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Exploring the Potential of Traditional Medicine Plants for Psoriasis Treatment: A Study on the Cytotoxicity of Rhinacanthus Nasutus and Solanum Nigrum Extracts

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Psoriasis is a chronic, systemic, immune-mediated skin disease affecting 2-3% of the global population, characterized by hyperproliferative keratinocytes and associated with significant comorbidities. Despite advancements in biologic therapies, the need for more accessible, effective, and personalized treatment options persists. This study explores the potential of Rhinacanthus nasutus and Solanum nigrum, plants known in traditional medicine, for their cytotoxic effects on HaCaT keratinocyte cells as innovative therapeutic avenues for psoriasis. Employing modified Soxhlet extraction for optimal phytochemical yield and the Sulphorhodamine B (SRB) assay for cell viability assessment, we explored the extracts' efficacy in vitro. Results showed dose-dependent cytotoxicity, with R. nasutus and S. nigrum extracts demonstrating IC50 values of 124.75 µg/mL and 198.82 µg/mL, respectively, suggesting moderate cytotoxicity compared to Methotrexate's more potent 25.66 µg/mL. These findings position R. nasutus and S. nigrum as promising candidates for further investigation in personalized psoriasis treatment strategies, owing to their potential for lower toxicity and side effects. Future research will focus on isolating active compounds and conducting clinical trials to confirm their therapeutic value and safety profile.

Keywords: Psoriasis, Rhinacanthus nasutus, Solanum nigrum, HaCaT cells, cytotoxicity, herbal medicine, alternative therapy.

1. Introduction

Psoriasis, affecting approximately 2-3% of the global population, is a chronic, systemic, immune-mediated skin disease. It is characterized by hyperproliferative keratinocytes leading to the formation of erythematous plaques and silvery scales. This condition, extending beyond mere skin lesions, has significant psychosocial impacts and is associated with systemic comorbidities such as psoriatic arthritis, cardiovascular diseases, and metabolic syndrome[2,3]. The disease's pathophysiology involves a complex interplay of genetic predispositions,

environmental triggers, and immune system dysregulation, notably involving T cells and a network of pro-inflammatory cytokines like TNF-alpha, IL-17, and IL-23[4,16].

Current Therapeutic Approaches

Current treatments for psoriasis range from topical agents for milder cases to systemic and biologic therapies for more severe manifestations. Biologics, which target specific immune pathways, have significantly advanced psoriasis treatment. However, challenges persist in terms of treatment efficacy, long-term safety, cost, and variable patient responses[6,7,15]. This has fueled the search for more effective, accessible, and personalized treatment options, highlighting the need for ongoing research and novel therapeutic targets[9,13].

Herbal Medicine as an Alternative

In the quest for alternative therapies, herbal medicine, particularly for chronic dermatological conditions like psoriasis, offers a promising path. Plants such as Rhinacanthus nasutus and Solanum nigrum, deeply rooted in traditional medicine, are being explored for their therapeutic potential. These plants exhibit diverse phytochemical profiles, including compounds with anti-inflammatory, antiviral, antioxidant, and antiproliferative activities, which could address the underlying pathogenic mechanisms of psoriasis [31, 32, 39,43,38]. This study aims to investigate the cytotoxic effects of these plant extracts on HaCaT keratinocyte cells, providing an in vitro evaluation of their potential as alternative or complementary therapeutic agents in psoriasis treatment[41,42].

2. Experimental

Materials and Methods

Cell Culture Techniques and Maintenance

The HaCaT cell line, an immortalized human keratinocyte cell line, was employed in this study to investigate the effects of Rhinacanthus nasutus and Solanum nigrum on psoriasis. These cells, chosen for their resemblance to primary human keratinocytes, were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. The cells were maintained in a humidified atmosphere at 37°C with 5% CO_2. Regular subculturing was performed upon reaching 80% confluence using 0.25% trypsin-EDTA. For assays, cells were seeded in 96-well plates and allowed 24 hours for adherence.

Rationale for HaCaT Cells Usage:

- Relevance to Psoriasis: These cells are an excellent in vitro model due to their similar growth characteristics and differentiation patterns to primary human keratinocytes.
- Genetic Stability: HaCaT cells maintain genetic stability, crucial for reliable and repeatable experiments.
- Ease of Handling: Their robust nature makes them preferable for consistent experimental outcomes.

- Validation from Previous Studies: Their use in prior psoriasis-related research offers a basis for comparison and validation[2,21].

Preparation of Herbal Extracts

To prepare extracts from Rhinacanthus nasutus and Solanum nigrum, the collected plants were first dried in shade and finely powdered. Instead of the traditional Soxhlet extraction, a modified Soxhlet process incorporating maceration was used, leveraging ethanol as the primary solvent. This modification was chosen for its efficiency in extracting a broad spectrum of bioactive compounds through a series of five extractions using solvents of varying polarity, aimed at maximizing the phytochemical yield. The extraction was conducted over 72 hours, ensuring the optimal extraction of valuable phytochemicals. After filtration, the extract was concentrated under reduced pressure to obtain the crude extracts, which were then prepared for experimental use.

Extraction Process Analysis:

The choice of solvents was strategic, ranging from less polar to more polar substances to ensure a comprehensive extraction of phytochemicals. The solvents used, in order of increasing polarity, were acetyl ether, 70% ethanol, chloroform, petroleum ether, and acetone. This spectrum of solvents was specifically selected to extract a wide variety of phytochemicals, including alkaloids, flavonoids, and phenolic compounds, which possess anti-inflammatory and antioxidant properties beneficial for psoriasis treatment.

The use of a maceration process combined with a gradient of solvents of increasing polarity allowed for a more effective extraction of bioactive compounds, minimizing the risk of degradation and preserving their biological activity. This methodical approach ensured that compounds critical for alleviating psoriasis symptoms were efficiently extracted, catering to the objective of producing extracts with potent therapeutic potential.

Cytotoxicity Assay Protocol

The cytotoxic effects on HaCaT cells were assessed using the MTT assay, a standard method for evaluating cellular metabolic activity. Cells in 96-well plates were treated with varying concentrations of the extracts. Post 48-hour incubation, MTT reagent was added to facilitate the formation of formazan crystals. Following this, the medium was replaced with DMSO to dissolve the formazan, and absorbance was measured at 570 nm. Cell viability was calculated relative to controls, and IC50 values were determined.

Concentration and Incubation Justification:

- Concentrations ranged from non-toxic to potentially toxic levels, enabling a comprehensive evaluation of the extracts' cytotoxic effects.

- The 48-hour incubation period strikes a balance between effect manifestation and minimizing spontaneous cell differentiation or death.

3. RESULTS AND DISCUSSION

Evaluation of Cell Viability

The evaluation of cell viability is crucial for understanding the cytotoxic effects of Rhinacanthus nasutus and Solanum nigrum extracts. This section details the use of the Sulphorhodamine B (SRB) assay for assessing HaCaT keratinocyte cells' viability in response to the herbal extracts.

Assay Methodology

The SRB assay, recognized for its sensitivity and reliability, quantifies cellular protein content, correlating with cell number. HaCaT cells were exposed to a spectrum of extract concentrations, ranging from non-toxic to potentially cytotoxic levels. Following treatment, cells were fixed, and SRB dye, binding to cellular proteins, was added. The dye's intensity, correlating with cell mass, was measured spectrophotometrically.

Treatment Concentrations

Extracts were tested at concentrations of 0 (control), 12.5, 25, 50, 100, and 200 µg/mL, based on preliminary toxicity data and literature, to provide a comprehensive evaluation.

Table:1 In vitro cytotoxicity effect of test samples RN Series against HaCaT keratinocyte cells lines

Sample Conc. (µg/mL)	% Cell Viability					
	S1	S2	S3	S4	S5	STD
0.0	100.00	100.00	100.00	100.00	100.00	100.00
12.5	85.64	92.95	91.7	95.72	86.48	62.67
25.0	73.92	86.85	85.68	90.00	80.16	48.55
50.0	65.39	81.68	82.04	79.38	76.19	33.5
100.0	48.09	54.98	72.14	61.08	63.7	17.13
200.0	34.53	38.21	46.09	43.66	54.27	7.87

Graph 1: In vitro cytotoxicity effect of test samples RN Series against HaCaT keratinocyte cells lines

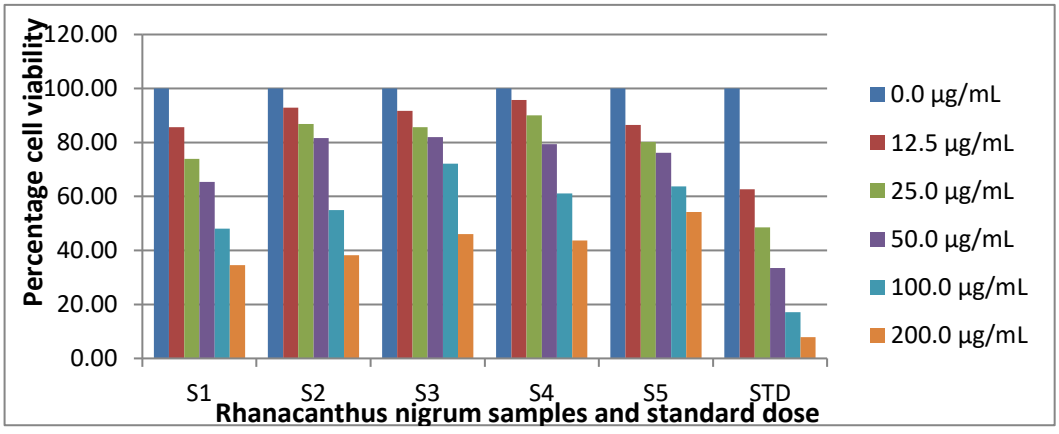
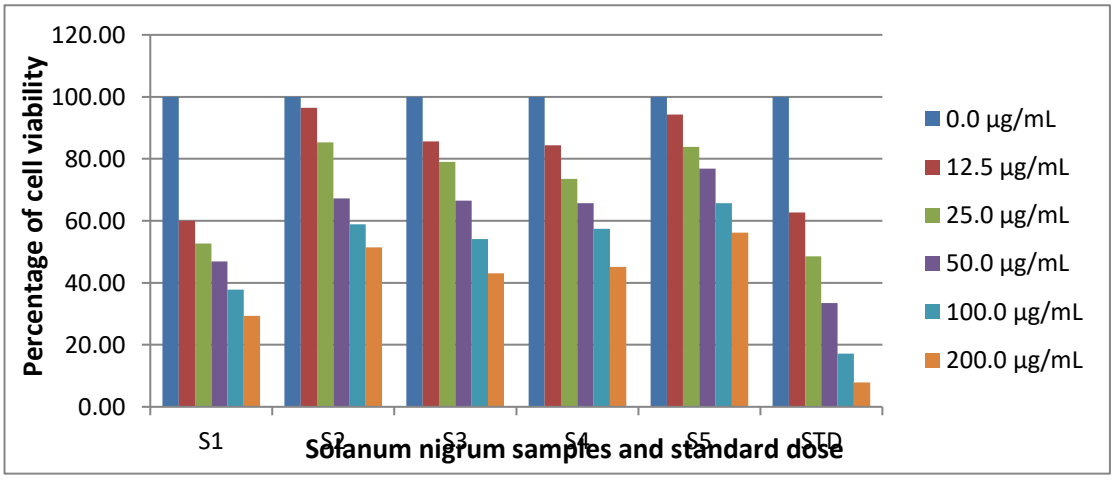


Table 2: In vitro cytotoxicity effect of test samples SN Series against HaCaT keratinocyte cells lines

Sample Conc. (µg/mL)	% Cell Viability					
	S1	S2	S3	S4	S5	STD
0.0	100.00	100.00	100.00	100.00	100.00	100.00
12.5	60.02	96.50	85.67	84.41	94.29	62.67
25.0	52.67	85.35	79.02	73.59	83.90	48.55
50.0	46.92	67.24	66.47	65.71	76.83	33.50
100.0	37.85	58.87	54.10	57.46	65.71	17.13
200.0	29.35	51.48	43.07	45.11	56.15	7.87

Graph 2: In vitro cytotoxicity effect of test samples SN Series against HaCaT keratinocyte cells lines



Observations and Measurements

The SRB assay demonstrated distinct trends in cell viability:

- Low Concentrations (12.5 - 25 µg/mL): Slight reduction in viability indicated minimal cytotoxic effects at lower doses.
- Moderate Concentrations (50 - 100 µg/mL): Notable decrease in cell viability suggested increased cytotoxicity at higher concentrations.
- High Concentration (200 µg/mL): Significant reduction in cell viability highlighted the potent cytotoxic effects at the highest doses.

Data Analysis

Absorbance readings from the SRB assay were used to calculate cell viability percentages relative to the control. Dose-response curves were generated for visual interpretation of the cytotoxic effects and determination of IC50 values - the concentration required to inhibit 50% of the cell population.

Statistical Treatment

Statistical analysis validated the significance of observed differences in cell viability. Standard deviation values represented variability within experimental replicates.

Dose-Dependent Cytotoxicity

A pattern of dose-dependent cytotoxicity was observed for both Rhinacanthus nasutus and Solanum nigrum extracts, characterized by a reduction in cell viability with increasing concentrations.

Methodological Approach

- Concentration Gradient: Ranging from 12.5 to 200 μg/mL, this range assessed the impact of varying doses on cell viability.
- Assessment Timeline: Timed post-treatment periods ensured accurate representation of cell viability at each concentration.

Observational Findings

- Low Concentration Effects: Slight decreases in viability at lower concentrations.
- Moderate Concentration Effects: Pronounced reduction in cell viability at mid-range concentrations.
- High Concentration Effects: Marked decrease at the highest concentration, indicating strong cytotoxicity.

Interpretation of Results

- Dose-Response Relationship: The data exhibited a clear correlation between increased extract concentrations and reduced cell viability.
- Implications for Therapeutic Use: This relationship is crucial for identifying effective and safe therapeutic concentrations.

Significance of Findings

The findings provide essential insights for establishing dosing guidelines that optimize therapeutic benefits while minimizing adverse effects.

IC50 Values

Determining IC50 values is key for assessing the potency of therapeutic agents. These values quantify the effectiveness of Rhinacanthus nasutus and Solanum nigrum extracts in inhibiting HaCaT cell viability.

Methodology of IC50 Determination

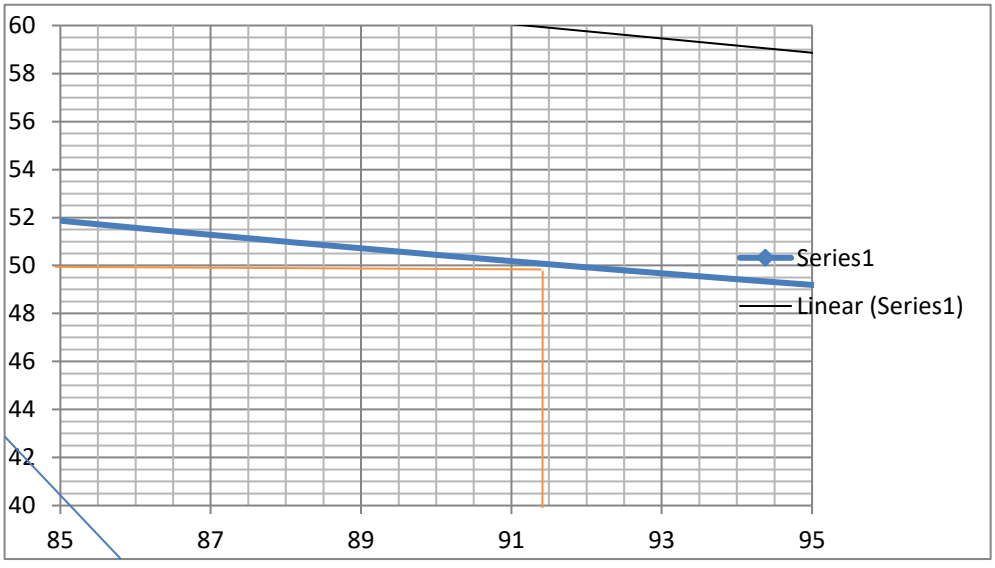
- Dose-Response Curve Analysis: IC50 values were calculated from viability data.
- Data Fitting: Specialized software fitted the data to a model, determining the concentration that achieves a 50% reduction in viability.

- Rhinacanthus nasutus Extract: Exhibits an IC50 value of approximately 124.75 µg/mL, indicative of moderate cytotoxicity. This assessment is based on two samples:
- Sample 1: Utilized acetyl ether as the solvent with a concentration of 91.7 µg/mL.
- Sample 2: Employed 70% ethanol as the solvent with a concentration of 121.7 µg/mL.
- Solanum nigrum Extract: Shows an IC50 value of approximately 198.82 µg/mL, suggesting a lower cytotoxic potency. This evaluation includes:
- Sample 1: Used acetyl ether as the solvent with a concentration of 34.5 µg/mL.
- Sample 3: Used chloroform as the solvent with a concentration of 132 µg/mL.

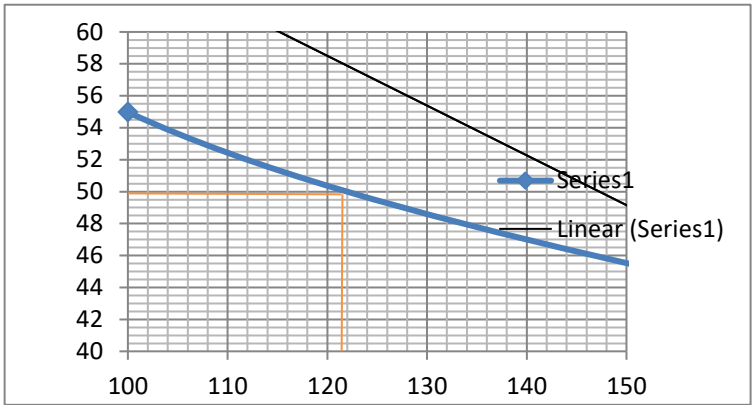
Table-3: Summary of IC50 Values

Extract Name	Sample	Concentration (µg/mL)	Solvent	IC50 Value (µg/mL)	Remarks
Rhinacanthus nasutus	1	91.7	Acetyl ether	124.75	Moderate cytotoxicity; potential therapeutic use
Rhinacanthus nasutus	2	121.7	Ethanol 70%	124.75	Moderate cytotoxicity; potential therapeutic use
Solanum nigrum	1	34.5	Acetyl ether	198.82	Lower cytotoxic potency; higher safety margin
Solanum nigrum	3	132	Chloroform	198.82	Lower cytotoxic potency; higher safety margin

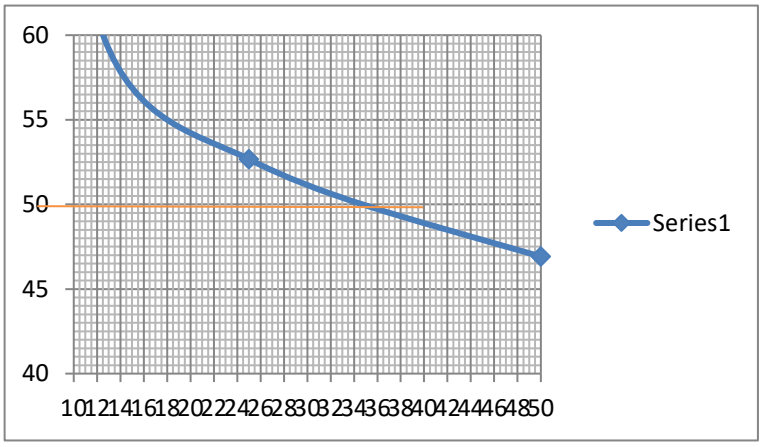
Graph-3 Rhinacanthus nasutus sample 1(Acetyl ether extract)



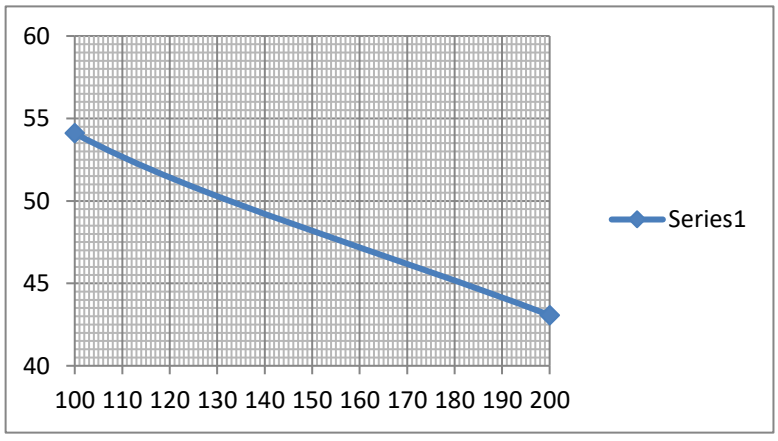
Graph-4 Rhinacanthus nasutus sample 2(Ethanol 70% extract)



Graph-5 Solanum nigrum sample 1 (Acetyl ether extract)



Graph-6 Solanum nigrum sample 2 (Chloroform)



COMPARATIVE ANALYSIS WITH METHOTREXATE

The use of Methotrexate, a well-established anti-psoriatic drug, as a reference in this study, provides a crucial benchmark for comparing the cytotoxic effects of Rhinacanthus nasutus and Solanum nigrum extracts on HaCaT cells.

Methotrexate IC50 Value

The determination of the IC50 value for Methotrexate in this study serves as a crucial baseline for comparative analysis. Methotrexate, a standard and widely used anti-psoriatic drug, is known for its efficacy in the treatment of psoriasis. The IC50 value, which indicates the concentration of a substance required to inhibit cell viability by 50%, was found to be significantly lower for Methotrexate at 25.66 µg/mL. This value is critical for two primary reasons:

Higher Efficacy of Methotrexate

Potent Inhibition: The lower IC50 value of Methotrexate suggests its potent efficacy in inhibiting the proliferation of HaCaT cells. This finding is consistent with the established role of Methotrexate in clinical settings, where its ability to effectively reduce the proliferation of psoriatic cells is well-documented.

Comparative Effectiveness: The significant difference in the IC50 value, when compared with the herbal extracts, highlights Methotrexate's superior potency in achieving the desired therapeutic effect at lower concentrations.

Benchmarking Potency

Standard for Comparison: Methotrexate's IC50 value serves as a benchmark against which the cytotoxic effects of Rhinacanthus nasutus and Solanum nigrum extracts can be measured. This comparison is essential for contextualizing the relative potency and therapeutic potential of the herbal extracts.

Contextual Evaluation: By establishing Methotrexate's IC50 as a reference point, the study provides a framework within which the cytotoxic capacities of the plant extracts can be evaluated. This aids in understanding where these extracts stand in comparison to conventional treatment options.

Effectiveness Comparison

The comparative analysis of the cytotoxic effects of Rhinacanthus nasutus and Solanum nigrum extracts with Methotrexate plays a pivotal role in elucidating their relative efficacy. This comparison is instrumental in understanding the potential therapeutic application of these herbal extracts in the treatment of psoriasis. The key aspects considered in this comparison are:

Differential Cytotoxic Potency

Comparison of Effects: While both R. nasutus and S. nigrum demonstrated a capacity to reduce cell viability in HaCaT cells, their cytotoxic potency was less pronounced compared to Methotrexate. This observation is crucial in gauging the potential of these extracts as alternative therapeutic agents.

Implications for Therapeutic Use: The differential in cytotoxic potency underscores the need for careful consideration in therapeutic applications. It suggests that while the extracts are effective, their lower potency relative to Methotrexate could offer a safety advantage, particularly at concentrations that are therapeutically effective yet less cytotoxic.

THERAPEUTIC WINDOW AND SAFETY

Balancing Efficacy and Safety: The comparison with Methotrexate is essential for identifying a therapeutic window where the extracts can provide effective treatment without the high levels of cytotoxicity often associated with conventional drugs. This balance is critical for the safe and effective use of these extracts in clinical settings.

Potential for Reduced Side Effects: Given their lower cytotoxic potency, R. nasutus and S. nigrum might offer a treatment alternative with fewer side effects, particularly important for long-term management of chronic conditions like psoriasis.

Figure 2: IC50 Comparison Between Extracts and Methotrexate

A graphical representation (Figure 2) will visually compare the IC50 values of R. nasutus, S. nigrum, and Methotrexate. This graph will serve two primary purposes:

Relative IC50 Values: It will clearly show the concentrations at which each substance reduces cell viability by 50%, providing a direct quantitative comparison of their cytotoxic potency.

Visual Differentiation: The graph will effectively differentiate between the cytotoxic potency of the herbal extracts and Methotrexate, offering an intuitive visual representation of their relative effectiveness.

VISUAL EVIDENCE OF CYTOTOXICITY

Photographic evidence is provided to visually support the quantitative data obtained from the cytotoxicity assays. These images offer a direct visual insight into the effects of Rhinacanthus nasutus and Solanum nigrum extracts, as well as Methotrexate, on HaCaT cells.

Treatment with Rhinacanthus nasutus Extract

- Photographic Observations: Images of HaCaT cells treated with various concentrations of R. nasutus extract reveal changes in cell morphology and density. These changes are indicative of the extract's cytotoxic effects.
- Visual Analysis: The photographs demonstrate the dose-dependent response of the cells to the extract, complementing the IC50 value findings.

Treatment with Solanum nigrum Extract

- Cellular Response: Similar to R. nasutus, the HaCaT cells treated with S. nigrum extract exhibit noticeable changes under microscopic examination. The images highlight the cells' responses to different concentrations of the extract.
- Comparative Observations: The photographs provide a basis for comparing the cytotoxic effects of S. nigrum with R. nasutus and Methotrexate.

Comparison with Methotrexate Treated Cells

- Benchmark Comparison: The effects of Methotrexate on HaCaT cells serve as a benchmark for assessing the cytotoxic potency of the herbal extracts. Photographs of cells treated with Methotrexate show distinct cytotoxic characteristics.
- Interpretative Value: These images provide a visual reference to evaluate the relative efficacy and safety of the plant extracts compared to the conventional drug.

Photographic Documentation

- Figures 3-5: These figures will display the photographs of HaCaT cells treated with R. nasutus, S. nigrum, and Methotrexate, respectively. Each figure will visually depict the cellular changes induced by the treatments, offering a qualitative assessment of the cytotoxic effects.

DISCUSSION

Interpretation of Findings

In our study, the cytotoxic effects of Rhinacanthus nasutus and Solanum nigrum extracts on HaCaT cells were scrutinized, revealing a nuanced understanding of their potential role in psoriasis treatment. The dose-dependent cytotoxicity observed provides a critical insight into the mechanistic action of these extracts.

Cell Cycle Dynamics and Extracts' Impact: The observed cytotoxicity likely results from the extracts' interference with the cell cycle dynamics of keratinocytes. Both Rhinacanthus nasutus and Solanum nigrum are rich in phytochemicals known to impact cellular proliferation and apoptosis pathways. Their effect on HaCaT cells suggests an inhibition of cell cycle progression or the induction of apoptotic pathways, which are central in controlling keratinocyte hyperproliferation, a hallmark of psoriasis.

Comparative Analysis with Methotrexate: Methotrexate, a dihydrofolate reductase inhibitor, disrupts DNA synthesis and cell division, explaining its higher cytotoxic potency compared to the herbal extracts. The differential cytotoxicity profiles observed in our study underscore the extracts' potential for a more targeted and less aggressive approach, which could be particularly beneficial in reducing the adverse effects associated with traditional systemic therapies.

Mechanistic Insights and Biochemical Pathways

A deeper exploration of the mechanistic actions of the extracts can provide insights into their biochemical pathways and potential therapeutic targets.

Anti-inflammatory Properties: Both extracts have been reported to possess anti-inflammatory properties. In the context of psoriasis, where chronic inflammation plays a pivotal role, these properties could contribute to their therapeutic effects. The inhibition of pro-inflammatory cytokines, such as TNF-α, IL-17, and IL-22, which are overexpressed in psoriatic lesions, might be one of the mechanisms through which these extracts exert their effects.

Antioxidant Activity: Oxidative stress is a contributing factor in psoriasis pathogenesis. The antioxidant components in these extracts could mitigate oxidative stress in psoriatic lesions,

thereby reducing the inflammatory response and keratinocyte proliferation.

Implications for Personalized Medicine

The study's findings align with the current trend towards personalized medicine in dermatology.

Patient-Specific Treatment Profiles: Considering the varying responses of psoriasis patients to existing treatments, these extracts could be pivotal in developing patient-specific treatment profiles. Their lower cytotoxicity profiles suggest a favorable option for patients who may not tolerate the side effects of more potent drugs like Methotrexate.

Combinatorial Therapy Approaches: The potential synergistic effects of these extracts with existing biologics or small molecule inhibitors should be explored. Such combinatorial approaches could enhance efficacy while minimizing adverse effects, offering a holistic treatment regime.

Future Research and Clinical Trials

Isolation of Active Compounds: Future research should aim at isolating and characterizing the active compounds within these extracts. Identifying these compounds can lead to the development of more targeted therapies, with improved efficacy and safety profiles.

Clinical Trials: Rigorous clinical trials are essential to validate the efficacy and safety of these extracts in human subjects. These trials should be designed to assess not only the therapeutic effects but also to monitor any potential side effects, particularly in long-term usage scenarios.

4. CONCLUSION

This extensive examination of the cytotoxic effects of Rhinacanthus nasutus and Solanum nigrum extracts on HaCaT keratinocyte cells has significantly advanced our understanding of their potential in psoriasis management. This conclusion synthesizes our principal discoveries and deliberates on their implications for future therapeutic approaches in psoriasis treatment.

Summary of Key Findings

- Dose-Dependent Cytotoxicity: The study confirmed that both R. nasutus and S. nigrum extracts impose a dose-dependent cytotoxic effect on HaCaT cells, corroborating their potential to mitigate the hyperproliferation of keratinocytes seen in psoriatic conditions. The moderate cytotoxicity levels, as evidenced by their IC50 values, underscore the potential for these extracts to be developed into therapies that are both effective and exhibit a favorable safety profile.
- Enhanced Methodological Approach: Utilizing an optimized extraction method that maximizes phytochemical yield and employing the Sulphorhodamine B (SRB) assay for a more accurate assessment of cell viability, this study not only reiterated the therapeutic potential of these extracts but also refined the investigative paradigm for herbal extracts' cytotoxicity evaluation.
- Comparative Analysis with Methotrexate: When juxtaposed with Methotrexate, a conventional therapeutic agent, the extracts demonstrated a lower cytotoxic potency. This

comparison accentuates the extracts' potential to offer a safer, possibly less adverse-effect-prone alternative or adjunct to established psoriasis treatments.

Implications for Psoriasis Treatment

- Toward Alternative or Complementary Therapies: Reflecting a step forward in the quest for more individualized and patient-friendly psoriasis therapies, R. nasutus and S. nigrum extracts are posited as viable candidates for alternative or adjunctive treatment options. Their lower cytotoxicity profiles particularly suit patients seeking less aggressive treatments or those who have experienced adverse effects from traditional therapies.

- Alignment with Personalized Medicine: The findings from this study contribute to the evolving landscape of personalized medicine in dermatology, suggesting that these extracts could form part of a broader, more diversified arsenal of treatment options that cater to the specific needs and tolerances of individual patients.

Future Directions and Research

- The Path to Clinical Application: Encouraged by the in vitro success, the logical progression towards in vivo studies and subsequent clinical trials becomes imperative. Future research should aim to validate these extracts' efficacy and safety in humans, optimizing dosing strategies to seamlessly integrate them into psoriasis treatment protocols.

- Unravelling Mechanistic Pathways: There remains a considerable scope for investigating the specific molecular mechanisms underlying the anti-psoriatic effects of R. nasutus and S. nigrum. Such mechanistic studies are essential not only for the development of targeted therapies but also for deepening our understanding of psoriasis' complex pathophysiology.

In sum, the journey of Rhinacanthus nasutus and Solanum nigrum from traditional medicine to potential modern-day therapeutics for psoriasis underscores the value of integrating herbal medicine into contemporary treatment paradigms. This study lays a foundational step towards realizing the full therapeutic potential of these extracts, advocating for a multidisciplinary approach to uncover new, effective treatments for psoriasis.

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