Examining the Ability of Flavone Analogs to Selectively Inhibit Bacterial Topoisomerase I

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Aim and Conclusion

To characterize both the antibacterial and anticancer activities of novel flavonoid analogs.
I found that almost all flavonoid derivatives from the synthesized library were able to inhibit DNA gyrase but only one inhibits topoisomerase I.

Introduction

Topoisomerases are the essential enzymes that play critical roles in many cellular processes, especially DNA replication and chromosome segregation (1). There are three main classes of topoisomerases: types IA, IB and IIA.

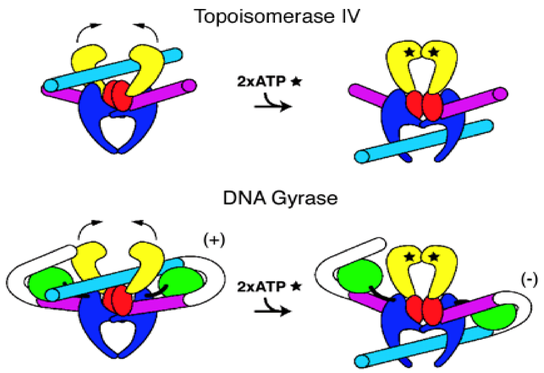

Figure 1. Representation of the action of bacterial type II topoisomerases in decatentation and supercoiling of DNA.

Many pathogens are drug-resistant and there is urgent need for novel antibacterial drugs (2). Thus, type IA topoisomerases are attractive targets for novel antibacterial drugs due to potent inhibitors for type IA being discovered in the last few years (3). Certain flavonoids have exhibited antibacterial and anticancer activities by inhibiting topoisomerases such as genistein, an isoflovone that inhibits human topoisomerase II (4).

Dr. Hiasa's group has created a small library of novel quercetin analogs to test their activities against DNA gyrase. My project was to examine the activities of quercetin analogs against bacterial type IA topoisomerase (5).

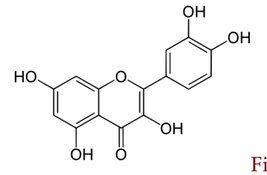

Figure 2. Structure of quercetin

Methods and Results

I examined the effect of each natural flavonoid and novel quercetin analogs on *E. coli* DNA gyrase, a type II enzyme, and *E. coli* topoisomerase I, type IA enzyme, using a DNA supercoiling assay and a relaxation assay, respectively.

The supercoiling assay allows for the measurement of DNA gyrase's ability to induce negative supercoils into relaxed DNA. Although a few quercetin analogs exhibited modest activities (Table 1), none of the analogs tested in my study showed significant activity against E. coli DNA gyrase. SD8 is an antibiotic that inhibit DNA gyrase and used as a positive control.

Table 1.
Effects of flavone analogues on *E. coli* DNA gyrase

Compound	Supercoiling assay IC_{50} (μM)[a]	DNA Cleavage (fold-stimulation)[b]
9a	48.6 ± 0.8	7.8
9b	84.7 ± 5.5	5.0
9c	>200	3.0
9d	>200	1.8
9e	>200	1.9
10	>200	<1
SD8	0.41	<1[14]

a The IC_{50} values were determined based on the results from two independent experiments.

b Fold-stimulation in the generation of linear DNA at 200 μM of the compound over the amount of linear DNA in the absence of any compound. The level of stimulation was determined based on the results from two independent experiments.

Next, I performed a relaxation assay to assess the ability of natural flavonoid and novel quercetin analogs to inhibit the catalytic activity *E. coli* topoisomerase I. I found that one compound, compound 17, can inhibit the relaxation activity of topoisomerase I (Figure 3).

Based on my finding, we are creating a new analogs of compound 17 to identify a novel topoisomerase I inhibitor(s).

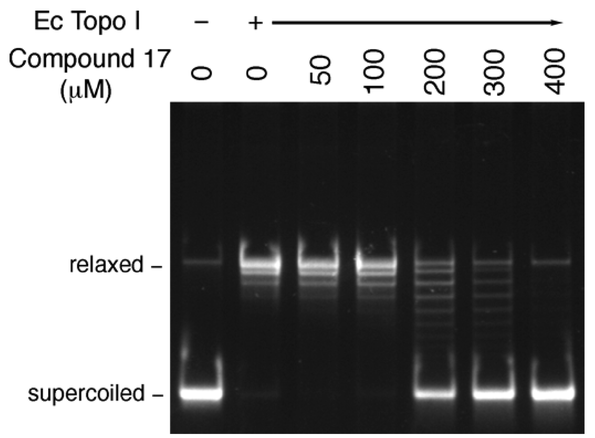

Figure 3. Results of the relaxation assay. Compound 17 inhibited the relaxation activity of E. coli topoisomerase I. IC_{50} was 145 ± 24 μM.

References

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