Original Article

In vitro and *in vivo* Antibacterial Activities of 1,4-naphthoquinone Derivatives in Silkworm Model

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Abstract:

Background: *The 1,4-naphthoquinone pharmacophore is known to impart several pronounced biological and pharmacological activities.* ***Objective:*** *The objective of this study was to investigate the in vitro and in vivo antibacterial activities of napthoquinone derivatives against Staphylococcus aureus (MSSA1), methicillin-resistant S. aureus (MRSA4), and Escherichia coli (O157), with the in vivo investigation performed in the invertebrate silkworm model.* ***Methods:*** *Sensitivity of S. aureus (MSSA1), S. aureus (MRSA4), and E. coli (O157) to 1,4-naphthoquinone and derivatives were determined in vitro using broth microdilution method. Toxicity and antibacterial activity of 1,4-naphthoquinone derivatives were evaluated in silkworm model.* ***Results:*** *The 1,4-naphthoquinone exhibited the most significant in vitro antibacterial activity against both gram-positive and gram-negative bacteria. The MIC values for S. aureus (MSSA1), S. aureus (MRSA4), and E. coli (O157) were 6.3, 8.3, and 25 μg/mL, respectively. The 1,4-naphthoquinone showed significant antibacterial activity in silkworm infected S. aureus (MSSA1) by oral administration with an ED_{50} of 0.3 ± 0.07 (mean ± SD) mg/larvae. Plumbagin and 5-hydroxy-1,4-naphthoquinone did not show activity at any dose level.* ***Conclusion:*** *Results of this preliminary screening in an invertebrate animal model suggested that 1,4-naphthoquinone could be a promising candidate for further development as an antibacterial drug against S. aureus as well as E. coli infections.*

Keywords: ● *Silkworm* ● *1,4-naphthoquinone* ● *Staphylococcus aureus (MSSA1)* ● *Methicillin-resistant Staphylococcus aureus (MSSA4)* ● *Antibacterial activities*

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Introduction

Staphylococcus aureus (*S. aureus*) is a common bacterium that lives on the skin or in the nose of humans. In most situations, the infection caused by *S. aureus* is harmless and treatable with most of the available antibacterial drugs. However, if the microorganism enters the body through a cut in the skin, it can cause a range of mild to severe infections, which may lead to death in some cases. With the emergence and spread of resistance to antibacterial drugs, there is a pressing need for ongoing drug discovery and development of novel antibacterial molecules that will provide effective and affordable antibacterial agents from various sources[1,2].

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Natural products including medicinal plants may offer cheap alternative sources of new drug candidates for combating pathogenic bacteria.

The 1,4-naphthoquinone pharmacophore is known to impart pronounced biological activities including antibacterial, anticancer, antiplatelet, anti-inflammatory, anti-allergic, antimalarial, and antileishmanial activities[3-8]. This structure is commonly found in numerous natural products such as plumbagin, lawsone, and juglone. The 5-hydroxy-2-methyl-1,4-naphthoquinone (plumbagin) is a natural product found in the plants of the *Plumbaginaceae, Droseraceae, Ancestrocladaceae*, and *Dioncophyllaceae* families. It has a yellow naphthoquinone pigment[9]. Plumbagin is the major constituent of *Plumbago indica* Linn. This compound has been shown to display a wide spectrum of biological and pharmacological activities such as antibacterial, antimalarial, antifungal, anticancer, antiviral, and antioxidant activities[10]. The objective of this study was to investigate the *in vitro* and *in vivo* antibacterial activities of 1,4-napthoquinone derivatives against *S. aureus* (MSSA1), *S. aureus* (MRSA4), and *Escherichia coli* (O157), with the *in vivo* investigation performed in the invertebrate silkworm model.

Material and Methods

Microorganisms and Chemicals

Clinical isolates of *Staphylococcus aureus* (MSSA1) and methicillin-resistant *S. aureus* (MRSA4) were obtained from Kyushu University Hospital, Fukuoka, Japan. *Escherichia coli* (O157 strain) was provided by Genome Pharmaceuticals Institute Co., Ltd., Japan. The authentic plumbagin (5-hydroxy-2-methyl-1, 4-napthoquinone: 98.2% purity) was purchased from Apin Chemicals Co., Ltd. (Oxford, UK). The 1,4-naphthoquinone, 3-hydroxyphthalic anhydride, 5-hydroxy-1-tetralone, and dimethylsulfoxide (DMSO) were purchased from Wako Pure Chemicals (Tokyo, Japan). The 5-Hydroxy-1,4-naphthoquinone and 2-hydroxy-1,4-naphthoquinone were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). The 2,5-Dihydroxypropiophenone was purchased from Alfa Aesar A Johnson Matthey Company (MA, USA). Luria-Bertani 10 and Muelle-Hinton Broth (MHB) were purchased from Gibco BRL Life Technologies (NY, USA). Vancomycin and tetracycline were purchased from Shionogi and Co., Ltd. (Osaka, Japan) and Sigma Aldrich (St. Louis, USA), respectively.

Preparation of standard solutions of 1,4-naphthoquinone and derivatives

The stock solution of 5-hydroxy-2-methyl-1,4-naphthoquinone (plumbagin), 1,4-naphthoquinone, 5-hydroxy-1,4-naphthoquinone, 2-hydroxy-1,4-naphthoquinone, 3-hydroxyphthalic anhydride, 5-hydroxy-1-tetralone, and 2,5-dihydroxypropiophenone were prepared in DMSO and diluted with 0.9% sodium chloride and used as working solutions. Stock and working solutions of vancomycin and tetracycline were prepared in 0.9% sodium chloride.

Preparation of bacterial inoculum

S. aureus (MSSA1), *S. aureus* (MRSA4), and *E. coli* (O157) preserved in nutrient agar (at 4°C) were revived in LB10 broth (5 mL) and incubated overnight at 37°C with shaking (150 rev/min). Controls with LB10 broth (5 ml) without test compound and that without bacterial inoculum were included in the experiments.

Animals

Bombyx mori eggs (Hu Yo × Tsukuba Ne) were purchased from Ehime Sansyu (Ehime, Japan). Hatched larvae were fed with the artificial food, Silkmate 2S (Nosan Corporation, Yokohama, Japan) at 27°C. Silkworm larvae were reared according to the previously described procedure[11,12].

Determination of *in vitro* antibacterial activities of 1,4-naphthoquinone and derivatives against *S. aureus* (MSSA1), *S. aureus* (MRSA4), and *E. coli* (O157)

Sensitivity of *S. aureus* (MSSA1), *S. aureus* (MRSA4),

and *E. coli* (O157) to 1,4-naphthoquinone and derivatives were determined *in vitro* using broth microdilution method. The minimum inhibitory concentration (MIC) is defined as the lowest concentration of the drug that completely inhibits the growth of bacteria compared with that of the drug-free control. The culture medium of *S. aureus* (MSSA1), *S. aureus* (MRSA4), and *E. coli* (O157) were diluted in MHB (1: 400) at a density of 0.5 McFarland turbidity standard. The suspension (100 μL) was placed in each well of the 96-well microplate. A two-fold serial dilution of 1,4-naphthoquinone and each derivative was dispensed into each well (final volume of 100 μL/well) and the plate was sealed and incubated at 37°C for 18-20 h (overnight). The MIC values were determined as previously described[11,13]. Vancomycin was used as a positive control drug and MHB culture medium was used as a negative control.

Toxicity testing of 1,4-naphthoquinone and derivatives in silkworm model

For the intra-hemolymph route of administration, silkworms were fed with an antibacterial-free artificial food for one day. The 1,4-Naphthoquinone and each derivative (50 μL in 0.9% sodium chloride) at various concentrations (0.25, 0.5, 1, and 2 mg/mL for 1,4-naphthoquinone; 0.001, 0.01, 0.1, and 1 mg/mL for plumbagin; and 0.5, 1, 2, and 5 mg/mL for 5-hydroxy-1,4-naphthoquinone) was injected into the hemolymph (50 μL) of the silkworm using a 27-gauge needle (n = 6 for each group). Sodium chloride (0.9%) was used as control solution[11,12]. For the oral route administration, all of the test compounds were mixed in food at various concentrations (0.3, 0.6, 1.25, 2.5, 5, 10, and 20 mg/g diet for 1,4-naphthoquinone; 0.025, 0.25, 0.5, 1, 2, 4, 8, and 16 mg/g diet for plumbagin; and 0.3, 0.6, 1.25, 2.5, 5, 10, and 20 mg/g diet for 5-hydroxy-1,4-naphthoquinone) and fed to the silkworms overnight (n = 10 for each group). Silkworms were placed in a safety cabinet with controlled ambient temperature at 27°C with 50% humidity (Air tech class IIA/B_3). The survival of silkworms was determined 2 days after feeding with the test compounds[12].

Investigation of *in vivo* antibacterial activities of 1,4-naphthoquinone and derivatives

The 1,4-naphthoquinone, plumbagin, and 5-hydroxy-1,4-naphthoquinone were mixed in food at various concentrations (0.08, 0.15, 0.3, and 0.6 mg/g diet for 1,4-naphthoquinone; 0.25, 0.5, and 1 mg/g diet for plumbagin; and 2.5, 5, and 10 mg/g diet for 5-hydroxy-1,4-naphthoquinone). Each test compound was fed to the silkworms overnight before injection of *S. aureus* (MSSA1) suspension in 0.9% sodium chloride (10-fold dilution in 50 μL) into the hemolymph through dorsal surface (n = 6 for each group). Tetracycline (0.08 mg/g diet) was mixed in food and used as a positive control and artificial food without drug was used as a negative control. After injection of the pathogen, silkworms were placed in a safety cabinet with controlled ambient temperature at 27°C with 50% humidity (Air tech class IIA/B_3). The survival of silkworms was determined 2 days after injection of the bacterial suspension[11,14-16].

Results

Determination of *in vitro* antibacterial activities of 1,4-naphthoquinone and derivatives against *S. aureus* (MSSA1), *S. aureus* (MRSA4) and *E. coli* (O157)

Inhibitory activities of the test compounds (1,4-naphthoquinone, plumbagin, 5-hydroxy-1,4-naphthoquinone, 2-hydroxy-1,4-naphthoquinone, 3-hydroxyphthalic anhydride, 5-hydroxy-1-tetralone, and 2,5-dihydroxypropiophenone) including the reference drug vancomycin against *S. aureus* (MSSA1) are summarized in Table 1. The 1,4-Naphthoquinone exhibited the most significant *in vitro* antibacterial activity against both gram-positive and gram-negative bacteria. The MIC values for *S. aureus* (MSSA1), *S. aureus* (MRSA4), and *E. coli* (O157)

Table 1 Minimum inhibitory concentration (MIC, μg/mL) values of 1,4-naphthoquinone and derivatives against *S. aureus* (MSSA1), *S. aureus* (MRSA4), and *E. coli* (O157). The experiment was repeated in triplicate. Data are presented as [Mean (SD)].

Compound	*S. aureus* (MSSA1)	*S. aureus* (MRSA4)	*E. coli* (O157)
1,4-Naphthoquinone	6.3 (0)	8.3 (3.58)	25 (0)
Plumbagin	3.1 (0)	ND*	> 50 (0)
5-Hydroxy-1,4-naphthoquinone	9.37 (5.42)	ND*	> 250 (0)
2-Hydroxy-1,4-naphthoquinone	156 (0)	ND*	> 250 (0)
3-Hydroxyphthalic anhydride	1,250 (0)	ND*	1,250 (0)
5-Hydroxy-1-Tetralone	> 5,000 (0)	ND*	> 5,000 (0)
2,5-Dihydroxypropiophenone	5,000 (0)	ND*	2,500 (0)
Vancomycin	0.08	ND*	ND*

*ND = Not determined

were 6.3, 8.3, and 25 μg/mL, respectively. The MIC of vancomycin for *S. aureus* (MSSA1) was 0.8 μg/mL.

Toxicity testing of 1,4-naphthoquinone and derivatives in silkworm model

Following the oral administration of 1,4-naphthoquinone at dose levels of 0.3 and 0.6 mg/larvae, no toxicity was observed in any silkworm. However, when the dose was increased to 1.25 to 20 mg/silkworm larvae, significant growth inhibition (reduction in size) was observed; some silkworms died at the highest dose level (20 mg/larvae). All silkworms fed with diet-containing plumbagin at doses of 0.025, 0.25, 0.5, and 1 mg/larvae did not show any sign of toxicity and all survived. At higher dose levels of 2 to 16 mg/larvae, severe growth defect was observed and death was observed in some animals. For 5-hydroxy-1,4-naphthoquinone, all silkworms did not show any sign of toxicity and all survived following oral doses of 0.3, 0.6, 1.25, 2.5, 5, and 10 mg/larvae. Interference with movement (slow) was observed in all silkworms at the highest dose (20 mg/larvae) and death was observed in some animals (Table 2).

For the intra-hemolymph route of administration, 1,4-naphthoquinone at doses of 12.5 and 25 μg/larvae did not show any toxic effect and all silkworms survived. When the dose was increased to 50 and 100 μg/larvae, 50% of the silkworms died. Plumbagin at all dose levels did not produce any sign of toxicity. All silkworms injected with plumbagin at dose levels of 0.05, 0.5, 5, and 25 μg/larvae survived. All silkworms injected with 5-hydroxy-1,4-naphthoquinone at dose levels of 25, 50, and 100 μg/larvae survived. At the highest dose (250 μg/larvae) however, inhibitory effect on growth (reduction in size) was observed with death in some animals and 25% of the animals died (Table 2).

Investigation of *in vivo* antibacterial activities of 1,4-naphthoquinone and derivatives

The survival rates of the *S. aureus* (MSSA1) infected silkworms after oral doses of 1,4-naphthoquinone 0.15, 0.3, and 0.6 mg/larvae were 17, 50, and 67%, respectively. The ED_{50} [mean (SD)] of 1,4-naphthoquinone was 0.3 (0.07) mg/larvae (Table 3).

All infected animals died after feeding with diet containing plumbagin at dose levels of 0.25, 0.5, and 1 mg/larvae. For 5-hydroxy-1,4-naphthoquinone, all infected silkworms died after feeding with the compound at doses of 2.5, 5, and 10 mg/larvae. All silkworms infected with *S. aureus* (MSSA1) died after feeding with normal diet, whereas those which received diet-containing tetracycline (0.08 mg/larvae) survived (Table 3).

Table 2 Toxicity of 1,4-naphthoquinone and derivatives through oral administration (*p.o.*) and intra-hemolymph injection (*i.h.*) in silkworms larvae. At least 5 larvae were fed or injected with each drug concentration.

Compound	Toxicity (*p.o.*) for silkworm larvae (mg/larvae)	Toxicity (*i.h.*) for silkworm larvae (μg/larvae)
1,4-naphthoquinone	1.25	50
5-hydroxy-2-methyl-1,4-naphthoquinone	2	>25
5-Hydroxy-1,4-naphthoquinone	20	250

Table 3 *In vivo* antibacterial activities of 1,4-naphthoquinone, plumbagin and 5-hydroxy-1,4-naphthoquinone following oral administration in silkworm infected with *S. aureus* (MSSA1).

S. aureus (MSSA1)	Reagents in the diet (mg/larvae) silkworm		%Survival of
-	None		100
+	None		0
+	1,4-naphthoquonone	0.08	0
+		0.15	17
+		0.3	50
+		0.6	67
+	Plumbagin	0.25	0
+		0.5	0
+		1	0
+	5-Hydroxy-1,4-naphthoquinone	2.5	0
+		5	0
+		10	0
+	Tetracycline	0.08	100

The symbol + represents the presence of injected *S. aureus* (MSSA1), and the symbol – represents the absence of injected *S. aureus* (MSSA1) (0.9% sodium chloride).

Discussion and Conclusion

The silkworm model was used in this study to evaluate the antibacterial activities of 1,4-napthoquinone derivatives. This study is the first report that demonstrated the therapeutic effects of 1,4-naphthoquinone and derivatives in an invertebrate model. The use of mammals for drug development is expensive and highly problematic with regard to ethical issues and high cost for the maintenance of animals. Utilizing invertebrate infection model to evaluate potential therapeutic effects of antibacterial candidates in the early stages of drug development instead of mammals may overcome these problems. The main advantages of the model over other animal models include simplicity, inexpensiveness, and practicality[11,12,14,17]. As oral dose administration is the main route of clinical drug administration, the observed systemic bioavailability of the test compounds by this route in silkworms offers a great advantage particularly with the hydrophilic compounds. Furthermore, administration of large quantities of test compound is also possible. The body size of silkworm is large enough for hemolymph preparations and organ isolation. Results showing the antibacterial activity of

the study compounds suggested their permeability across biological membranes of silkworms. The invertebrate silkworm larvae model of human pathogenic bacteria was previously established by Kaito, et al. for the screening of candidate compounds with antibacterial activity[17,18]. In addition, the protocol for the evaluation of quantitative therapeutic effects of antibacterial activity using silkworms infected with human pathogen microorganisms was also developed by Hamamoto, *et al.*[11]. This insect invertebrate model provides a valid tool for the screening of antibacterial candidates due to its common innate immune system similar to that of the humans[11].

The antibacterial activity of 1,4-naphthoquinone by oral administration was well demonstrated in silkworm infected with *S. aureus* (MSSA1). *In vitro* antibacterial activity of 1,4-naphthoquinone has previously been reported[3,5,8]. The 1,4-Naphthoquinone showed toxicity to silkworm larvae following intra-hemolymph injection at LD_{50} dose level of 50 μg/larvae. The present study is the first which demonstrated its antibacterial activity against *S. aureus* in the invertebrate silkworm model. Besides the activity against *S. aureus* (MSSA1 and MRSA4), it also showed weak antibacterial activity against *E. coli* (O157) with a relatively high MIC (25 μg/mL). This compound could therefore be a promising candidate for further development as chemotherapeutics for bacterial infections of both gram-positive and gram-negative bacteria. Since the number of candidate compounds that are effective against gram-negative bacteria is relatively limited, it is worthwhile to consider 1,4-naphthoquinone as an alternative option for chemotherapeutics of infectious diseases caused by the gram-negative bacteria.

Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) and 5-hydroxy-1,4-naphthoquinone exhibited antibacterial activity against *S. aureus* but did not show significant activities in *S. aureus* (MSSA1) infected silkworms after oral administration. The stability of both compounds in the hemolymph of silkworm is considered low as both did not show toxicity when given by intra-hemolymph injection (LD_{50} greater than 25 and 250 μg/larvae, respectively).

In conclusion, results from the present study suggest that 1,4-naphthoquinone is a promising candidate for further development as antibacterial drugs against both gram-positive and gram-negative bacteria. Its pharmacokinetic characteristic provides achievement and maintenance of adequate antibacterial activity following oral administration. Further study should be performed to confirm these observations in vertebrate animal models.

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การทดสอบฤทธิ์ในการต้านเชื้อแบคทีเรียของ 1,4-naphthoquinone และสารอนุพันธ์ในหลอดทดลองและในหนอนไหมที่ติดเชื้อแบคทีเรีย

วิริยาภรณ์ สุ่มสกุล และ เกศรา ณ บางช้าง

โครงการบัณฑิตศึกษา สาขาวิชาชีววิทยาคลินิก คณะสหเวชศาสตร์ วิทยาลัยแพทยศาสตร์นานาชาติจุฬาภรณ์ มหาวิทยาลัยธรรมศาสตร์ศูนย์รังสิต ปทุมธานี 12121

บทคัดย่อ *1,4-naphthoquinone เป็นโครงสร้างที่มีอยู่ในสมุนไพรและพืชหลายชนิด ซึ่งโครงสร้างหลักนี้เป็นส่วนสำคัญที่ทำให้สารหล่านี้แสดงฤทธิ์ทางชีวภาพและเภสัชวิทยา* ***วัตถุประสงค์*** *ของการวิจัยครั้งนี้คือเพื่อศึกษาฤทธิ์ในการต้านเชื้อแบคทีเรียในหลอดทดลองและในสัตว์ทดลองของ 1,4-naphthoquinone และอนุพันธ์* ***วิธีการทดลอง*** *ทดสอบฤทธิ์ในการต้านเชื้อแบคทีเรีย S. aureus สายพันธุ์ MSSA1, MRSA4 และเชื้อแบคทีเรีย E. coli สายพันธุ์ O157 ของ 1,4-naphthoquinone และ อนุพันธ์ โดยวิธี Broth microdilution และศึกษาความเป็นพิษและฤทธิ์ต้านเชื้อแบคทีเรีย ในหนอนไหมที่ติดเชื้อ S. aureus สายพันธุ์ MSSA1* ***ผลการทดลอง*** *1,4-naphthoquinone ที่ความเข้มข้น 6.3, 8.3 และ 25 μg/mL แสดงฤทธิ์ในการยับยั้งการเจริญเติบโต ของแบคทีเรีย S. aureus สายพันธุ์ MSSA1, MRSA4 และเชื้อแบคทีเรีย E. coli สายพันธุ์ O157 ในหลอดทดลองได้ นอกจากนี้ 1,4-naphthoquinone ยังแสดงฤทธิ์ต้านแบคทีเรียในหนอนไหมที่ติดเชื้อ S. aureus สายพันธุ์ MSSA1 ได้ด้วยการให้ทางปาก โดยค่า ED_{50} คือ 0.3 ± 0.07 (ค่าเฉลี่ย ± ส่วนเบี่ยงเบนมาตรฐาน) mg/larvae ในขณะที่ plumbagin and 5-hydroxy-1,4-naphthoquinone ไม่มีฤทธิ์อย่างมีนัยสำคัญ จากผลการวิจัยแสดงว่า 1,4-naphthoquinone น่าจะเป็นสารที่จะสามารถนำไปพัฒนาไปเป็นยารักษาโรคติดเชื้อแบคทีเรียทั้งชนิดแกรมบวกและลบต่อไป*

Keywords: ● *หนอนไหม* ● *1,4-naphthoquinone* ● *เชื้อแบคทีเรีย S. aureus สายพันธุ์* ● *MSSA1 ฤทธิ์ในการต้านแบคทีเรีย*

เวชสารแพทย์ทหารบก 2557;67:155-62.