denaturation and enhanced membrane stabilisation ($p<0.001$), comparable to diclofenac sodium ($p>0.05$).

Conclusion: The novel ginseng gel demonstrated acceptable biocompatibility along with significant antioxidant and anti-inflammatory activity under In-vitro conditions, supporting its potential as a localised therapeutic formulation and warranting further in-vivo and clinical evaluation.

Keywords: Free radical scavengers, Oxidative stress, Phytotherapy, Plant extracts

INTRODUCTION

Natural bioactive compounds have gained considerable attention in biomedical research due to their ability to modulate oxidative stress, inflammation, and tissue healing pathways [1,2]. Among these botanicals, *Panax ginseng* stands out as a well-established medicinal herb traditionally valued for its rejuvenating and therapeutic effects [3]. Its major constituents including ginsenosides, polysaccharides, and phenolic compounds are recognised for exhibiting potent antioxidant, anti-inflammatory, and cytoprotective actions, making the plant a promising candidate for localised therapeutic delivery [4].

Inflammation and oxidative damage are central contributors to the pathogenesis of many oral and systemic conditions. Conventional pharmacologic agents used to counter these processes may produce adverse effects or lack sustained action at the target site [5]. This has led to the growing interest in developing biocompatible delivery systems capable of improving retention, stability, and bioactivity of natural therapeutics [6,7]. Gel-based formulations, in particular, offer significant advantages due to their hydrophilic nature, ease of intraoral application, patient comfort, and ability to maintain prolonged contact with soft-tissues. Their three-dimensional network structure enables encapsulation of bioactive agents while allowing controlled release, thereby enhancing therapeutic efficacy [8].

Ginseng-containing gels may provide an effective platform for delivering plant-derived antioxidants and anti-inflammatory molecules directly to affected tissues. By stabilising phytoconstituents and permitting localised delivery, such formulations have the potential to reduce oxidative stress, suppress protein denaturation, and minimise cellular injury [9]. Despite the documented benefits of ginseng extracts, limited data exist regarding their incorporation into topical gel matrices and the subsequent evaluation of their cytotoxicity, antioxidant potential, and anti-inflammatory activity under in-vitro conditions.

The present study aimed to formulate a novel ginseng gel preparation and assess its safety and biological activity using standardised in-vitro assays. The study investigates three key parameters: cytotoxicity, antioxidant capacity, and anti-inflammatory effects, comparing the results with established reference standards. The null hypothesis posits that the ginseng gel will not show significant antioxidant or anti-inflammatory activity and may demonstrate cytotoxicity similar to controls. Conversely, the alternative hypothesis proposes that the formulation will exhibit favourable biological properties with minimal cytotoxic effects. This work seeks to provide foundational evidence supporting the potential use of ginseng-based gels as a natural therapeutic modality for localised management of oxidative and inflammatory conditions in clinical applications.

MATERIALS AND METHODS

The present in-vitro study was conducted at the Department of Periodontics, Saveetha Dental College and Hospitals, Chennai,

Tamil Nadu, India, between July and October 2025. All experimental assays were performed in three replicates (n=3) to ensure statistical accuracy and reproducibility of results.The study protocol was approved by Institutional Scientific Review Board (SRB/SDC/PERIO-2403/24/531).

Study Procedure

Materials: Ginseng root powder was procured from Himalayan Nutraceuticals Pvt., Ltd., India. Carbopol 940, Hydroxypropyl Methylcellulose(HPMC), propylene glycol, triethanolamine, potassium dichromate ($K_2Cr_2O_7$), 2,2- DPPH, Butylated Hydroxytoluene (BHT), acetate buffer, 2,4,6-Tris(2-Pyridyl)-S-Triazine (TPTZ), ferrous sulfate heptahydrate ($FeSO_4 \cdot 7H_2O$), BSA were obtained from Sigma-Aldrich®, USA. Diclofenac sodium from T.O. Chemicals Ltd., Thailand was used. All reagents were of analytical grade.

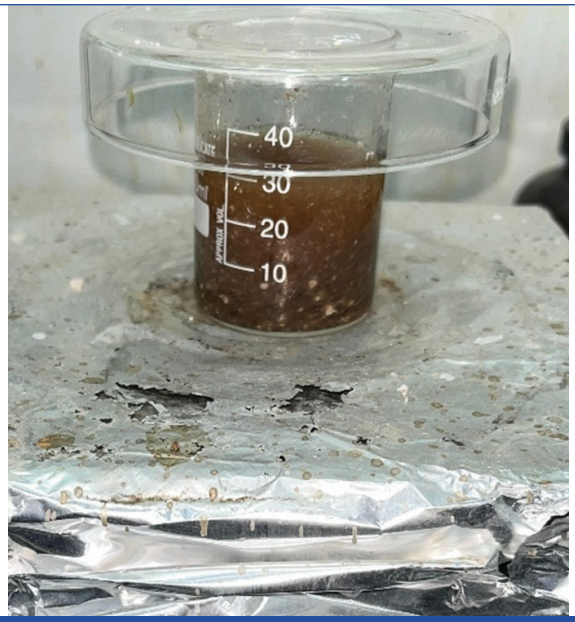
Preparation of Ginseng Extract: Ginseng root powder (250 g) was subjected to ethanolic extraction using the maceration technique [10]. The powder was immersed in 1000 mL of ethanol for 48 hours with intermittent stirring. The mixture was then filtered through Whatman filter paper, and the filtrate was evaporated to obtain a concentrated extract. The resulting extract [Table/Fig-1] was stored in airtight container at 4°C until further use [10].

[Table/Fig-1]: Ginseng extract.

Preparation of Ginseng Gel: A 2% ginseng gel formulation was prepared using a carbopol-based gel matrix. Carbopol 940 was dispersed in purified water containing 0.2% w/v sodium benzoate and allowed to hydrate overnight. Separately, Hydroxypropyl Methylcellulose (HPMC) was blended with propylene glycol using a tissue homogeniser to obtain a uniform polymer dispersion. To this, 2 mL of the prepared ginseng extract was incorporated and homogenised thoroughly. The extract-loaded HPMC mixture was then slowly added to the hydrated carbopol dispersion and mixed until a uniform gel base was achieved. Triethanolamine was added dropwise to adjust the pH to 6.0-6.5, facilitating gel formation. The final ginseng gel formulation [Table/Fig-2] was stored at ambient temperature in sterile container until evaluation [10].

Characterisation:

- **Cytotoxicity evaluation – brine shrimp lethality bioassay**: The cytotoxic potential of the prepared ginseng gel was assessed using the *Artemia salina* brine shrimp lethality assay, a widely accepted preliminary biocompatibility test [11]. Brine shrimp eggs (Aquatic Remedies, Chennai, India) were incubated in artificial seawater prepared by dissolving 40 g/L sea salt and supplemented with 6 mg/L dried yeast to facilitate hatching.

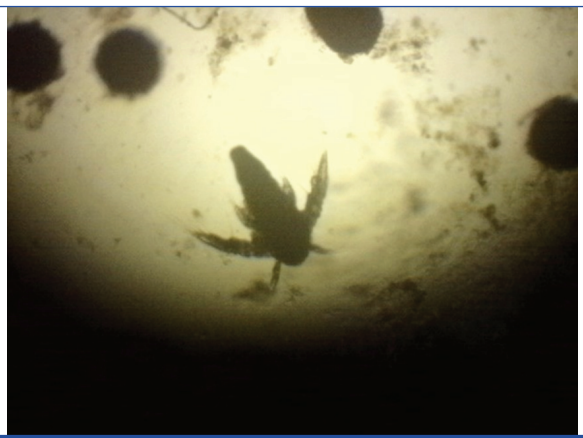


[Table/Fig-2]: Ginseng gel formulation.

The setup was maintained at 25±2°C with continuous aeration. After 48 hours, actively motile nauplii were harvested using a Pasteur pipette, and groups of ten nauplii were transferred into individual wells of a 24-well plate containing 1 mL of artificial seawater. Ten nauplii per well were used as recommended in standard brine shrimp lethality assay protocols to ensure consistent and reliable mortality assessment [12].

Different concentrations of the ginseng gel (10, 20, 30, 40, and 50 µL) were added to the wells, and each concentration was tested in triplicate wells. $K_2Cr_2O_7$ served as the standard control. Following 24 hours of exposure under static conditions, the number of surviving and dead nauplii was determined using a stereomicroscope [Table/Fig-3]. Cytotoxicity was expressed as percentage mortality using the formula [11]:

Mortality (%)=(Number of dead nauplii / Total number of nauplii)×100



[Table/Fig-3]: Microscopic image of *Artemia salina* nauplii employed in the brine shrimp lethality assay.

The mortality percentage was calculated for each well, and the results were expressed as mean±Standard Deviation (SD) of three replicates. In the *Artemia salina* lethality assay, materials producing 50% or greater mortality are generally considered non biocompatible, whereas lower mortality values indicate acceptable biocompatibility [13].

Antioxidant activity:

- **DPPH radical scavenging assay:** The free radical scavenging ability of the ginseng gel was determined using the DPPH assay [14]. Aliquots of the gel formulation (10-50 µL) were combined with 1 mL of 0.1 mM DPPH solution prepared in methanol

and 450 µL of 50 mM Tris-HCl buffer (pH 7.4). The reaction mixtures were incubated in the dark at room temperature for 30 minutes. Absorbance values were recorded at 517 nm using a Ultraviolet (UV)-Visible spectrophotometer. BHT served as the standard control. Radical scavenging activity was calculated using the equation [14]:

Inhibition (%)={(Absorbance of control - Absorbance of sample)/ Absorbance of control}×100

- **Ferric Reducing Antioxidant Power (FRAP) assay:** The reducing capacity of the formulation was quantified using the FRAP method [14]. A working FRAP reagent was prepared by mixing 300 mM acetate buffer (pH 3.6), 10 mM TPTZ solution in 40 mM HCl, and 20 mM $FeCl_3 \cdot 6H_2O$ in a 10:1:1 proportion. For each reaction, 3.6 mL of FRAP reagent and 0.4 mL of distilled water were combined, followed by the addition of 80 µL of the ginseng gel. The mixture was incubated at 37°C for 10 minutes, and absorbance was measured at 593 nm.$FeSO_4 \cdot 7H_2O$ was used as the standard control to prepare a calibration curve (0.1-1.5 mM). Antioxidant capacity was expressed as Fe^{2+} equivalents based on the standard curve.

Anti-inflammatory Activity

- **Human Red Blood Cell (HRBC) membrane stabilisation test:** The anti-inflammatory effect of the ginseng gel was examined by evaluating its ability to stabilise human Red Blood Cells (RBC) membranes exposed to hypotonic stress [15]. Blood samples were obtained from healthy adult volunteers after written informed consent. RBCs were isolated by centrifugation, washed thrice with Phosphate-Buffered Saline (PBS), and adjusted to a 10% v/v suspension. Samples containing 1 mL of the RBC suspension were treated with varying volumes of the gel (10-50 µL) and incubated at 37°C for 30 minutes. After centrifugation at 1000 rpm for 10 minutes, the absorbance of the supernatant was measured at 540 nm. Diclofenac sodium functioned as the standard control. Percentage membrane stabilisation was calculated as [15]:

  Inhibition (%)={(Absorbance of control - Absorbance of sample)/ Absorbance of control}×100

- **Protein denaturation inhibition - Bovine Serum Albumin (BSA) assay:** To determine the ability of the formulation to prevent protein denaturation, a BSA assay was performed [15]. Different volumes of the ginseng gel (10-50 µL) were added to 2 mL of 1% BSA solution adjusted to pH 6.8. The tubes were incubated in a water bath at 37°C for 20 minutes and then cooled to room temperature. Absorbance was measured at 660 nm. Diclofenac sodium was used as the standard control. Anti-denaturation activity was calculated as [15]:

  Inhibition (%)={(Absorbance of control - Absorbance of sample)/ Absorbance of control}×100

STATISTICAL ANALYSIS

All experiments were conducted in triplicate, and results were reported as mean±SD. Differences between concentrations were analysed using One-way ANOVA. Independent samples t-tests were used to compare the activity of the ginseng gel with the corresponding standard controls. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (Version 23.0; IBM Corp., Armonk, NY, USA).

RESULTS

Brine Shrimp Lethality (Cytotoxicity) Assay

The cytotoxic activity of the ginseng gel increased progressively with concentration. Mortality values rose from 3.3±5.8% at 10 µL to 10.0±0.0% (20 µL), 16.7±5.8% (30 µL), 26.7±5.8% (40 µL), and 36.7±5.8% at 50 µL. One-way ANOVA indicated statistically significant differences among concentrations (F=19.75, p<0.001), confirming a clear dose-dependent effect [Table/Fig-4]. Independent t-test comparison with the standard showed no statistically significant difference at any concentration (p>0.05), indicating comparable cytotoxic performance between the ginseng gel and the standard control [Table/Fig-5].

DPPH Radical Scavenging Assay

A concentration-dependent increase in free radical scavenging activity was observed for the ginseng gel. DPPH inhibition increased from 24.85±1.53% (10 µL) to 35.72±2.64% (20 µL), 52.96±1.84% (30 µL), 63.45±2.91% (40 µL), and 71.88±1.74% at 50 µL. The increase was statistically significant (F=92.16, p<0.001) [Table/Fig-4]. Independent t-tests revealed no significant differences between the gel and the standard (p>0.05), indicating similar antioxidant activity [Table/Fig-5].

FRAP Assay

FRAP values increased steadily with concentration, starting at 0.19±0.01 mM Fe^{2+} equivalents at 10 µL and rising to 0.31±0.02 (20 µL), 0.47±0.02 (30 µL), 0.59±0.02 (40 µL), and 0.72±0.03 at 50 µL. One-way ANOVA confirmed significant differences among all concentrations (F=104.87, p<0.001) [Table/Fig-4]. Independent t-test analysis showed no significant difference compared to the standard at any concentration (p>0.05) [Table/Fig-5].

BSA Assay

The ginseng gel exhibited strong inhibition of protein denaturation in a dose-dependent manner. Values increased from 27.56±1.88% at 10 µL to 46.90±1.51% (20 µL), 62.33±1.48% (30 µL), 69.12±0.52% (40 µL), and 74.80±1.10% at 50 µL. This increase was statistically significant (F=792.30, p<0.001) [Table/Fig-4]. Independent t-tests demonstrated no significant difference between the gel and the standard anti-inflammatory drug at any concentration (p>0.05) [Table/Fig-5].

Membrane Stabilisation Assay

Haemolysis inhibition also increased with concentration, from 25.74±0.51% at 10 µL to 42.66±1.78% (20 µL), 57.41±2.02% (30 µL), 67.20±0.83% (40 µL), and 72.05±2.11% at 50 µL. This trend was statistically significant (F=315.92, p<0.001) [Table/Fig-4]. Independent t-tests revealed no significant differences from the standard drug (p>0.05), confirming comparable membrane-stabilising activity [Table/Fig-5].

Assay	10 µL (Mean±SD)	20 µL (Mean±SD)	30 µL (Mean±SD)	40 µL (Mean±SD)	50 µL (Mean±SD)	F-statistic	p-value[a]
Cytotoxicity (% mortality)	3.3±5.8	10.0±0.0	16.7±5.8	26.7±5.8	36.7±5.8	19.75	<0.001*
DPPH (% inhibition)	24.85±1.53	35.72±2.64	52.96±1.84	63.45±2.91	71.88±1.74	92.16	<0.001*
FRAP (mM Fe^{2+} equivalents)	0.19±0.01	0.31±0.02	0.47±0.02	0.59±0.02	0.72±0.03	104.87	<0.001*
BSA (% inhibition)	27.56±1.88	46.90±1.51	62.33±1.48	69.12±0.52	74.80±1.10	792.30	<0.001*
Membrane Stabilisation (% hemolysis inhibition)	25.74±0.51	42.66±1.78	57.41±2.02	67.20±0.83	72.05±2.11	315.92	<0.001*

[Table/Fig-4]: Comparison of mean±SD values for cytotoxicity, antioxidant, and anti-inflammatory activities of ginseng gel across increasing concentrations.
[a]One-way ANOVA; *p-value<0.05 (Statistically Significant); DPPH: 2,2-diphenyl-1-picrylhydrazyl; FRAP: Ferric reducing antioxidant power; BSA: Bovine serum albumin

Assay	10 µL (Mean±SD)	20 µL (Mean±SD)	30 µL (Mean±SD)	40 µL (Mean±SD)	50 µL (Mean ±SD)
Cytotoxicity - test	3.3±5.8	10.0±0.0	16.7±5.8	26.7±5.8	36.7±5.8
Cytotoxicity - standard	6.7±5.8	13.3±5.8	20.0±0.0	30.0±0.0	40.0±0.0
Cytotoxicity - t-value	-0.71	-1.00	-1.00	-1.00	-1.00
Cytotoxicity - p-value[b]	0.52	0.37	0.37	0.37	0.37
DPPH - test	24.85±1.53	35.72±2.64	52.96±1.84	63.45±2.91	71.88±1.74
DPPH - standard	25.10±1.62	36.20±2.51	53.40±1.92	63.98±3.01	72.21±1.82
DPPH - t-value	-0.22	-0.49	-0.48	-0.27	-0.33
DPPH - p-value[b]	0.83	0.63	0.64	0.79	0.73
FRAP - test	0.19±0.01	0.31±0.02	0.47±0.02	0.59±0.02	0.72±0.03
FRAP - standard	0.20±0.01	0.33±0.02	0.49±0.02	0.61±0.03	0.75±0.03
FRAP - t-value	-1.02	-0.81	-0.71	-0.52	-0.63
FRAP - p-value[b]	0.19	0.41	0.49	0.61	0.54
BSA - test	27.56±1.88	46.90±1.51	62.33±1.48	69.12±0.52	74.80±1.10
BSA - standard	27.82±1.95	47.20±1.42	62.60±1.57	69.35±0.48	75.02±1.06
BSA - t-value	-0.31	-0.44	-0.38	-0.22	-0.28
BSA - p-value[b]	0.76	0.68	0.72	0.83	0.77
Membrane stabilisation - test	25.74±0.51	42.66±1.78	57.41±2.02	67.20±0.83	72.05±2.11
Membrane stabilisation – standard	25.92±0.55	42.95±1.85	57.80±1.96	67.52±0.79	72.40±2.04
Membrane stabilisation - t-value	-0.45	-0.37	-0.34	-0.40	-0.29
Membrane stabilisation - p-value[b]	0.67	0.72	0.75	0.69	0.78

[Table/Fig-5]: Independent t-test comparison between ginseng gel and corresponding standards.
[b]Independent t-test; p-value <0.05 (Statistically Significant); DPPH: 2,2-diphenyl-1-picrylhydrazyl; FRAP: Ferric reducing antioxidant power; BSA: Bovine serum albumin

DISCUSSION

Inflammation, oxidative stress, and cellular injury are closely interlinked biological processes that drive the progression of several oral and systemic disorders. Natural compounds such as ginseng have received increasing scientific attention for their ability to modulate these pathways through their rich content of ginsenosides, polyphenols, and polysaccharides. These bioactive molecules have been shown to exert potent antioxidant and anti-inflammatory actions by attenuating free radical generation, stabilising biological membranes, and protecting proteins from structural damage [16]. With growing interest in plant-based therapeutics and the need for safe, biocompatible intraoral delivery systems [17,18], gel formulations incorporating herbal extracts provide an attractive strategy for localised intervention [19,20]. The present study was designed to evaluate a newly formulated ginseng gel for its cytotoxicity, antioxidant behaviour, and anti-inflammatory potential using standardised in-vitro assays.

In the current investigation, the ginseng gel demonstrated minimal cytotoxicity across all tested concentrations in the brine shrimp lethality model, with mortality rates remaining low and statistically comparable to the standard control. This indicates that the formulation is biologically safe within the tested dose range. Antioxidant evaluation through DPPH and FRAP assays showed a clear dose-dependent improvement in free radical scavenging and ferric-reducing capacity, suggesting strong electron-donating and radical-neutralising properties. Similarly, anti-inflammatory performance assessed by HRBC membrane stabilisation and BSA protein denaturation assays revealed substantial protective effects, with inhibition values increasing consistently with concentration. Across all assays, the gel exhibited activity equivalent to their respective reference standards, reinforcing its potential as a multifunctional natural therapeutic agent.

The findings of this study are consistent with existing evidence on the biological efficacy of ginseng-derived compounds. Angeloni S et al., reported that ginsenosides markedly attenuated oxidative stress by reducing Reactive Oxygen Species (ROS), suppressing interferon-γ, and modulating mitochondrial activity- an antioxidant and anti-inflammatory profile comparable to the redox-scavenging effect observed with our ginseng gel [21]. Similarly, Zhang BZ et al., showed that *Panax ginseng* root extract attenuated Interleukin-1 alpha (IL-1α), Prostaglandin E_2 (PGE_2), and Nuclear Factor kappa-B (NF-κB) activation while maintaining greater than 80% cell viability [22]. Their results parallel our cytotoxicity data and the high antioxidant activity noted in the FRAP assay.

An MY et al., further reported that black ginseng reduced Reactive Oxygen Species (ROS), Nitric Oxide (NO), and inducible Nitric Oxide Synthase (iNOS) expression through an inositol-requiring enzyme 1 alpha-dependent mechanism [23]. Although our study did not evaluate endoplasmic reticulum stress pathways, the marked inhibition of protein denaturation suggests that the gel may influence similar upstream inflammatory cascades. Supporting this, Kang M et al., found that ginsenoside lowered intracellular ROS, decreased Matrix Metalloproteinase-1 (MMP-1), increased procollagen synthesis, and reduced inflammatory cytokines such as IL-1β and IL-6-effects consistent with the broad antioxidant and anti-inflammatory profile of our formulation [24].

Additionally, Hossen MJ et al., showed that ginsenosides suppressed NO production, inhibited iNOS expression, and blocked NF-κB activation while exhibiting strong radical-scavenging capacity [25]. This mirrors the significant anti-inflammatory response recorded in our protein denaturation assay, suggesting that the ginseng gel may act through related signalling pathways.

Overall, the results align well with the broader literature, reinforcing the cytoprotective, antioxidant, and anti-inflammatory potential of ginseng-based preparations and supporting the therapeutic relevance of the ginseng gel evaluated in this study. A major strength of the present study is the comprehensive evaluation of the formulation across multiple biologic endpoints, allowing a holistic assessment of safety, antioxidant efficacy, and inflammation suppression. Using simple, reproducible In-vitro assays provide reliable early-phase screening and facilitate comparison with standard reference drugs. The gel-based delivery system also offers translational relevance, particularly for intraoral applications where prolonged therapeutic contact is essential.

From a clinical perspective, the observed antioxidant and anti-inflammatory activities suggest that the ginseng gel may serve as a

promising adjunctive formulation for localised intraoral applications. Such properties may help mitigate oxidative stress and inflammatory responses associated with periodontal inflammation, mucosal irritation, or post-procedural tissue healing, thereby supporting improved local tissue stability and patient outcomes. Based on the statistically significant concentration-dependent antioxidant and anti-inflammatory activities observed in the present study, the null hypothesis stating that the ginseng gel would not exhibit significant biological activity was rejected. Furthermore, independent t-test analysis revealed no significant differences between the ginseng gel and the respective standard controls across all evaluated assays, indicating that the formulation demonstrates comparable antioxidant, anti-inflammatory, and cytocompatible properties.

Future research should include in-vivo preclinical evaluation, advanced cell-based assays, and molecular pathway analysis to better understand the mechanistic basis of its effects. Characterisation of ginsenoside profiles, rheological behaviour, and stability studies will additionally help optimise the formulation for clinical translation.

Limitation(s)

In-vitro assays, while informative, cannot fully replicate the complexity of in-vivo tissue interactions, pharmacokinetics, or long-term biocompatibility. The study also did not investigate mechanistic molecular pathways or quantify specific ginsenosides present in the formulation, which would provide deeper insight into the exact contributors to bioactivity. Furthermore, only short-term assessments were performed, leaving the sustained biological effects of the gel unexplored.

CONCLUSION(S)

The formulated ginseng gel exhibited favourable cytoprotective, antioxidant, and anti-inflammatory properties, with activity comparable to established reference standards under in-vitro conditions. These findings indicate its potential as a natural, localised therapeutic formulation for managing oxidative and inflammatory conditions and warrant further investigation through in-vivo and clinical studies.

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