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Research Article

Effective inhibition of bacterial sialidases by phenolic acids and flavonoids

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Abstract: As a pathogenicity factor in some microorganisms, sialidase is a key target for inactivation, as this would have curative and preventive effects on various diseases. Significant results are already achieved with viral sialidase inhibitors, while such studies on bacterial enzymes are scarce. Pure natural compounds representing phenols and flavonoids, were tested for their inhibitory effect on sialidases from *Vibrio cholerae* non-O1, *Arthrobacter nicotianae* and *Oerskovia paurometabola*. All three enzymes were isolated, purified beforehand and stored under suitable conditions. Quinic and gallic acids showed the highest inhibitory activity - 76 to 100% against the three sialidases. Fisetin had a significant inhibitory activity on two of the enzymes. The structurally related thymol and thymoquinone exerted from 80 to 100% inhibition on at least one of the enzymes. Catechin and rutin had significant inhibitory activity, varying from 49 to 100%, on some of the enzymes. Quercetin, known for its inhibitory effect on viral sialidases, had a lesser impact on the studied enzymes. The suppressive effect of quinic acid, rutin and fisetin on bacterial sialidases is observed for the first time.

1. INTRODUCTION

Sialidases are glycoside hydrolases (EC 3.2.1.18, exo-alpha sialidases, neuraminidases) that are present in the metabolism of humans and animals of the Deuterostomata lineage, and in some of their parasitic or commensal microorganisms such as viruses, bacteria, fungi, unicellular eukaryotes (Giacopuzzi *et al*., 2012). These enzymes cleave terminal sialic acids from complex sialosides including glycoproteins, glycolipids, polysaccharides, and polysialic compounds. As a result, free sialic acid is released (Schauer & Kamerling, 2018) (Figure 1). Sialic acids are a class of alpha-keto acid sugars with a nine-carbon backbone. The most common member of this group is N-acetylneuraminic acid (Neu5Ac) found in animals, humans, and some prokaryotes.

Some of the best-studied microbial sialidases are the viral ones, known so far in the families *Orthomyxoviridae* (for influenza viruses of type A and B) and *Paramyxoviridae*. They are a factor of pathogenicity, facilitating the adhesion and penetration of virus particles into host cells, as well as the spread of the newly formed virions. This enzyme is also a key factor in the pathogenesis of a number of bacterial infections, such as cholera, gas gangrene, meningitis,

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septicemia, cystic fibrosis, etc. (Corfield, 1992; Brittan *et al*., 2012). By cleaving terminal sialic residues from mucins, sialidase disrupts the mucosal layer, thereby allowing the infectious agent to penetrate to the tissue surface. By removing sialic residues from glycoproteins located on the cell surface, the enzyme reveals receptors to which the microorganisms adhere.

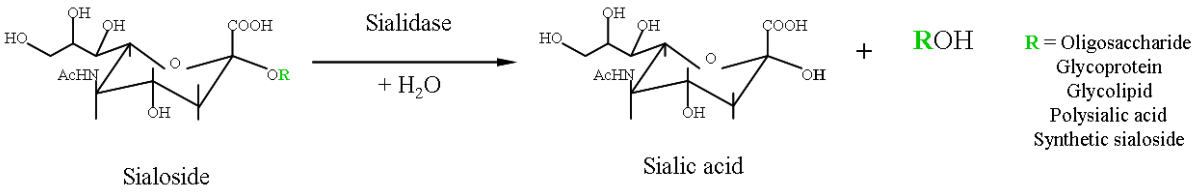


Figure 1. Schematic presentation of sialidase action.

The sialic acid derivative 2-deoxy-2, 3-didehydro-D-N-acetylneuraminic acid (Neu5Ac2en, DANA) was the first sialidase inhibitor, which mimics the oxocarbenium ion-like transition state (Meindl *et al*., 1974). DANA inhibits most sialidases and is a key compound in the search for antiviral drugs, leading to the synthesis of the highly effective commercial products Zanamivir™ and oseltamivir (Tamiflu™). At the same time, emergence of strains that are resistant even to these effective antiviral agents is reported (Grienke *et al*., 2012). Several triazole-linked derivatives of DANA were synthesized as selective inhibitors against *Vibrio cholerae* and *Arthrobacter ureafaciens* sialidases (Slack *et al*., 2018).

Since the discovery of the effective inhibitors of influenza virus sialidase and especially after the emergence of influenza strains resistant to them, the search for novel inhibitors is ongoing. It also develops in the direction of bacterial sialidases, where data are so far scarce. In recent years, a number of secondary plant metabolites have emerged as reliable sources of potential sialidase inhibitors (Sadati *et al*., 2019). Phenolic compounds are secondary metabolites including simple phenols, phenolic acids, flavonoids, xanthones, coumarins, stilbenes, tannins, lignans (Vuolo *et al*., 2019). A wide range of biological activities including antimicrobial, antioxidant, anti-inflammatory, antidiabetic, neuroprotective, and hepatoprotective have been reported for them. The health effect of these compounds is determined in many cases by their ability to inhibit enzymes associated with various human diseases like hypertension, metabolic problems, incendiary infections, and neurodegenerative diseases (Gonçalves and Romano, 2017; Rahman *et al*., 2021).

We have chosen for our study a set of substances, which include a precursor of oseltamivir (quinic acid), structurally related to it gallic acid; compounds with studied sialidase inhibition properties (catechin, quercetin), and ones that are not studied in this aspect (rutin, fisetin, thymol and thymoquinone).

2. MATERIAL and METHODS

2.1. Bacterial Sialidases

Sialidases from three bacterial producer strains were used: *Arthrobacter nicotianae* (AN), *Oerskovia paurometabola* Strain O129 (NBIMCC 9093) (O129), and *Vibrio cholerae* non-O1 Strain V13 (NBIMCC 8716) (V13). The enzymes were purified earlier and stored as lyophilized powder for AN (Abrashev *et al*., 2005), or as phosphate buffered saline (PBS) solution kept at -20 ºC for O129 and V13 (Eneva *et al*., 2015; Eneva *et al*., 2022). Before performing the inhibition test, the enzymes were standardized to solutions with 10 U/mL sialidase activity by dilution in PBS.

2.2. Chemical Compounds

In the present study, flavonoid aglycones: quercetin (3,3′,4′,5,7-pentahydroxyflavone), fisetin (3,3′,4′,7-tetrahydroxyflavone), catechin (3,3′,4′,5,7-pentahydroxyflavane) and flavonoid glycoside rutin (quercetin 3-rutinoside,) were selected for evaluation of their sialidase

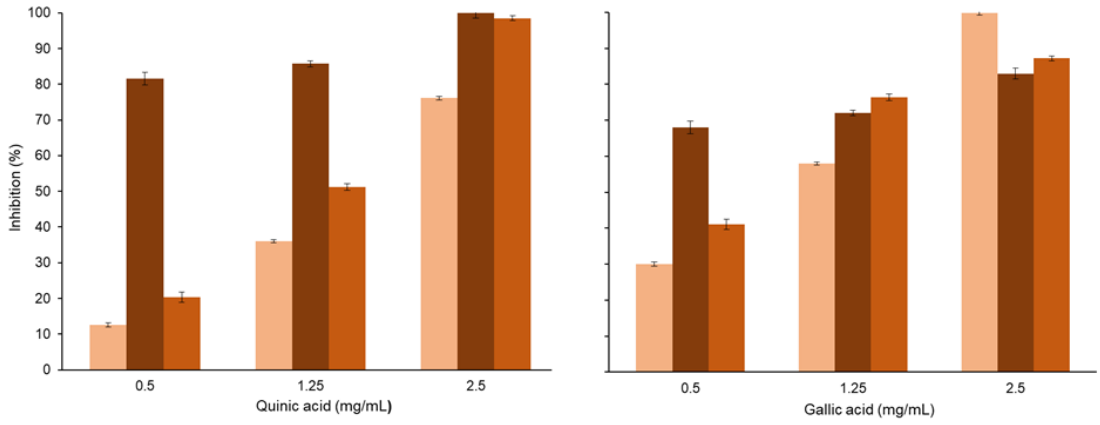
inhibitory activity. Gallic acid, ellagic acid and quinic acid from the phenolic acids and thymol (2-isopropyl-5-methylphenol), and thymoquinone (2-isopropyl-5-methyl-1, 4-benzoquinone) as monoterpenoid phenols were assayed too. Thymol, thymoquinone, gallic acid, ellagic acid, quinic acid, fisetin, rutin, catechin, and quercetin were obtained from Sigma–Aldrich.

2.3. Enzyme Assay

Sialidase activity was assayed according to the thiobarbituric acid method of Uchida *et al.* (1977). Glucomacropeptide (GMP) obtained from cheese whey was used as a substrate (Abrashev *et al.*, 1980). Separate 200-µl enzyme samples were mixed with 200 µl of each of the tested compounds dissolved in 5% dimethyl sulfoxide (DMSO). Control 200-µl enzyme samples mixed with 200 µl 5% DMSO in PBS were also prepared. Samples of each incubation mixture were assayed and the absorbance of samples and controls was measured on a UV-VIS 75 at λ=551nm. The amount of sialic acids released was determined as the difference (ΔE) in the extinctions of the sample and control was plotted on a standard curve, created using sialic acid as a standard. One unit of sialidase activity is defined as the amount that releases 1 µmol of N-acetylneuraminic acid (Neu5Ac) for 1 min at 37 °C using GMP as a substrate. Results are displayed as relative activity compared to the control, which was set as 100% activity. All experiments were performed in triplicate, and the data is reported as the average of three sample replicates, accompanied by the standard deviation.

3. RESULTS and DISCUSSION

Since the enzymes used in this study and most of the tested substances are being studied for the first time, we applied relatively high concentrations of all components (0.5, 1.25, 2.5 mg/mL). Our results show that quinic and gallic acids have the highest inhibitory activity. With the three sialidases tested, they exert inhibition in the range of 76-100% for the concentration of 2.5 mg/mL. AN and V13 sialidases are weakly inhibited with decreasing the acid concentration, while O129 enzyme retains approximately the same levels of high inhibition independently from the decreasing acid concentration (Figure 2). The inhibition effect is expected given the fact that quinic acid is a starting substance for the synthesis of oseltamivir, and gallic acid is close to it in structure. Quinic acid is a cyclic polyol, found in the bark of *Cinchona* trees, in the coffee beans, and also in *Urtica dioica*. In plants, quinic acid and compounds similar to it are precursors to lignins and phenols and they accumulate to some extent, especially in gymnosperms and woody dicotyledons (Farina and Brown, 2006).



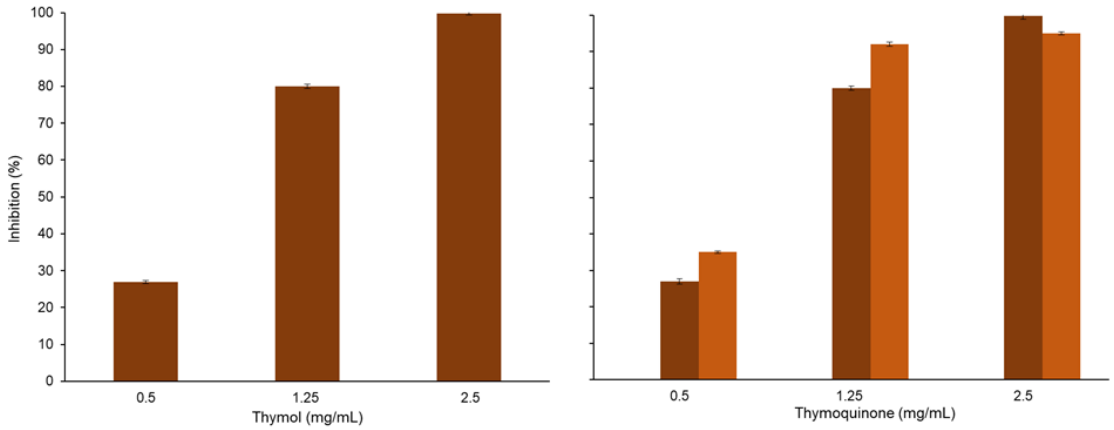
Legend: sialidase from *A. nicotianae*, from *O. paurometabola*, from *V. cholerae*

Figure 2. Inhibition effects of quinic and gallic acid on three bacterial sialidases

To our knowledge, the results we obtained are the first to describe the direct inhibitory effect of quinic acid on bacterial sialidase. It is known for its significantly suppressive effect on influenza A and PPR virus sialidases (Gattani *et al.*, 2020). Gallic acid is found in gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants (Haslam and Cai, 1994). They

represent a large family of plant secondary metabolites which is found in gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants. Gallic acid has antioxidant, antifungal, antimicrobial, and anticancer activities (Haslam and Cai, 1994; Rosas *et al*., 2019).

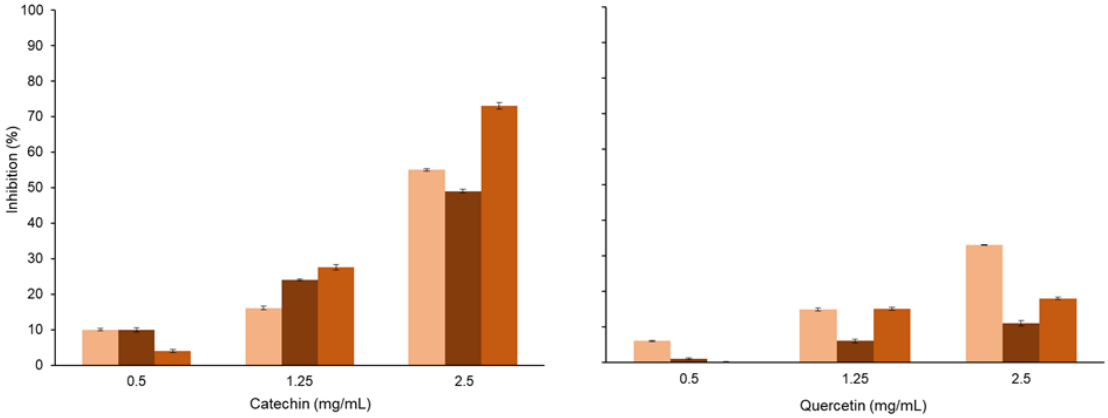
The monoterpenes thymol and thymoquinone have a similar strong effect, but with two of the sialidases. When tested in concentration 2.5 mg/mL, thymol has practically 100% inhibitory effect on only one of the enzymes - that of O129, and thymoquinone - on the enzyme of O129 and V13 (Figure 3). Thymol is a monoterpenoid phenol that is contained in thyme and other plants such as *Ocimum gratissimum* L., *Origanum* L., *Carum copticum* L., different species of the genus *Satureja* L., *Oliveria decumbens* Vent, etc., and has strong antiseptic properties. Thymol has shown an inhibitory effect on biofilms *in vitro* (Escobar *et al*., 2020). Both thymol and thyme essential oil were proved to have antibiofilm, antifungal, antileishmanial, antiviral, and anticancer properties (Kowalczyk *et al*., 2020). Thymoquinone is found in many plants of the Lamiaceae family, such as *Origanum*, *Monarda*, *Satureja*, *Thymus*, but in a particularly high concentration was found in *Nigella sativa* (Farkhondeh *et al*., 2017). However, it belongs to the group of substances that interfere with many qualitative reactions, as it reacts non-specifically with a large number of substances of interest (Baell, 2016), therefore, the results of this trial should be interpreted with caution.



Legend: sialidase from *A. nicotianae*, from *O. paurometabola*, from *V. cholerae*

Figure 3. Inhibition effects of thymol and thymoquinone on three bacterial sialidases.

The tested substances from the flavonol group inhibit the three sialidases to varying degrees. Catechin, at the highest tested concentration (2.5 mg/mL) displays strong suppressing activity - from 49 to 73% for all three enzymes (Figure 4). Some catechins were proved to interact with influenza neuraminidase. Moreover, these compounds bind to a site different from that to which known inhibitors like zanamivir and oseltamivir bind, in the vicinity of a structurally conserved cavity adjacent to residue 430 that has been suggested to be a secondary sialic acid binding site, thereby overcoming mutations limiting influenza therapy (Mueller and Downard, 2015). In addition to influenza virus neuraminidase, epigallocatechin-3-gallate successfully suppresses *Clostridium perfringens* neuraminidase (Li *et al*., 2011; Kim *et al*., 2013). Catechins are a class of flavonoids, secondary metabolites in plants distributed in a variety of foods and herbs including tea, apples, persimmons, cacaos, grapes, and berries and is known for its anticancer, anti-obesity, antidiabetic, anticardiovascular, anti-infectious, hepatoprotective, and neuroprotective properties (Isemura, 2019). Regarding the bacterial sialidases tested by us, no significant inhibition of enzyme activity by quercetin was observed. Quercetin has a variety of pharmacological properties including anti-SARS-CoV-2, antioxidant, anticancer, antiaging, antiviral, and anti-inflammatory activities (Wang *et al*., 2022). A recent study revealed that O-methylated quercetin derivatives from the aerial parts of *Siegebeckia pubescens* have inhibitory effect on bacterial sialidase (Son *et al*., 2023). According to Sadati *et al*. (2019), quercetin and catechin, along with other flavonoids such as naringenin, luteolin, hispidulin, vitexin, chrysin and kaempferol may effectively block the sialidase active site.

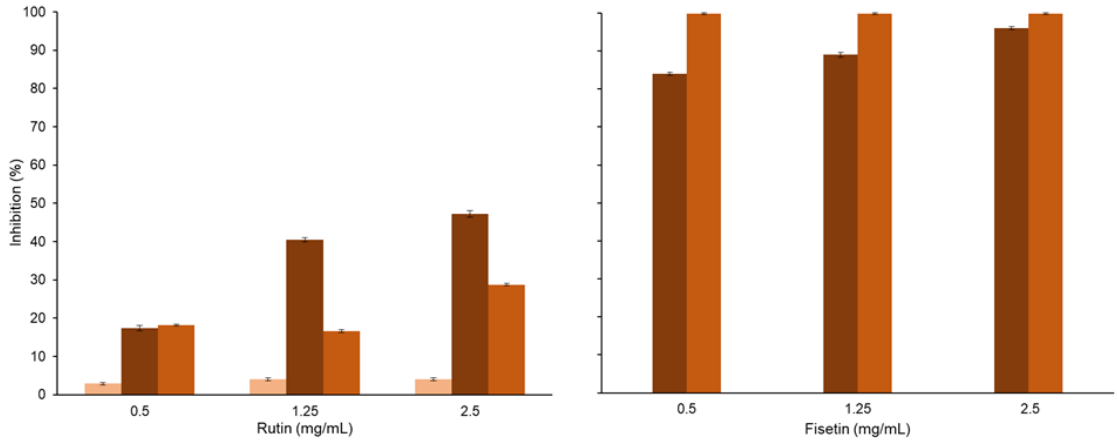


Legend: sialidase from *A. nicotianae*, from *O. paurometabola*, from *V. cholerae*

Figure 4. Inhibition effects of catechin and quercetin on three bacterial sialidases.

A recent study on influenza virus NA revealed that the presence of a glycosylation group greatly reduces NA inhibition (Chon, 2012). In our study, the glycosylated flavonol rutin had the best inhibitory effect only on sialidase from O129 – 49% inhibition (Figure 5). Studies that have tested this flavonol for inhibition of viral sialidases report its action as moderate to weak (Liu *et al*., 2008, Mercader and Pomilio, 2010). Rutin is widespread in plants, such as passion flower, buckwheat, tea, and apple. It has a number of pharmacological activities, including anticarcinogenic, antioxidant, antiviral, vasoprotective and hepatoprotective activities (Ganeshpurkar and Saluja, 2017). There is no evidence of suppressive effect of rutin on bacterial sialidases in the literature till now. This compound is described to exhibit a significant inhibitory effect on α-amylase and α-glucosidase - enzymes with a related mechanism of action to that of sialidase (Dubey *et al*., 2017).

In contrast to rutin, for two of the sialidases, produced by O129 and V13, the inhibitory effect of the plant flavonol fisetin was comparable and even higher than that of quinic and gallic acids, 96 and 100%, respectively. As could be seen in Figure 5, fisetin significantly decreases the effectiveness (about 96%) of O129 and V13 sialidases even at the lowest tested concentration (0.5 mg/mL). Further studies are required to establish the minimum concentration of fisetin that has significant inhibitory effect on these enzymes. Fisetin is present in several fruits and vegetables including strawberries, apples, persimmons, onions and has antioxidant, anti-inflammatory and anticancer activity (Sahu *et al*., 2014). There are no data in the available literature regarding inhibitory activity of fisetin towards sialidase.



Legend: sialidase from *A. nicotianae*, from *O. paurometabola*, from *V. cholerae*

Figure 5. Inhibition effects of rutin and fisetin on tree bacterial sialidases.

4. CONCLUSION

Inhibition of bacterial sialidase activity is a practical approach for the treatment of different microbial infections. In our study, quinic and gallic acids, close to the compounds from which oseltamivir is produced, were tested and found to significantly suppress all the three enzymes examined. Fisetin is of interest for additional research due to its strong inhibition of *V. cholerae* and *O. paurometabola* sialidases, even at the lowest concentration tested. The specific effect that most of the tested substances gave on each of the enzymes indicates that specific inhibitors for individual bacterial sialidases can be sought among such natural products. Future studies on the still poor explored kinetics of bacterial sialidases inhibition by pure phenolic and flavonoid compounds will provide useful information on their potential application as antibacterial and therapeutic substances of natural origin. Our findings prove that the tested substances are able to inhibit enzymes that represent factors of pathogenicity.

Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors.

Authorship Contribution Statement

Yana Gocheva: Conception, Design, Analysis, Literature Review, Writing, Critical Review. **Milena Nikolova**: Materials, Literature Review, Writing. **Stephan Engibarov**: Data Collection, Analysis, Literature Review, Writing, Critical Review. **Irina Lazarkevich:** Literature Review, Writing. **Rumyana Eneva:** Supervision, Analysis and Interpretation, Writing.

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