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Onion thiolanes as multifunctional molecules: a story about recently discovered compounds from a well-known vegetable

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Onion (*Allium cepa* L.) contains various bioactive organosulfur compounds, including recently identified species with a 3,4-dimethylthiolane ring structure. In this study, the biological activities of 24 onion-derived thiolane samples were comprehensively evaluated, focusing on antioxidant, anti-inflammatory, antidiabetic, and antimicrobial potential. Tested thiolanes showed significant antioxidant activity by reducing intracellular reactive oxygen species (ROS) levels in THP1-Blue™ NF-κB cells; however, some tested derivatives exhibited mild pro-oxidant effects. In assays targeting metabolic regulation, several compounds showed partial activation of the peroxisome proliferator-activated receptor gamma (PPARγ) pathway, particularly allithiolane B isomers, achieving 22–26% of the maximal response induced by the known full agonist rosiglitazone, suggesting potential as PPARγ modulators. Anti-inflammatory assessments revealed minimal direct inhibition of NF-κB signaling, except for onionin A, which modestly attenuated NF-κB activity. Cytotoxic evaluation indicated safety at physiological concentrations (up to 10 μM), though some thiolanes significantly reduced cell viability at higher concentrations (50 μM), highlighting their potential for selective cytostatic applications. Antimicrobial screening indicated limited activity against bacteria and fungi at tested concentrations, except for moderate antifungal effectiveness against *Candida albicans* shown by allithiolane D and cepathiolactols F. Overall, these results emphasise that onion thiolanes are multifunctional molecules capable of modulating oxidative stress, metabolic regulation and inflammation, supporting their potential use in nutraceutical strategies aimed at chronic disease prevention and management.

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1. Introduction

Onion (*Allium cepa* L.) is a ubiquitous culinary and horticultural crop that has also attracted considerable attention for its health-promoting properties. Modern research has shown that onion and its constituents exhibit diverse bioactivities, including antimicrobial, anticancer, antidiabetic, antioxidant, antiplatelet, and anti-inflammatory effects.[1–6] These physiological effects make onion a paradigmatic "functional food" that combines nutrition and health. Many of the beneficial effects of onion are attributed to its rich content of organosulfur and phenolic compounds, which are known to affect biological targets relevant to chronic diseases. This convergence of nutrition and biochemistry has stimulated great interest in identifying the specific onion-derived molecules responsible for their diverse bioactivity.

Recent phytochemical studies on onion have uncovered a new kingdom of sulfur-containing compounds with a 3,4-dimethylthiolane (saturated five-membered sulfur heterocycle) ring. These discoveries greatly expanded the classical profile of onion organosulfur metabolites (*e.g.*, thiosulfinates, lachrymatory sulfine, and cepaenes)[7] with numerous additional stable cyclic sulfides (Fig. 1). Onionins A and cepathiolanes A were the first characterized representatives of this structural class.[8,9] Subsequently, Kubec and co-workers reported a series of nine novel sulfur compounds from onion, termed allithiolanes A–I,[10] followed by the discovery of cepadithiolactone, together with additional types of onionins and cepathiolanes.[11] Most recently, Štefanová *et al.* described two novel families of onion thiolane compounds, named cepathiolactols and cepathiolactones, which also possess a 3,4-dimethylthiolane core with various disulfide-linked side chains.[12] Collectively, these sulfur

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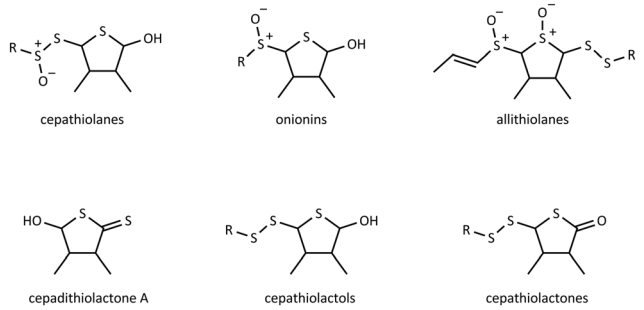

Fig. 1 General structures of onion thiolanes identified in onion.

metabolites – here referred to as "onion thiolanes"– represent a previously unrecognized group of onion phytochemicals that has rapidly become the focus of food chemistry and nutrition research.

Apart from their intriguing chemistry, onion thiolanes are also of interest for their biological activities, which appear to contribute to the health-promoting effects of onion. In particular, several studies point to their potent anti-inflammatory and immunomodulatory properties. Onionin A has been shown to suppress pro-inflammatory signalling in immune cells: it blocks the alternative (M2) activation of macrophages, thereby limiting the tumour-promoting functions of these cells. This mechanism, *i.e.* inhibition of M2 macrophage polarization, was associated with reduced cancer cell proliferation in ovarian and osteosarcoma models, highlighting the dual anti-inflammatory and anticancer effects of onionin A.[9,13–15] More generally, onion organosulfur extracts can downregulate key inflammatory mediators. For example, a methanol extract of onion inhibited LPS-induced expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in microglial cells, leading to a decrease in nitric oxide and cytokine (TNF-α, IL-1β, IL-6) levels. Such findings suggest that onion thiolanes may modulate the NF-κB pathway and other inflammation-related signalling, thereby attenuating inflammatory responses.[2,16,17] This anti-inflammatory capacity is significant given the role chronic inflammation plays in diseases ranging from arthritis to cancer.

Onion thiolane compounds may also potentially serve as antioxidants or to boost the body's antioxidant defence systems. Organosulfur molecules are often redox-active, capable of scavenging reactive oxygen species (ROS) or triggering adaptive stress responses. Consistent with this, cell and animal studies show that onion-derived compounds enhance antioxidant enzymes and molecules. Treatment with onion extracts leads to an upregulation of cytoprotective enzymes such as heme oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase-1 (NQO1), and catalase, which help neutralize ROS.[2] *In vivo*, onion consumption increases levels of superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione, thereby reducing oxidative damage in tissues.[2] These effects are consistent with the observed antioxidant activity of onion and its organosulfur constituents. By scavenging free radicals and mitigating oxidative stress, onion thiolanes may possibly contribute to the prevention of oxidative stress-related diseases and aging processes.

Another remarkable facet of onion thiolanes is their potential as antimicrobial agents. *Allium* species are known for their potent antimicrobial sulfur compounds (*e.g.* allicin in garlic), and onions produce analogous substances that defend the plants against pathogens.[18–21] Although the newly identified thiolane derivatives have not yet been fully evaluated against microbes, there is evidence that the organosulfur fraction of onion exhibits a broad spectrum of antimicrobial effects. Organosulfur compounds isolated from onion have shown significant antibacterial activity against both Gram-positive and Gram-negative bacteria, including antibiotic-resistant strains.[22] Proposed mechanisms for this antimicrobial action include disruption of microbial cell membranes and inhibition of thiol-dependent enzymes in pathogens, as has been demonstrated for other *Allium* sulfur compounds. In addition to antibacterial effects, onion essential oils and extracts have also shown antifungal activity (*e.g.*, against *Aspergillus*, *Fusarium*, and dermatophyte fungi).[2] Therefore, it is plausible that onion thiolanes may contribute to the antimicrobial spectrum of onion, helping to inhibit bacteria and fungi *via* chemical defence mechanisms inherent to this vegetable.

Emerging research also suggests that the onion thiolane compounds support metabolism and have antidiabetic effects.[8] Onion has long been recognized for its hypoglycemic influence in traditional medicine, and scientific studies have demonstrated its role in regulating blood glucose levels.[1] Compounds from onion can support glucose metabolism through several pathways. Onion skin and peel extracts (rich in phenolic compounds) can inhibit carbohydrate-hydrolysing enzymes such as α-glucosidase and α-amylase, thereby slowing the breakdown of starch into sugars.[2] Remarkably, quite potent α-glucosidase inhibiting activity was observed for cepathiolane A.[8] This enzyme inhibition can reduce postprandial blood sugar spikes, a mechanism analogous to that of some antidiabetic drugs. In addition, onion consumption may improve insulin activity: a recent clinical trial reported that daily consumption of fresh onion improved hyperglycemia and insulin resistance in patients undergoing chemotherapy.[2] These findings suggest a multifaceted antidiabetic effect of onion constituents, in which thiolane-based compounds, in addition to phenolic compounds, may play a supportive role in promoting insulin secretion, increasing insulin sensitivity, and protecting pancreatic β-cells from oxidative stress.

In summary, the recent discoveries of 3,4-dimethylthiolane-containing compounds in onion have opened many new avenues for understanding how this familiar vegetable provides broad health benefits. These onion thiolanes – including allithiolanes, onionins, and cepathiolactols – potentially exhibit a remarkable range of bioactivities, from modulating inflammation and oxidative stress to fighting microbes and improving metabolic parameters.[8,9,14,15,17] Ongoing and future studies in food science and biomedicine are poised to elucidate the full significance of onion thiolanes and stimulate

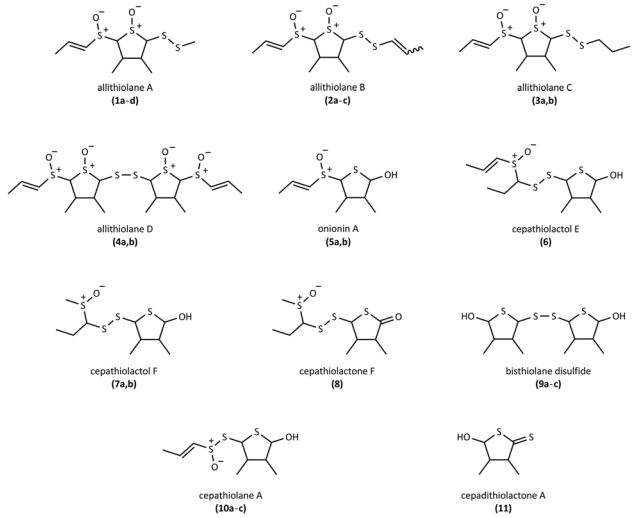

Fig. 2 Structure of onion thiolanes included in this study.

interest in their potential applications to prevent chronic diseases and promote human health.

In this study, we describe anti-inflammatory, antioxidant, antidiabetic, and antimicrobial potential of a large number of 11 thiolane-based compounds isolated from onion, including allithiolanes A–D (**1–4**), onionins A (**5**), cepathiolactols E (**6**) and F (7), cepathiolactone F (**8**), bisthiolane disulfides (**9**), cepathiolanes A (**10**), and cepadithiolactones A (**11**) (Fig. 2). In some cases, several stereoisomers were tested, making a total of 24 different samples. As far as we know, this represents the most comprehensive group of onion thiolanes tested for their biological activity to date.

2. Experimental

2.1. Test compounds

In this study, 24 samples of onion thiolanes were evaluated in total (Fig. 2). This group of thiolane-based compounds included allithiolanes A_1, A_3, A_5–A_7, and A_8 (**1a–d**, respectively), allithiolanes B_3, B_4, and B_5 (**2a–c**, respectively), allithiolanes C_1 and C_2 (**3a** and **3b**, respectively), allithiolanes D_x and D_2 (**4a** and **4b**, respectively), onionins $A_2 + A_4$ and $A_1 + A_5$ (**5a** and **5b**, respectively), cepathiolactols $E_1 + E_2$ (**6**), cepathiolactols F_1 and $F_2 + F_3$ (**7a** and **7b**, respectively), cepathiolactones F_1–F_3 (**8**), bisthiolane disulfides A_1, A_2, and A_3 (**9a–c**, respectively), cepathiolanes $A_1 + A_2$, $A_3 + A_4$, and $A_5 + A_6$ (**10a–c**, respectively), and cepadithiolactone A (**11**). The test compounds were isolated and structurally characterized (^{1}H and ^{13}C NMR, IR, HRMS, MS/MS) as described in detail in Kubec *et al.*[10] and Štefanová *et al.*[11,12]

2.2. Cell maintenance

Genetically modified human monocytic leukemia THP1-Blue™ NF-κB (Invivogen, San Diego, CA, USA) cells were used for *in vitro* viability determination, for evaluation of NF-κB activity and antioxidant properties of test compounds. Cells were routinely cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine, antibiotics (100 U mL^{-1} penicillin and 100 mg mL^{-1} streptomycin) (all from Sigma–Aldrich), and antimicrobial agent Normocin (Invivogen). Cells were passaged twice a week.

U2OS osteosarcoma cells were genetically engineered to stably express the PPARγ2 receptor, along with a luciferase reporter gene under the control of a peroxisome proliferator response element (PPRE). These PPARγ2 CALUX cells, obtained from BioDetection Systems BV (Amsterdam, Netherlands), are used to assess PPARγ2 activation through luciferase expression.[23] The cells were cultured in DMEM/F12 GlutaMAX medium supplemented with 7.5% foetal bovine serum (FBS), 1% non-essential amino acids, 100 U mL^{-1} penicillin, and 100 mg mL^{-1} streptomycin. G418 (Roche, Mannheim, Germany) was added weekly at 200 μg mL^{-1} concentration to maintain selection pressure. All cell cultures were incubated at 37 °C in a humidified environment containing 5% CO_2.

2.3. Determination of cell viability

The effect of the tested compounds on cell viability was determined using a Cell Counting Kit-8 (CCK-8; Abcam, Cambridge, UK) according to the manufacturer's instructions. The thiolanes were dissolved in dimethylformamid (DMF; Sigma–Aldrich) and added to the cell suspension in the RPMI 1640 medium without FBS (5×10^5 cells per ml). Subsequently, the cells were incubated at 37 °C with 5% CO_2 for 24 h. Then, the relative cell viability (the ratio between cells treated with tested compounds and cells treated only with DMF) was determined by CCK-8 kit. All measurements were done at least 3-times in triplicate.

2.4. Evaluation of anti-NF-κB activity

The effect of the tested compounds on the activity of pro-inflammatory transcription factor NF-κB was determined on lipopolysaccharide (LPS)-challenged THP1-Blue™ NF-κB cells as we described previously.[24] Briefly, the cells were pre-treated by the tested material dissolved in DMF at concentration of 10 μM for 1 h. This concentration was determined as non-cytotoxic (cell viability was >95%). Then, LPS from *Escherichia coli* 0111:B4 (Merck) dissolved in serum-free RPMI 1640 medium (1 μg mL^{-1}) was added. After 24 h incubation, the activity of NF-κB was determined as the amount of secreted embryonic alkaline phosphatase using Quanti-Blue™ medium (Invivogen).

2.5. Determination of redox activity

A modified version of the Wolfe and Liu method was employed to determine the antioxidant and pro-oxidative activities of the test compounds.[25] THP-1 monocytes (600 000 cells per mL^{-1}) were pre-incubated in serum-free RPMI 1640 medium containing 25 μM 2′,7′-dichlorodihydrofluorescein-diacetate ($DCFH_2$-DA; Sigma–Aldrich) dissolved in DMSO (final DMSO concentration of 0.1%) at 37 °C for 1 h. Following this incubation, the

cells were centrifuged, washed with PBS, resuspended in fresh serum-free RPMI 1640, and plated in 96-well plates (6×10^4 cells per well). After an additional 1-hour incubation for required cell adaptation, the cells were treated with the tested compounds (10 μM in DMF, each substance in triplicate) for another 1 h. To evaluate antioxidant activity, 600 μM 2,2′-azobis(2-methylpropionamidine) dihydrochloride (AAPH; Sigma–Aldrich) was added to induce intracellular reactive oxygen species (ROS) production. Quercetin (10 μM in DMF) served as the positive antioxidant control. One hour after AAPH addition, the fluorescence of oxidized 2′,7′-dichlorofluorescein (DCF) was measured at 37 °C using a FLUOstar Omega microplate reader (BMG Labtech) (excitation: 485 nm; emission: 538 nm). Antioxidant activity was expressed as the ratio of average fluorescence in wells containing test substances and AAPH to that in control wells treated with AAPH alone.

The pro-oxidative activity was assessed using the same experimental setup, except that AAPH was omitted during the final incubation step for wells containing test compounds. In this case, $DCFH_2$-DA–loaded cells were treated with the test compounds (10 μM) only. To serve as a positive control for oxidative stress induction, AAPH was added to a separate set of $DCFH_2$-DA–loaded cells without any test compounds. Wells containing $DCFH_2$-DA–loaded cells without any treatment served as the negative control. Fluorescence in all wells was measured 1 h after the addition of AAPH to the appropriate wells. Pro-oxidative activity was calculated as the ratio of average fluorescence in wells treated with test compounds (without AAPH) to the average fluorescence of the untreated control wells (also without AAPH).

2.6. Determination of PPARγ2 pathway activation

PPARγ is a key regulator of adipogenesis, glucose metabolism, and fatty acid storage. Its activation is crucial for managing metabolic processes and is implicated in the pathogenesis of diseases such as type 2 diabetes and cardiovascular disorders, making it an important therapeutic target for metabolic and inflammatory conditions.[26,27] Luciferase activity in PPARγ2 CALUX reporter cells was measured to assess the ability of thiolanes to induce PPARγ2 expression. PPARγ2 CALUX cells were plated in 96-well plates (TPP, Switzerland) at a density of 10 000 cells per well in 100 μL of assay medium (DMEM/F12 without phenol red, supplemented with 5% charcoal-stripped FBS and 1% non-essential amino acids; all from Merck KGaA, Darmstadt, Germany). After a 24-hour incubation for cell adherence and monolayer formation, the test compounds were added to the central sixty wells in quadruplicate at a final concentration of 10 μM. The final DMF concentration was maintained at 0.1% in all treatments. The remaining margin wells were filled with 200 μL of PBS. After 24 h, the cells were examined microscopically for cytotoxicity. The medium was then removed, and the plates were frozen at −80 °C for 15 minutes. Cells were lysed using 30 μL of lysis buffer (25 mM Tris, pH 7.8; 2 mM dithiothreitol; 2 mM 1,2-diaminocyclohexanetetraacetic acid; 10% glycerol; 1% Triton X-100; from BDS, Amsterdam, Netherlands). Luciferase activity was measured using a FLUOstar Omega luminometer (BMG Labtech, Germany) after the addition of 100 μL of flash mix (20 mM tricine, 1.07 mM $(MgCO_3)_4{\cdot}Mg(OH)_2$, 2.67 mM $MgSO_4$, 0.1 mM EDTA, 2.0 mM dithiothreitol, 470 μM luciferin, and 5.0 mM ATP; purchased from BDS). The results were expressed as relative light units (RLU) per well.

2.7. Determination of antimicrobial effect

To determine the antimicrobial efficacy of test thiolanes, a modified method according to EUCAST (European Committee on Antimicrobial Susceptibility Testing) was used to determine the minimum inhibitory concentration (MIC; bacterial viability less than 90%) by the microdilution method. Six concentrations (12.5 mM, 6.25 mM, 3.125 mM, 1.563 mM, 0.781 mM, 0.390 mM) of each compound were tested. The reference strains of microorganisms used in the experiment were *Staphylococcus aureus subsp. Aureus* CCM 4223, *Escherichia coli* CCM 3954 and *Candida albicans* CCM 8261 from the Czech Collection of Microorganisms of the Department of Experimental Biology, Faculty of Science, Masaryk University. Experiments that included cultivation of *S. aureus* and *E. coli* were done on MUELLER-HINTON broth (Sigma–Aldrich) and *C. albicans* was inoculated on Malt Extract Broth (Sigma–Aldrich). Inoculum concentration was adjusted to approximately $1–2 \times 10^8$ CFU mL^{-1} corresponding to suspension standard of 0.5 degrees McFarland. Final concentration in the wells was adjusted by dilution to $10^4–10^5$ CFU mL^{-1}. The inoculated plates were incubated for 18 h at 35–37 °C. After incubation, the absorbance (turbidity) in plates was measured spectrophotometrically using a microplate reader and the inhibition was calculated from the obtained data. To visualize the results, a TTC (triphenyl tetrazolium chloride) chemical was used, which stains the wells red when a microorganism is present in the well. The reaction reduces tetrazolium chloride to red formazan when bacterial and yeast dehydrogenases are present.

2.8. Statistical evaluation

Statistical analyses were carried out using GraphPad Prism 7.05 software (San Diego, CA, USA). The data were graphed as means ± standard error of mean (SE). Outlying values were identified by ROUT algorithms ($Q = 5\%$) and removed from the analysis. Comparisons between groups were made using a one-way ANOVA test followed by the uncorrected Fisher's LSD *post-hoc* test for multiple comparison.

3. Results and discussion

3.1. Cell viability evaluation

The cytotoxicity of bioactive compounds is a double-edged sword: some toxicity can be beneficial for killing cancer cells or pathogens, but high toxicity can damage normal cells. The onion thiolanes were tested for their cytotoxic effects on mammalian cells to evaluate their safety and potential as cyto-

statics. The experimental data indicate that at the concentration of 10 μM, the onion thiolanes exhibit any cytotoxicity, showing no significant loss of viability in cultured THP1-Blue™ NF-κB immune cells. This concentration (10 μM) was used for further experiments as the highest non-cytotoxic concentration. Low cytotoxicity indicates a good safety margin for physiological exposures, as was demonstrated on the example of cycloalliin in the study of Ichikawa *et al.* (2006).[28] In this study, the maximal concentration of cycloalliin in rat blood plasma was 1.59 μg mL^{-1} (~ 9 μM) after oral administration of 50 mg kg^{-1} of this compound. However, at a higher concentration (50 μM), a subset of thiolane compounds caused significant reductions in cell viability (Fig. 3). Specifically, 10 out of 24 tested compounds reduced viability by more than 20%, with the two most potent (compounds **4a** and **9c**) reducing cell viability by ~40% after 24 h. Compounds **4a** and **9c** correspond to specific structural classes (allithiolane D and a bisthiolane disulfide, respectively), indicating that particular structural motifs (such as disulfide-linked thiolane rings) confer higher cytotoxicity. This level of cytotoxic effect (~40% kill at 50 μM) is not extreme, but it does show that some onion thiolanes can act as cytostatic or cytotoxic agents at higher doses. In a therapeutic context, this could be used for anticancer effects if selectively delivered to tumour cells, but it also flags these compounds for potential side effects if concentrations accumulate in normal tissues.

3.2. Anti-NF-κB effect determination

Onion extracts have been shown to reduce the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 in various cell models, indicating their potential to alleviate inflammation.[29,30] This effect may be caused by a reduction of activity of transcription factor NF-κB, which plays an important role in the treatment of inflammation.[31] It has been hypothesized that onion thiolanes may suppress NF-κB activation. However, experiments using an NF-κB reporter (in LPS-challenged immune cells) revealed that most onion thiolane compounds did not significantly inhibit NF-κB activity at 10 μM (Fig. 4). In fact, none of the tested molecules reduced NF-κB-driven transcription by more than about 10%, and a few had no effect. One compound (bisthiolane disulfide, **9c**) unexpectedly increased NF-κB activity by ~15%, suggesting a mild pro-inflammatory signal at this concentration. This could also contribute to its higher cytotoxicity. The most active inhibitor in the group was onionin A (**5b**), which attenuated NF-κB activity by about 10%. These results suggest that direct NF-κB inhibition is not the primary anti-inflammatory mode of action for onion thiolanes in acute inflammatory stimulation. This contrasts with some other phytochemicals (for instance, quercetin in onions strongly inhibits NF-κB).[31]

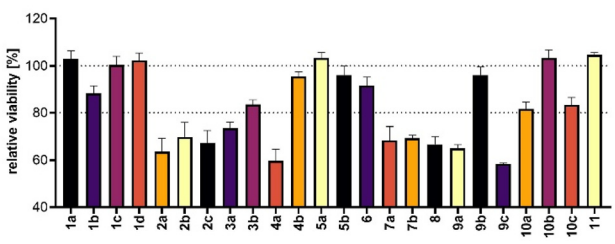

Fig. 3 Effect of tested onion thiolanes at the concentration of 50 μM on relative viability of THP1-Blue™ NF-κB cells after 24 h incubation in serum-free medium. Data are presented as mean ± SEM.

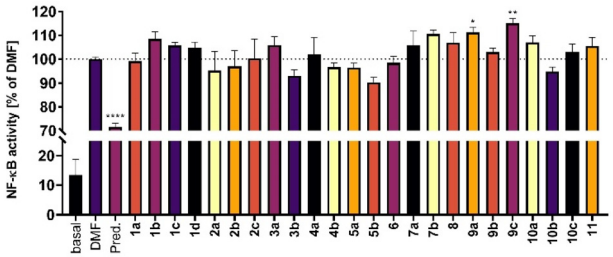

Fig. 4 Effect of tested onion thiolanes on the activity of NF-κB after LPS challenge. THP1-Blue™ NF-κB cells were pre-treated by the thiolanes at the concentration of 10 μM or vehicle (DMF) only and 1 h later, NF-κB was activated by LPS. The activity of this transcription factor was evaluated 24 h after adding the compounds. Data are presented as mean ± SEM. Pred. – prednisolone 1 μM. * means $p < 0.05$ in comparison with DMF group; ** means $p < 0.01$ in comparison with DMF group; **** means $p < 0.0001$ in comparison with DMF group.

3.3. Redox activity

One of the prominent biological effects of onion thiolanes is their ability to modulate oxidative stress by influencing ROS levels. Onion and its constituents are known as antioxidants, as they decrease lipid peroxidation and enhance antioxidant defences (SOD, CAT, glutathione peroxidase, *etc.*) in biological systems.[31] In line with this, our experiments show that a wide range of onion-derived thiolane compounds significantly reduce intracellular ROS levels in immune cells at 10 μM concentrations (Fig. 5A). This indicates that thiolanes contribute to the antioxidant potential of onion, probably by scavenging free radicals or by upregulating cellular antioxidant metabolic pathways. Remarkably, some specific structures showed a pro-oxidant effect (Fig. 5B): for example, cepathiolanes A (**10a**, **10c**) and cepadithiolactone A (**11**) actually increased oxidative stress level. These exceptions suggest that slight differences in structure can turn an organosulfur compound from an antioxidant to a pro-oxidant. A slight, non-significant elevation of oxidative stress (assessed as lipid peroxidation) caused by acyclic disulfides was also observed by Higuchi *et al.*[32] This was partially confirmed in another study in which Matrella *et al.* described higher ROS level after treatment of H9c2 cells with different onion extracts.[33] Increased ROS content by these compounds may be due to their higher sulfur content or redox-active disulfide bonds that can undergo redox cycling. Indeed, in a previous study, mild lipid peroxidation was observed with certain linear disulfides, supporting this dual behaviour.[32]

The antioxidant properties of onion-derived thiolanes may also contribute to their potential in the treatment of type 2 diabetes mellitus (T2DM). Oxidative stress is a key factor in the

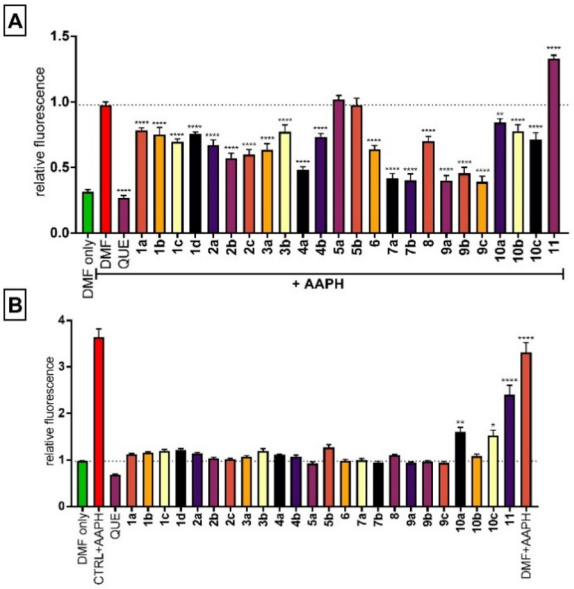

Fig. 5 Effect of tested onion thiolanes on ROS production. (A) Antioxidant activity of tested compounds. THP-1 cells were pre-treated by thiolanes at the concentration of 10 μM or vehicle (DMF) only and 1 h later, ROS production was induced by AAPH. (B) Prooxidant activity of tested thiolanes. The level of ROS was evaluated 1 h after adding the compounds. Data are presented as mean ± SEM. QUE – quercetin. * means $p < 0.05$ in comparison with reference group (DMF for A, and DMF only for B); ** means $p < 0.01$ in comparison with reference group (DMF for A, and DMF only for B); **** means $p < 0.0001$ in comparison with reference group (DMF for A, and DMF only for B).

progression and complications of diabetes, and onions have been shown to mitigate this stress through their antioxidant activity.[34] El-Demerdash *et al.* documented that onion extracts significantly reduce markers of oxidative stress, thereby protecting tissues and organs susceptible to diabetic complications, such as neuropathy and nephropathy.[35]

3.4. PPARγ2 pathway activation

Onion-derived sulfur compounds demonstrate potential for the treatment of T2DM – through several mechanisms, as shown by multiple studies. A primary mechanism is their effect on blood glucose levels and one of the possible mechanisms involved is the modulation of the PPARγ pathway. Peroxisome proliferator-activated receptors (PPARs) are ligand-inducible transcription factors that have been identified in three isoforms: PPARα, PPARβ/δ, and PPARγ. Among these, the PPARγ isoform plays a critical role in maintaining glucose balance and regulating lipid metabolism, making it an important therapeutic target for T2DM and also for metabolic syndrome.[36–38] When PPARγ is activated by specific ligands, it affects gene expression, resulting in improved insulin sensitivity, enhanced fatty acid storage and overall glucose homeostasis. Despite being effective in the normalization of blood glucose levels, the currently used PPARγ agonists from the thiazolidinedione type have serious side effects. Although synthetic PPARγ agonists such as rosiglitazone have been shown to increase insulin sensitivity, their use has been restricted due to side effects such as cardiovascular risks and weight gain, limiting their suitability for long-term treatment.[39] The severe adverse side effects associated with thiazolidinediones are attributed to their complete activation of PPARγ, in contrast to the weaker agonistic effects of endogenous ligands (*e.g.*, fatty acids). This has sparked interest in selective PPARγ modulators (SPPARMs) that provide partial agonism, offering improved glucose homeostasis with fewer side effects.[40]

Our results show that among the 24 samples tested, several demonstrated statistically significant induction of PPARγ pathway activity, expressed as a percentage of the maximal response to 10 μM rosiglitazone, which served as a positive control (Fig. 6). In particular, the allithiolane B group (compounds **2a–c**) and allithiolanes A_5–A_7 (**1c**) induced PPARγ activity to about 22–26% of the maximal response elicited by the full agonist rosiglitazone. This activation at a concentration of 10 μM was highly significant, although, as expected with partial agonists, none of the onion thiolanes reached the 100% activation level of the drug. Several other thiolanes (*e.g.*, bisthiolane disulfides **9a,b** and allithiolane D **4a**) achieved an activation of about 18–20%. These data indicate that certain structural classes of onion thiolanes serve as PPARγ agonists with low potency (partial agonism). In fact, the thiolanes identified could be considered PPARγ modulators rather than potent agonists – a profile that is potentially ideal for long-term metabolic therapy.

The metabolic significance of PPARγ activation by onion compounds is supported by existing studies on the antidiabetic effects of onion. Onion extracts and sulfur compounds have demonstrated antidiabetic and hypoglycemic activities in animal models as well as in humans. For example, Jung *et al.* reported that onion peel extract improved insulin sensitivity and reduced oxidative stress in diabetic rat models.[41] Similarly, Kang *et al.* demonstrated that Welsh onion root

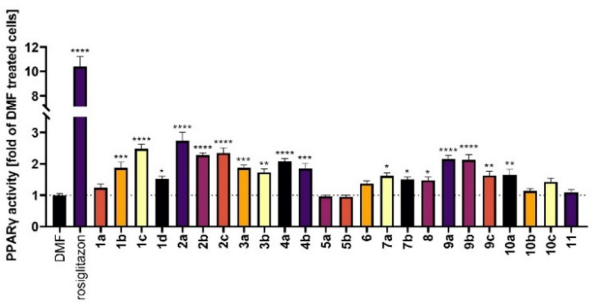

Fig. 6 Effect of tested thiolanes on the activity of PPARγ. PPARγ2 CALUX reporter cells were pre-treated by thiolanes at the concentration of 10 μM or vehicle (DMF) only. The activity of this transcription factor was evaluated 24 h after adding the compounds. Data are presented as mean ± SEM. * means $p < 0.05$ in comparison with DMF group; ** means $p < 0.01$ in comparison with DMF group; *** means $p < 0.001$ in comparison with DMF group; **** means $p < 0.0001$ in comparison with DMF group.

extract reduced fasting and postprandial hyperglycemia in diabetic animal models by inhibiting α-glucosidase, an enzyme involved in carbohydrate digestion.[42] However, these studies primarily used complex onion extracts, often without detailed analysis of the specific active compounds.

Another advantage of onion-derived compounds is their positive impact on insulin sensitivity. In a clinical study involving 105 patients with T2DM, the consumption of 100 g of raw onion on an empty stomach led to a significant reduction in blood glucose levels after one and three months compared to the control group. This effect was attributed to 1-propenyl propyl disulfide, a sulfur-containing compound found in processed onion.[43] Histological studies also underline the protective effect of onion compounds against tissue damage associated with T2DM. A study by Awwad *et al.* reported that onion consumption in diabetic rats helped to restore normal histological structures in damaged tissues, such as the tongue papillae, indicating a potential to reduce tissue-specific complications related to T2DM.[44] In addition, sulfur-containing compounds from onions help to improve the lipid profile improvement. Yoshinari *et al.* demonstrated that these compounds reduce triglyceride levels and free fatty acids, thus improving metabolic status in diabetic models. Certain compounds, such as *S*-methylcysteine sulfoxide (methiin) and cycloalliin, inhibited the differentiation of preadipocytes, suggesting an anti-obesity effect that may complement their role in the treatment of T2DM.[45]

Our study has shown that several onion thiolane-based compounds, particularly allithiolane B_3 (**2a**), significantly activate the PPARγ pathway, with activity levels reaching up to 26% of the maximal response of rosiglitazone. These results are consistent with previous studies highlighting the potential of onion compounds to influence metabolic pathways related to glucose regulation. Further investigation is needed to clarify how the PPARγ activation observed in tested thiolane compounds contributes to the broader antidiabetic effects reported in studies using complex onion extracts.

3.5. Antimicrobial potential

Onions possess antimicrobial properties, although generally milder than those of garlic. The antimicrobial activity of onion is largely due to its sulfur-containing volatile compounds that are produced when the onion is cut or crushed. Typical onion volatiles include thiosulfinates such as propyl-propane thiosulfinate (PTS) and its oxidized form propyl-propane thiosulfonate (PTSO), which are analogous to allicin (allyl-allyl thiosulfinate) in garlic. These compounds in onions can inhibit a number of microorganisms. For example, PTS and PTSO have demonstrated broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria, including multidrug-resistant clinical isolates.[46] They even exhibit vapour-phase activity, which means that the gases from fresh onion can kill bacteria in the enviroment.[46] Onions have also shown antifungal effects: onion extracts can inhibit the growth of yeast and filamentous fungi, but again at higher concentrations than is usual for garlic extracts.

Our experimental data indicate that the cyclic, less volatile onion sulfur compounds, have only mild direct antimicrobial effects. In assays, the onion thiolanes did not show strong bactericidal or fungicidal activity at the concentrations tested (millimolar levels were often required to achieve an effect). No growth reduction of Gram-negative *Escherichia coli* was observed after cultivation with tested thiolanes at concentaton of 6.25 mM (data not shown). However, all compounds, except of **5b**, were able to decrease the population of *Staphylococcus aureus* by 33–53% at the concentration of 12.5 mM (Fig. 7). Moreover, allithiolane D (**4a**) and cepathiolactols F (**7a,b**) showed a moderate activity against *Candida albicans*, with the MIC value (growth inhibition >90%) of 6.25 mM. However, compounds **3a**, **9a**, **10c**, and **11** inhibited the growth of *C. albicans* by 75–80%. Interestingly, compound **4b** slightly support the growth of *C. albicans*. In comparison, allicin and analogous thiosulfinates have been observed to have much higher activity against *C. albicans* (MIC values in the range of 0.1–1 mM).[18–21] This is not surprising as the tested thiolanes lack the highly reactive thiosulfinate moiety –S(O)S– (except for

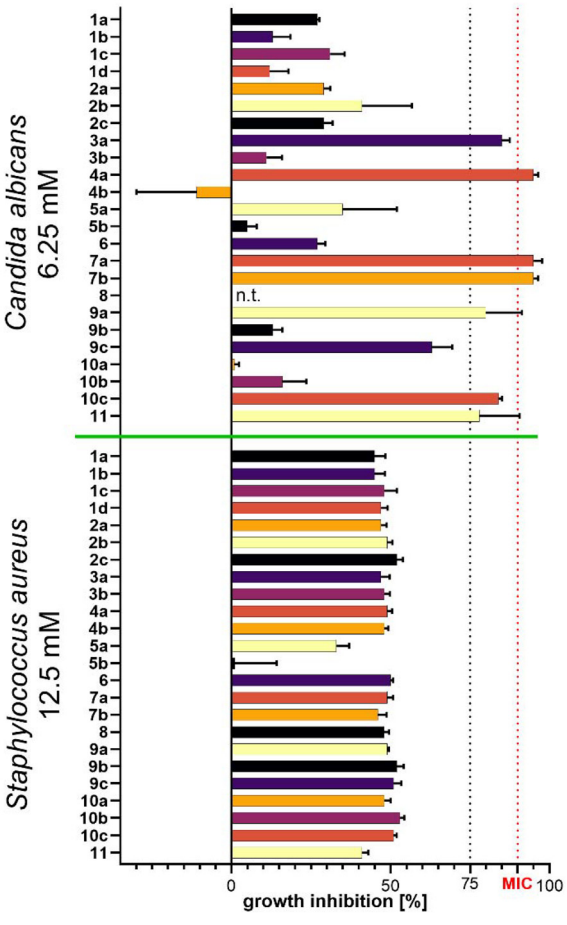

Fig. 7 Growth inhibition of *Candida albicans* and *Staphylococcus aureus* caused by tested thiolanes (12.5 mM for *S. aureus* and 6.25 mM for *C. albicans*). Data are presented as mean ± SEM. MIC – minimal inhibition concentration (90%); n.t. – not tested.

10a–c) that gives allicin and its analogues their potent antimicrobial effect.

4. Conclusions

Onion-derived thiolanes and related sulfur compounds represent a convincing example of food-based molecules exerting pharmacological effects. Their ability to modulate oxidative stress, inflammation and metabolic regulation suggests therapeutic relevance in chronic diseases characterised by these intertwined pathophysiological factors. For example, in metabolic syndrome and T2DM – disorders marked by insulin resistance, low-grade inflammation, and oxidative stress – onion compounds could address multiple aspects simultaneously. By reducing ROS and activating PPARγ, thiolanes improve cellular insulin response and glucose uptake while attenuating inflammatory signalling that exacerbates insulin resistance.[31] Indeed, the clinical and preclinical studies mentioned earlier show that onion consumption improves glycemic control and lipid profiles.[45] This suggests that thiolane-rich onion extracts may have a role to play as adjuncts or nutraceuticals in the treatment of T2DM. They may never be as effective as pharmaceuticals, but their safety and multi-targeted nature are advantages. In particular, the partial PPARγ activation by the thiolanes opens the door to safer PPARγ-targeted therapies – perhaps as part of a "food-as-medicine" approach or as templates for new drugs. Given the urgent need for insulin sensitisers that do not cause weight gain or cardiotoxicity, molecules that provide 20–30% PPARγ activation could yield benefits with fewer side effects.

In the realm of inflammatory diseases, while onion thiolanes alone are mild, their synergistic effects with other onion constituents (flavonoids such as quercetin) can be utilised. In some traditional applications, onions have been shown to help with conditions such as osteoarthritis and respiratory inflammation.[31] One could imagine an "anti-inflammatory diet" where onions (along with garlic, turmeric, *etc.*) contribute specific bioactives: quercetin and kaempferol from onion inhibit NF-κB activity and histamine release, and act as antioxidants, whereas thiolanes from onion contribute to general redox balance and help maintain metabolic health *via* PPARγ activation, collectively reducing inflammation. The immunomodulatory aspect (such as the effect of onionin A on macrophages) suggests a potential in diseases where the immune response is impaired, such as autoimmune conditions or even cancer. In cancer prevention, long-term consumption of *Allium* vegetables (onions, garlic) has been associated with a lower risk of certain cancers (*e.g.*, gastrointestinal cancer).[31] Mechanistically, this may be due to organosulfur compounds inducing detoxifying enzymes, scavenging radicals that cause DNA damage, and altering the inflammatory environment that can promote tumour growth. Onion thiolanes likely contribute to these protective effects by boosting antioxidant defences and moderating the behaviour of immune cells in the microenvironment that might otherwise promote tumorigenesis.

In conclusion, onion-derived thiolanes are biologically active components of a common food with significant health effects. They emphasise the importance of functional foods, where compounds present in the food have drug-like effects. Furthermore, the thiolanes also reinforce the concept that even long-familiar foods can harbour novel compounds with valuable biological functions. By modulating ROS levels, activating the PPARγ pathway, and exhibiting anti-inflammatory, cytotoxic and antimicrobial effects, these organosulfur molecules of onion act at the interface of oxidative stress, inflammation, and metabolism. Many chronic diseases develop at these interfaces, so compounds that can influence all three areas simultaneously are particularly valuable. Whether consumed as part of a healthy diet or potentially isolated and administered in form of dietary supplements, onion thiolanes show promise for supporting health and treating disease, deserving their further study in comparison and combination with other sulfur-rich phytochemicals.

Author contributions

Conceptualization: J. H., R. K.; Formal analysis: J. H.; Investigation: J. H., D. N., I. Š., P. B., M. N., O. S.; Methodology: J. H., D. N., M. N., J. T.; Project administration: J. H., J. T.; Supervision: J. H.; Visualization: J. H.; Writing – original draft: J. H., D. N., M. N., O. S., R. K.; Writing – review & editing: J. H., D. N., R. K. All authors read and approved the final manuscript.

Data availability

The data supporting this article have been included as part of the SI.

Conflicts of interest

There are no conflicts to declare.

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