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The effect of SIRT1 aptamer on thioredoxin interacting protein as an anti-inflammatory therapy via an *in vitro* study

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Abstract

Introduction: The NLRP3 inflammasome can be activated by host-derived molecules including reactive oxygen species (ROS). Oxidative stress induces the movement of thioredoxin interacting protein (TXNIP) from the nucleus to the mitochondria, where it forms a bond with TRX2 (thioredoxin 2). Then, this interaction hinders TRX2s ability to regulate ROS levels ultimately leading to inflammasome activation. Suppressing the initiation of inflammasome activation could have a significant therapeutic impact on various clinical disorders.
Objectives: To investigate whether the sirtuin1 activator (SIRT1 aptamer) can be used to treat inflammation by inhibiting TXNIP and ROS.
Materials and Methods: In this *in vitro* experimental study, the RAW 264.7 cell line served as the model system for macrophages. The cells were cultured in RPMI-1640 medium, supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin, and then incubated at 37 °C in a humidified 5% CO2 environment. Variable concentrations of the SIRT1(silent information regulator 2 homolog 1) aptamer were applied to the cells. The viability of the RAW 264.7 cell line was assessed for cytotoxic effects of the SIRT1 aptamer using the tetrazolium bromide (MTT) assay analyzed by nonlinear regression analysis using GraphPad Prism software 9.2. The expression of SIRT1 and TXNIP proteins was examined using the western blot technique and analyzed with GraphPad Prism software 9.2. Additionally, ROS levels were determined using a fluorometric assay kit and analyzed by one-way ANOVA with Tukey test.
Results: The SIRT1 aptamer was able to inhibit the growth rate of RAW 264.7 cells after 72 hours with an IC_{50}= 1.98 µM. Additionally, it significantly increased the expression level of SIRT1 protein ($P<0.05$). The expression of TXNIP protein decreased when treated with SIRT1 aptamer at concentrations of 0.99 µM and 3.9 µM, and completely disappeared in samples treated with the IC_{50}=1.98 µM. Furthermore, the SIRT1 aptamer dramatically reduced lipopolysaccharide (LPS)-stimulated ROS levels at concentrations of 1.9 µM and 4 µM by 55% and 75% respectively, compared to the ROS induced by LPS (ROS=195%).
Conclusion: There is a crosstalk between the SIRT1 protein and TXNIP, as this interaction results in the reduction of TXNIP expression, thereby protecting the cell from the damaging effects of ROS after treatment with a SIRT1 activator. The discovery highlights the potential of a novel anti-inflammatory biotherapy.

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Introduction

Inflammation involves sequential cellular and microvascular reactions that remove injured tissue and regenerate new tissue (1). However, if the initiation of the inflammatory reaction is not controlled, it can lead to further tissue damage and injury (2). The NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) inflammasome is a vital component of the innate immune system responsible for triggering the activation of caspase-1 and the release of proinflammatory cytokines IL-1β/IL-18 in response to microbial infection and cellular injury (3). The NLRP3 inflammasome can be triggered by the body's own molecules, including reactive oxygen species (ROS), excess ATP, and glucose (4). Silent information regulator 2 homolog 1 (SIRT1) is a member of the sirtuin family that deacetylates a variety of substrates using NAD^+ as the substrate (5). Biological processes, such as cellular senescence (6), apoptosis (7), sugar metabolism (8), lipid metabolism (9), oxidative stress (10,11) and inflammation (12) are significantly influenced by SIRT1-mediated deacetylation. The thioredoxin (TRX) pathway is a crucial system of antioxidant proteins, and thioredoxin interacting protein (TXNIP) is an endogenous inhibitor of this pathway (13). TXNIP as a member of the α-arrestin protein

Key point

The results support the potential advancement of silent information regulator 2 homolog 1(SIRT1) activators as the innovative treatments for inflammation. If SIRT1 activators prove effective, they could offer a more cost-effective and precise therapeutic approach for inflammatory diseases, potentially reducing healthcare expenses associated with chronic inflammation and its related conditions. The promising in vitro results with RAW 264.7 cells provide a foundation for further preclinical and clinical trials. The investigation of SIRT1 and its function in inflammation is further encouraged by the study, which advocates for more comprehensive research to investigate additional potential therapeutic targets and validate these findings. Providing training to healthcare workers on the administration of novel therapeutic agents, such as SIRT1 activators, can ensure their readiness to effectively administer these therapies once they are introduced into clinical practice.

superfamily members involved in the inflammatory response to oxidative stress (14). It acts as an upstream activator that exacerbates the inflammatory response and plays a critical role in inflammation and redox regulation (15,16). Redox regulation by TXNIP is a component of its functionality in certain circumstances, reducing the thioredoxin-reducing activities caused by overexpression of TXNIP. ROS plays a crucial role in cellular signaling and homeostasis. But excessive ROS production can occur under various of pathological and infectious conditions, leading to protein and nucleic acid oxidation and potentially harmful effects on cellular structures (17). Given the critical role of inflammation in various diseases and the need for effective anti-inflammatory therapies, understanding the mechanisms that regulate inflammation is crucial. Silent information regulator 2 homolog 1 (SIRT1) has emerged as a potential therapeutic target due to its regulatory effects on various biological processes, including inflammation and oxidative stress. Therefore, the primary objective of this study is to examine whether activating SIRT1 might alleviate the adverse effects of inflammation by reducing the expression of TXNIP and inhibiting the excessive generation of ROS using the RAW 264.7 mouse macrophage cell line as a model system. This study has the potential to aid in developing novel anti-inflammatory therapies targeting SIRT1, offering possible advantages for diseases characterized by excessive inflammation and oxidative stress.

Objectives

The aim of this study is to determine whether the SIRT1 aptamer could potentially be conducted to prevent inflammation through a negative regulatory relationship between SIRT1 and TXNIP. Additionally, the study sought to investigate whether the SIRT1 aptamer can defend against oxidative stress.

Materials and Methods

In this *in vitro* experimental study, the RAW 264.7 cell line provided by the American Type Culture Collection (ATCC) was conducted as a model system. The culture medium used to maintain the cell line is RPMI-1640 medium (Capricorn, Germany). The lipopolysaccharide (LPS) was ordered from Solarbio LIFE Sciences. The Western blot kit, SDS-PAGE kit, and SIRT1 polyclonal antibody were purchased from Elabscience Biotechnology, USA, while the TXNIP polyclonal antibody was purchased from Thermo Fisher Scientific, Invitrogen. The goat anti-rabbit IgG secondary antibody was also purchased from Elabscience Biotechnology, USA. Dimethyl sulfoxide (DMSO) was purchased from Thomas Baker, India. The MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] was from Sigma, USA, and the Trypan blue stain was from Thermo Scientific. The ROS Fluorometric Assay Kit ordered from Elabscience Biotechnology, USA. Additionally, phosphate buffered-saline (PBS) was prepared from Capricorn, Germany.

Preparation of SIRT1 aptamer stock solution

The solution is prepared by dissolving 100 pmol of SIRT1 aptamer stock solution powder (Bioneer, Korea) in nuclease-free water, and then stored at -20 °C until ready for use.

Study design

The experiments for the current *in vitro* study were from September 2023 to January 2024, RAW 264.7 cells were cultured in 75 cm^3 tissue culture flasks, maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS), 1% penicillin/streptomycin and incubated at 37 °C in a humid 5% CO_2 environment. The cells were then seeded in a 96-well plate at a density of 5×10^3 cell/mL and incubated for 24 hours, until they reached 80%-90% confluence. Serial dilutions of the SIRT1 aptamer (0.075, 0.15, 0.35, 0.75, 1.56, 3.12, 6.25, 12.5, 25, 50 and 100μM) were prepared and applied to the cultured cells to determine the suitable concentration for the subsequent experiments. Western blot analysis was employed to quantify the levels of SIRT1 and TXNIP proteins, then the ROS levels were assessed using a Fluorometric Assay Kit before and after stimulating the RAW 264.7 cell line with LPS. This study design was developed internally and does not reference any external sources.

Cell viability assay (MTT assay)

The MTT assay was carried out to assess the impact of the SIRT1 aptamer on the viability of RAW 264.7 cells. Each well in the 96-well plate was seeded with 5×10^3 cells suspended in 100 µL of culture medium and then incubated for 72 hours at 37 °C in a humidified 5% CO_2 environment. A 3 mg/mL MTT solution was prepared using PBS. Subsequently, 20 µL of the MTT solution was added to each well and incubated for 3hours at 37 °C. The medium containing MTT was then discarded, and 100 µL of DMSO was added to all the wells. The plates were incubated in a light-deprived environment for approximately 30minutes. The optical density was measured at 560 nm

using a Promega® microplate reader and adjusted for a background absorbance at a wavelength of 600 nm (18). After 72 hours of treatment, cells underwent nonlinear regression analysis to determine the (IC_{50}).

Western blot analysis

RAW 264.7 cells were cultured in a 6-well plate at a density of 1×10^5 cells per well and treated with 0.9, 1.9 and 4 µM of SIRT1 aptamer for 72 hours, while the control group received only culture medium. The cells were then lysed using RIPA lysis buffer (radioimmunoprecipitation assay). Prior to centrifugation at 12000 rpm for 10minutes at 4 °C, the cell lysate was sonicated (for one minute in a sonicator filled with ice for two second followed by two seconds intervals) and incubated at 4 °C for 30 minutes. The protein concentration was quantified using the BCA (bicinchoninic acid) protein assay reagent. To confirm the desired molecular weight and membrane transfer, 10 µL of protein was subjected to electrophoresis on an 8% SDS-polyacrylamide gel for SIRT1 and a 10% SDS-polyacrylamide gel for TXNIP and GAPDH. This included 5 µL of pre-stained protein marker. The electrophoresis was conducted at 80 V, which was then increased to 120 V for a total duration of 2 hours. The separated proteins were transferred to a polyvinylidene difluoride (PVDF) membrane via a Trans-Blot Turbo manufactured by Bio-Rad. A blocking buffer of 5% skimmed milk in TBST buffer (Tris-buffered saline with 0.1% Tween® 20 detergent) was added to the membrane and incubated at room temperature with shaking for 1hour. Subsequently, the membrane was incubated overnight at 4°C with the primary antibody (1:1000 dilution) targeting SIRT1, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and TXNIP. After three 15-minute washes with TBST buffer, the membrane was incubated at room temperature for one hour with a diluted secondary antibody 1:5000. The membrane was then rinsed three times for 15 minutes (19). Each protein bands were visualized using enhanced chemiluminescence (ECL) reagent. To quantify the intensity of the observed band corresponding to the target proteins, normalization to GAPDH was performed using a ChemiDoc TM XRS+ imaging device software version 6.0 (2017) (Bio-Rad Laboratories, France) (Figure 1).

Measuring intracellular reactive oxygen species

Cells were seeded in a 24-well plate at a concentration of 1×10^5 cells/mL and incubated for 48 hours at 37 °C in a humidified 5% CO_2 environment. When cells reached confluence of more than 75%, they were pre-treated with 1.9 and 4µM of SIRT1 aptamer before stimulation of RAW 264.7 cells with 10 µg/mL LPS for 24 hours. Next, the samples were incubated with 10µM DCFH-DA a fluorescent probe at 37 °C for 30 minutes. They were subsequently rinsed two times with working solution, and after centrifugation, cell pellets were collected for fluorescence detection. Fluorescence representing intracellular ROS levels was measured at an excitation wavelength of 500nm and an emission wavelength of 525 nm (18).

Statistical analysis

All statistical analysis of the SIRT1 aptamer were conducted using GraphPad Prism software version 9.2. The IC_{50} was determined by using nonlinear curve fitting

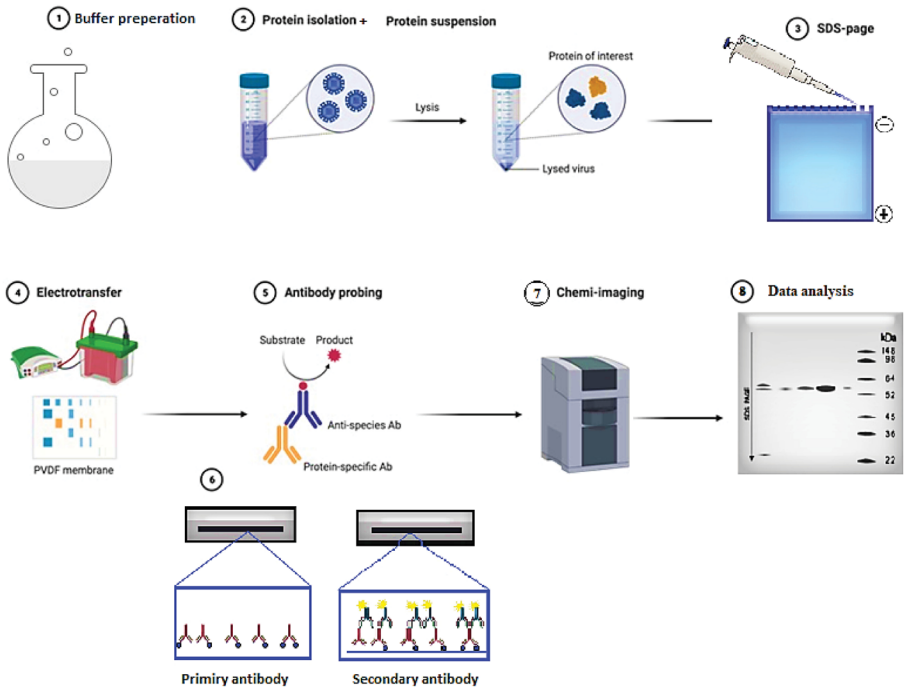

Figure 1. Protocol steps of the western blot.

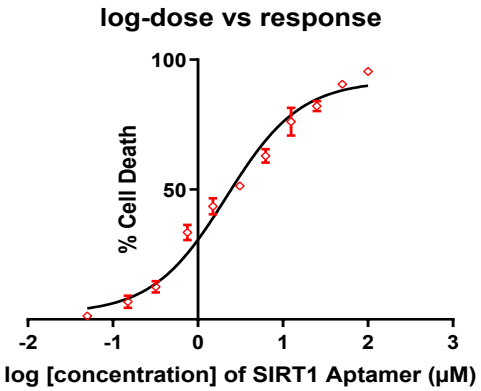

Figure 2. Dose-response curves for the SIRT1 aptamer. The RAW 264.7 cells were treated with varying concentrations of the SIRT1 aptamer for 72 hours, ranging from 0.075 to 100μM. The dose response was plotted using log transformed SIRT1 aptamer concentrations. IC50 values were calculated through nonlinear regression analysis using GraphPad Prism 9.2. The results include the standard error of the mean (SEM) for triplicate data.

software within the prism software. The Western blot data was analyzed using a t-test. Statistical significance was considered of values of $P < 0.05$ ROS level were compared between all groups on the same plate using one-way ANOVA with Tukey test in the Prism software suite.

Results

Different concentrations of SIRT1 aptamer, ranging from 0.075-100 μM, were used to treat the RAW 264.7 cells.

Table 1. The average IC_{50} value, 95% confidence Interval and R2 for RAW 264.7 cell line after 72 hours of SIRT1 aptamer treatment

Incubation time	IC50 (μM)	HillSlope	95% CI (μM)	R^2
72 h	1.9	0.643	1.626 to 2.866	0. 9788

After 72 hours, the IC_{50} of the SIRT1 aptamer in the RAW 264.7 cell line was found to be 1.9 μM as shown in Figure 2 and Table 1.

Figures 3A and 3B show the western blot analysis of SIRT1 in RAW 264.7 cell lines. The results indicate that SIRT1 aptamer at three different concentrations led to an increase in SIRT1 expression compared to the control (SIRT1 level in RAW 264.7 cell lines without SIRT1 aptamer treatment) ($P < 0.001$).

Figures 4A and 4B demonstrate the Western blot analysis of TXNIP in RAW 264.7 cell lines. The results revealed that SIRT1 aptamer at three different concentrations caused a decrease in the TXNIP expression compared with the control (TXNIP level in RAW 264.7 cell lines without SIRT1 aptamer treatment) ($P < 0.05$).

The fluorescent dye 2,7-dichlorofluorescein diacetate (10 mmol/L DCFH-DA) was utilized to measure intracellular levels of ROS in RAW 264.7 cell lines. The SIRT1 aptamer significantly decreased ROS production stimulated by LPS at concentrations of 1.9 μM and reducing levels by 55% and 75% respectively compared to the ROS induced by LPS alone (ROS = 195%). This indicates that the SIRT1

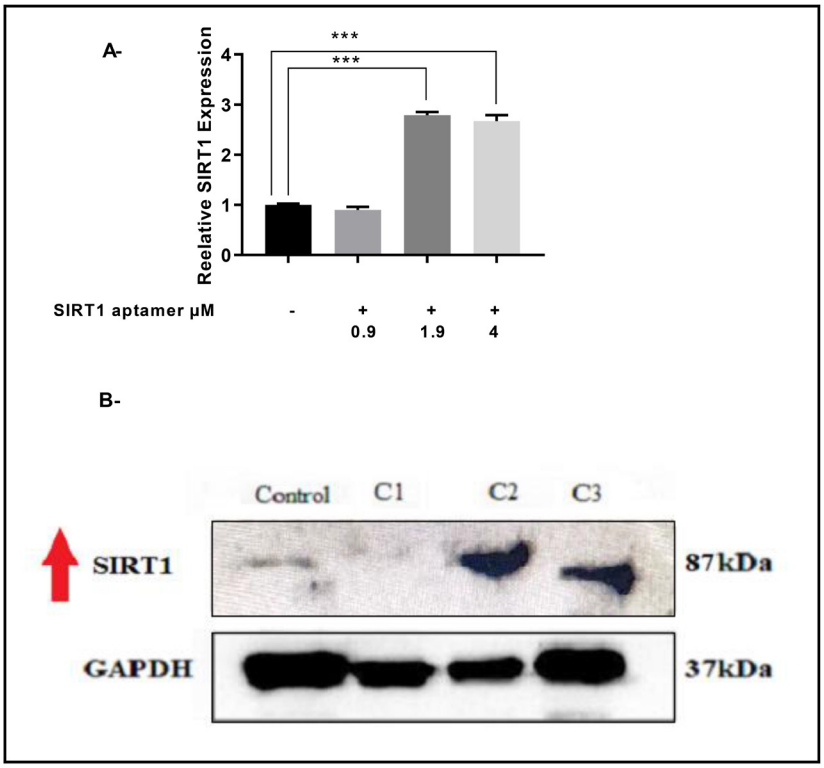

Figure 3. The effect of the SIRT1 aptamer on SIRT1 in the RAW 264.7 cell line using western blot. Panel A indicates that the SIRT1 aptamer leads to an increase in SIRT1 expression, with different concentrations of the aptamer labeled at the bottom (μM) ($P < 0.05$). Panel B presents the western blot analysis results of SIRT1 expression, showing significant difference compared to the control group. The Y-axis represents SIRT1 expression relative to GAPDH.

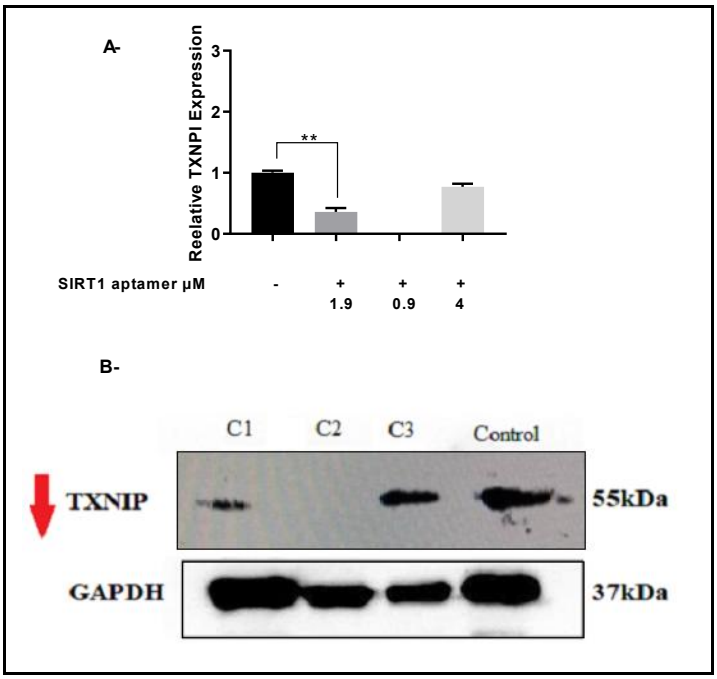

Figure 4. The effect of SIRT1 aptamer on TXNIP in RAW 264.7 cell lines using western blot. (A) Analysis SIRT1 aptamer leads to decreased TXNIP expression with concentrations labeled at the bottom (μM) ($P < 0.05$). (B) The results of the western blot analysis depict significant variation in TXNIP expression compared to the control group. The Y-axis represent TXNIP expression versus GAPDH.

aptamer protected cells against LPS-induced toxicity (Figure 5).

Discussion

Studying the various aspects of inflammation helps us better understand how to prevent its harmful effects on damaged tissues during the acute phase as well as its specific function. Chronic inflammatory disorders are the leading cause of death globally, making them the biggest threat to human health according to the World Health Organization (WHO) (21).

In the current study, the SIRT1 dose-response curve shown in Figure 2 demonstrates that SIRT1 aptamer decreased the viability of cells at high concentrations (6.25, 12.5, 25, 50 and 100μM). This suggesting that the aptamer has no toxicity on cells at concentrations below 6.25μM. According to the study by Zong et al, the percentage of RAW 264.7 macrophage cell viability significantly increased when incubated the cells with or without LPS (5 μg/mL) in the presence or absence of resveratrol (SIRT1 activator compound) at concentrations of 1, 5, and 10 μM, resulting in cell viability rates of 85%, 90%, and 95%, respectively (22). Interestingly, the finding revealed that the cytotoxicity of resveratrol according to

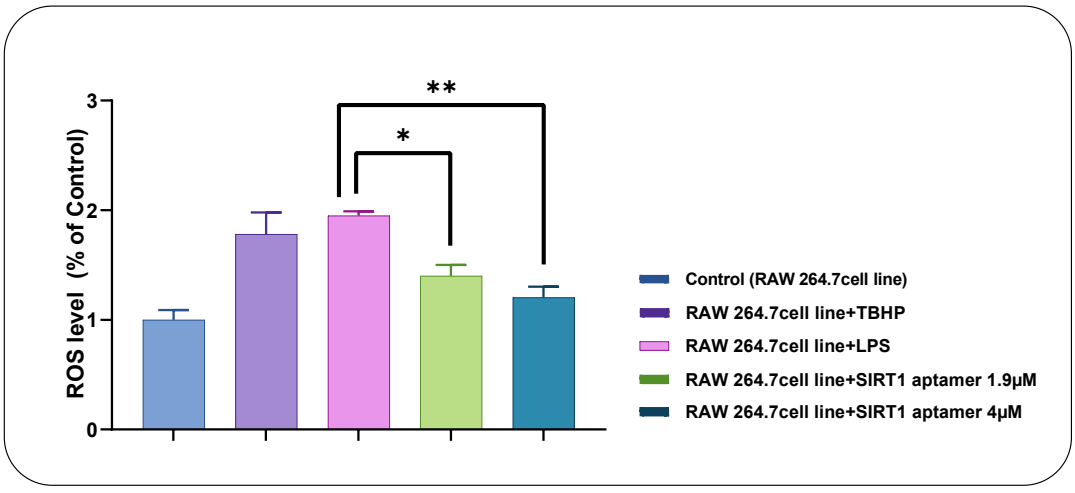

Figure 5. The effect of the SIRT1 aptamer on ROS levels generated by LPS. In RAW 264.7 cell line. Cells were exposed to LPS (10 μg/mL) in the presence or absence of the SIRT1 aptamer (1.9 and 4μM). The DCF test was utilized to assess the ROS level. The values presented are the mean SEM of at least three separate experiments. *$P<0.05$, **$P<0.001$ compared to the group treated with 10 μg/mL LPS alone.

the study by Zong et al was higher in RAW 267.7 cell lines than SIRT1 aptamer in this study. This aptamer likely contributes to the anti-inflammatory activity observed in this study. Therefore, the 1.9μM dose was considered the half- maximal non-cytotoxic dose of SIRT1 aptamer and was selected for the subsequent experiments.

Based on the results shown in Figure 3, the expression of SIRT1 in RAW 264.7 cells treated with the SIRT1 aptamer significantly increased at concentrations of 1.9μM and 4μM compared to the control group cells ($P<0.05$), which were not treated with the SIRT1 aptamer. Additionally, the expression of TXNIP in RAW 264.7 cells treated with the SIRT1 aptamer was downregulated at different concentrations and it was completely depleted at IC_{50} compared to the control group as illustrated in Figures 4A and 4B.

The mechanism by which SIRT1 regulates TXNIP involves TXNIP binding, a crucial step in activating the NLRP3 inflammasome. A recent discovery by Lian et al sheds light on the molecular mechanisms regulating NLRP3 inflammasome activation showing that SIRT1 is a potent negative regulator of TXNIP/NLRP3 inflammasome activation. In fact, SIRT1 agonists reduce the production of both TXNIP and NLRP3, leading to a more potent and broad inhibitory effect on NLRP3 inflammasome-induced inflammation compared to NLRP3 inhibitors (23). These findings align with a more recent study by Jiang et al, who established an in vitro model to study the impacts and fundamental signaling mechanisms of resveratrol (an activator of SIRT1). Additionally, key findings show that resveratrol effectively reduces the expression of inflammatory genes by inhibiting the ROS/TXNIP/NLRP3 pathway (24).

On the other hand, oxidative stress resulting from the overproduction of ROS can lead to potential consequences such as apoptosis, ischemia and inflammation (25). Oxidative stress promotes the translocation of TXNIP from the nucleus to the mitochondria. The direct binding of TXNIP, released from oxidized TRX, to leucine-rich regions of NLRP3 leads to the formation of the inflammasome. Inflammatory processes are closely linked to the activity of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α). Inflammatory response is significantly worsened when PGC-1α levels are reduced, which often occurs in inflammatory conditions (26,27). Meanwhile, PGC-1α helps maintain the balance between ROS production and removal during inflammation by regulating the expression of key antioxidant genes (26). Therefore, decreased level of PGC-1α in inflamed tissues lead to increased ROS formation and subsequent oxidative stress damage (28). A previous study by Tsuruoka et al demonstrated that SIRT1 plays a crucial role in activating PGC-1α in various disorders. They found that SIRT1 regulates PGC-1α through two distinct pathways: either directly influencing the expression of PGC-1α or by modulating its activity (29). In addition, Abu Shelbayeh et al revealed that PGC-1α plays a crucial role in the intracellular communication that maintains ROS homeostasis between the cytosol, nucleus, and mitochondria. This process is achieved through regulation by SIRT1which activates PGC-1α through deacetylation, a process that is NAD^+-dependent. Likewise, many known pharmaceuticals that enhance cellular functions either directly or indirectly, target the mitochondria via PGC-1 (30). In line with the data available in Figure 5 both concentrations of the SIRT1 aptamer (1.9 and 4μM) effectively counteracted ROS ($P<0.05$, $P<0.001$) compared to the group treated with 10 μg/mL LPS alone.

Based on the results of this study, the SIRT1 aptamer may serve as an anti-inflammatory biotherapy for treating chronic inflammation and its harmful effects. The ideal compound should inhibit the production and/or effects of oxidants while maintaining physiological functions and not interfering with the activity of natural antioxidants. Furthermore, SIRT1 plays a role in mediating the protective effects against oxidative stress through the SIRT1/PGC-1α pathway.

Conclusion

This study enhances our understanding of inflammation and its regulation with a particular focus on the role of SIRT1. The SIRT1 aptamer effectively increases SIRT1 expression and decreases TXNIP expression in RAW 264.7 cells, indicating its potential anti-inflammatory properties. Additionally, it shows that inflammation resulting from oxidative stress is exacerbated by reduced levels of PGC-1α, which play a critical role in regulating the balance of ROS. The SIRT1 aptamer effectively reduces levels of ROS, demonstrating its ability to protect against oxidative stress by activating the SIRT1/PGC-1α pathway. Hence, the SIRT1 aptamer shows potential as a novel biotherapy for chronic inflammation, offering a possible therapeutic approach to control and alleviate the detrimental consequences of chronic inflammatory illnesses while maintaining the effectiveness of natural antioxidants.

Limitations of the study

It is possible that the way in which cell lines react to medications and therapies does not exactly reflect how an entire organism would react. This is because the cellular environment in cell culture can differ significantly from in vivo conditions, potentially influencing cellular behavior and responses.

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Authors' contribution

Conceptualization: Ahmed A. Mohammed.
Data curation: Safa Abd Abbas Nahi.
Formal analysis: Inam Sameh Arif.
Funding acquisition: Safa Abd Abbas Nahi.

Investigation: Safa Abd Abbas Nahi.
Methodology: Safa Abd Abbas Nahi.
Project administration: Inam Sameh Arif.
Resources: Safa Abd Abbas Nahi.
Software: Ahmed A. Mohammed.
Supervision: Inam Sameh Arif.
Validation: Inam Sameh Arif.
Visualization: Ahmed A. Mohammed.
Writing–original draft: Safa Abd Abbas Nahi.
Writing–review & editing: Ahmed A. Mohammed.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research adhered to the principles of the Declaration of Helsinki. It was conducted in the postgraduate laboratory of the Pharmacology and Toxicology Department (Cell Culture Laboratory) at Mustansiriyah University's Pharmacy College in Baghdad, Iraq. This study is part of the MSc thesis of Safa Abd Abbas Nahi from the same university. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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