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Antimicrobial Drug Susceptibility Test of *Pythium insidiosum* by Disc Diffusion Method

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Background: Pythiosis is a life-threatening disease caused by the fungus-like organism *Pythium insidiosum.* It causes disease in both animals and humans. Amphotericin B antifungal is less effective because it lacks ergosterol, a drug target in the cell membrane.

Objective: To evaluate antimicrobial susceptibility test of *P. insidiosum* isolated from human pythiosis by disc diffusion method.

Methods: The antimicrobial drug susceptibility test by disc diffusion method was tested against 10 clinical isolated strains of *P. insidiosum.* Antimicrobial drugs comprise of 8 antibiotics (chloramphenicol, cefotaxime, ciprofloxacin, gentamycin, tetracycline, meropenem, oxacillin, and vancomycin) and 2 antifungal drugs (itraconazole and amphotericin B) which were included in the test.

Results: Antimicrobial drugs susceptibility tests were performed on 10 clinically isolated strains of *P. insidiosum.* Six of them showed susceptibility to antimicrobial drugs. The cutaneous pythiosis strain (SIMI 8569) showed the highest number of susceptibilities to antimicrobial agents (chloramphenicol, ciprofloxacin, gentamycin, tetracycline, vancomycin, and itraconazole). In addition, 4 strains of *P. insidiosum* (M 29, SIMI 6666, SIMI 7873, and SIMI 2989-42) were not inhibited by all antimicrobial drugs.

Conclusions: This result concluded that chloramphenicol, tetracycline, and itraconazole inhibited the mycelial growth of *P. insidiosum* better than the other drugs. The inhibition effects of these drugs were observed in 40% - 60% of the strains. Further experiments should be carried out to evaluate the tested drugs in various concentrations with other more susceptible methods to get more precise concentrations exposed to *P. insidiosum* isolates such as broth dilution or dilution assays.

Keywords: *Pythium insidiosum*, Pythiosis, Antimicrobial drug

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Introduction

Pythiosis is an infection caused by an oomycete fungus-like organism *Pythium insidiosum.* This organism is found in environments such as soil, swampy areas, and freshwater reservoirs that might be inhabited by the infective stage, zoospore which can cause infection in both animals and humans.[1-4] Clinical manifestations of human infection are characterized into 4 types (vascular, ocular, cutaneous, and disseminated pythiosis). The most common type of infection has been vascular pythiosis but the most aggressive was ocular infection according to patients, who lost their eyes within a week after infection.[5] The incomplete ergosterol biosynthesis pathway and lacking ergosterol in its cytoplasmic membrane lead to an ineffective treatment of antifungal treatment.[6]

This leads to finding the natural bioactive compounds with anti-*P. insidiosum* properties, which in combination with antifungal drugs or antibacterial drugs demonstrate effectiveness.[7] The use of antibacterials in human pythiosis as an adjunctive therapy is due to the failure of antifungal and immunotherapy to treat patients with vascular infection.[8] Itraconazole and terbinafine were effective as they showed synergistic effects against Brazilian animal *P. insidiosum* isolates and also from an Australian child with deep facial tissue infection.[9-11]

Despite the unfavorable minimum inhibitory concentrations (MICs) and lack of synergy effect from itraconazole, this drug is still used to treat pythiosis patients in Thailand. Combination therapy, including radical surgery, antifungal therapy and immunotherapy, have been the main regimens for treatment of pythiosis in humans.[12] More reports of the effectiveness of antibacterial and antifungal drugs were found in the *in vitro* susceptibility against *P. insidiosum.*[9, 10] This data guided the successful treatment by supporting the selection of antibiotics in singly or in combination with other drugs to treat pythiosis patients.[7]

This study was conducted to test the antimicrobial susceptibility of antibiotics against *P. insidiosum* Thai clinical isolates by disc diffusion method. Data available from this research will guide and promote the susceptible profile of Thai isolates' case and support the effective antibacterial for combination treatment.

Methods

Ethics

The study was approved by the Naresuan University Institutional Biosafety Committee (NUIBC), Thailand (No. NUIBC-MI 58-10-61).

Pythium insidiosum Isolates

Ten *P. insidiosum* clinical isolates, including 3 cutaneous strains (SIMI 2989-42, SIMI 8569, and SIMI 8727), 4 vascular strains (M29, MCC5, SIMI 7873, and SIMI 7874) and 3 ocular strains (SIMI 18093, SIMI 6666, and SIMI 322-37) were listed (Table 1). All clinical isolates were confirmed by morphological and molecular characteristics as previously described by Thongsri et al.[13]

Antimicrobial Drug

All 10 standard antimicrobial discs were commercially obtained from Oxoid (Basingstoke, Hants, UK) including 8 antibiotics (cefotaxime [CTX, 30 µg], ciprofloxacin [CIP, 5 µg], chloramphenicol [C, 30 µg], gentamycin [CN, 10 µg], meropenem [MEM, 10 µg], tetracycline [TE, 30 µg], oxacillin [OX, 1 µg], and vancomycin [VA, 30 µg]), and 2 antifungal drugs (amphotericin B [Am B], 20 µg and itraconazole [IT, 10 µg]). The drug susceptibility test using disc diffusion method was performed according to Clinical and Laboratory Standards Institute (CLSI) document (M51-A) guidelines for filamentous fungi which was modified for *P. insidiosum* against 10 antimicrobial drugs.

Table 1. Sources of *Pythium insidiosum* Strains From Clinical Isolates

Type of Infection	Reference Number	Clinical Specimen	Patient's Information		
			Age/Sex	Year	Residential Province
Vascular pythiosis	M 29	Systemic infection	NA	NA	Ratchaburi
	MCC 5	Arteritis	NA	NA	NA
	SIMI 7873	Thrombus from left iliac artery	31/F	1988	Chanthaburi
	SIMI 7874	Tissue from left iliac artery	31/F	1988	Chanthaburi
Ocular pythiosis	SIMI 18093	Ophthalmic infection	50/F	1995	Samut Sakhon
	SIMI 6666	Pus from corneal ulcer	42/M	1986	Patthalung
	SIMI 322-37	Fibrin from corneal ulcer	26/M	1994	NA
Cutaneous pythiosis	SIMI 2989-42	Tissue and blood clot	72/F	1999	Suphan Buri
	SIMI 8569	Tissue from skin, thrombus	52/M	1988	Suphan Buri
	SIMI 8727	Pus and bone tissue from leg	19/M	1988	Yasothon

Abbreviations: NA, data not available; F, female; M, male.

Inoculum Preparation and Drug Susceptibility Test

The inoculum consisted of each strain from *P. insidiosum* isolates previously cultured on Sabouraud dextrose agar (SDA) and incubated at 25°C for 3 - 5 days. The disc diffusion susceptibility method was performed by applying an agar block inoculum of approximately 1×1 cm to the surface of a 100 mm diameter SDA plate. The culture plate was incubated at 25°C for 3 days without contamination on the agar plate and up to 4 commercially prepared, fixed concentration, paper antibiotic discs and a blank disc control (B) were placed on the agar surface 2 cm from the mycelial edge of the test plate. Plates were incubated at 25°C and the inhibition zone was measured at days 3, 6, and 9 or until the mycelial reached to blank disc control. The zones of growth inhibition around each of the antibiotic discs were measured to the nearest millimeter (mm) by 3 individual staff (Figure 1.) The drug susceptibility test of all strains was duplicated, and an inhibition zone indicated a positive drug susceptibility result.

Statistical Analysis

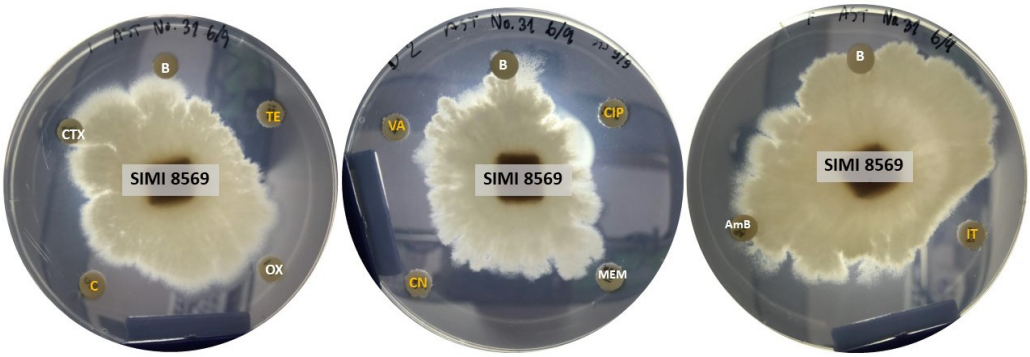
The inhibition zone of all antimicrobial discs was measured at days 3, 6, and 9 of incubation by 3 individual staff using vernier calipers. The results of the inhibition zone (mm) were recorded as the mean from 3 individual staff of measurements each day. The geometric mean (GM) inhibition zone was the average inhibition zone from each drug from days 3 to 9.

Results

Itraconazole was the most susceptible antifungal drug to 6 strains of *P. insidiosum* clinical isolates (60%), while chloramphenicol (5/10 strains) and tetracycline (4/10 strains) were the most effective antibacterials respectively (Table 2). All 3 cutaneous strains (SIMI 8569 and SIMI 8727, and SIMI 2989-42) were not inhibited by cefotaxime. The strain SIMI 8569 was inhibited by 6 antimicrobial drugs (chloramphenicol, ciprofloxacin, cefotaxime, tetracycline, vancomycin, and itraconazole) whereas SIMI 8727 was susceptible to only 2 antimicrobial

drugs (tetracycline and itraconazole). The inhibition zone GM of SIMI 8569 and SIMI 8727 ranged from 0.64 - 5.09 mm and 1.49 - 4.82 mm, respectively (Figure 1 and Table 2). Vascular pythiosis, strain SIMI 7874 was the only strain that was susceptible to cefotaxime (1.93 - 6.00 mm). The maximum inhibition zone of chloramphenicol (3.37 - 7.94 mm) was found from the MCC5 strain. Two strains, SIMI 18093 and SIMI 322-37 from ocular infection were susceptible for chloramphenicol, tetracycline, and itraconazole. The inhibition zone of strain SIMI 18093 was susceptible from chloramphenicol (2.67 - 7.37 mm) and itraconazole (0.41 - 2.09 mm). In addition, the strain SIMI 322-37 showed inhibition zones for chloramphenicol (1.78 - 5.30 mm), tetracycline (1.48 - 3.52 mm), and itraconazole (1.84 - 2.23 mm). Four strains of *P. insidiosum* had no effect from all antimicrobial agents including strains M 29, SIMI 6666, SIMI 7873, and SIMI 2989-42 as they indicated no inhibition zone until day 9 of incubation.

Figure 1. Drug Susceptibility Test of Cutaneous Pythiosis Strain (SIMI 8569) Against Antibiotic and Antifungal Drugs on SDA Plate on Day 9 With Incubation at 25°C.



Abbreviations: Am B, amphotericin B; B, blank disc control; C, chloramphenicol; CIP, ciprofloxacin; CN, gentamycin; CTX, cefotaxime; IT, itraconazole; MEM, meropenem; OX, oxacillin; TE, tetracycline; VA, vancomycin.

Table 2. Antimicrobial Susceptibility Test of 10 *Pythium insidiosum* Clinical Isolates Against Antibiotics and Antifungal Drugs

Drug	Inhibition Zone of Clinical Isolates, Range, mm*									
	Vascular Pythiosis				Ocular Pythiosis			Cutaneous Pythiosis		
	M 29	MCC 5	SIMI 7873	SIMI 7874	SIMI 18093	SIMI 6666	SIMI 322-37	SIMI 2989-42	SIMI 8569	SIMI 8727
Chloramphenicol	NI	3.37 - 7.94	NI	4.46 - 5.17	2.67 - 7.37	NI	1.78 - 5.30	NI	2.19 - 4.21	NI
Cefotaxime	NI	NI	NI	1.93 - 6.00	NI	NI	NI	NI	NI	NI
Ciprofloxacin	NI	NI	NI	NI	NI	NI	NI	NI	0.64 - 1.43	NI

Table 2. Antimicrobial Susceptibility Test of 10 *Pythium insidiosum* Clinical Isolates Against Antibiotics and Antifungal Drugs (Continued)

Drug	Inhibition Zone of Clinical Isolates, Range, mm*									
	Vascular Pythiosis				Ocular Pythiosis			Cutaneous Pythiosis		
	M 29	MCC 5	SIMI 7873	SIMI 7874	SIMI 18093	SIMI 6666	SIMI 322-37	SIMI 2989-42	SIMI 8569	SIMI 8727
Gentamycin	NI	NI	NI	NI	NI	NI	NI	NI	1.49 - 5.09	NI
Meropenem	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Oxacillin	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Tetracycline	NI	NI	NI	3.04 - 4.28	NI	NI	1.48 - 3.52	NI	3.56 - 4.81	1.61 - 2.87
Vancomycin	NI	NI	NI	NI	NI	NI	NI	NI	1.61 - 3.17	NI
Amphotericin B	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Itraconazole	NI	3.50 - 4.21	NI	4.47 - 5.63	0.41 - 2.09	NI	1.84 - 2.23	NI	4.61 - 4.93	1.49 - 4.82

Abbreviation: NI, no inhibition zone.

* Range of the mean inhibition zone (mm) from days 3, 6, and 9 recorded by 3 individual staff.

Discussion

Human pythiosis in Thailand still emerges and causes public health problems among Thai population due to no effective antimicrobial drug treatment. A previous report from Worasilchai et al[14] has demonstrated *in vitro* study of tetracycline and macrolide antibiotics showed the most effectiveness against Thai *P. insidiosum*. Our finding correlated with that report and demonstrated that chloramphenicol, tetracycline, and itraconazole had more effect upon the cutaneous pythiosis strains and the ocular strains were less effected. Combination therapy was successfully managed in a case of *P. insidiosum* keratitis (minocycline, chloramphenicol, and linezolid).[15] In this study the ocular strains susceptible to chloramphenicol, tetracycline, and itraconazole provide presumptive data to guide a combination therapy for more effective treatment. The mechanisms of action of tetracyclines and macrolides against *P. insidiosum* have been hypothesized that they are effective due to theirmain mechanism of action to inhibit protein synthesis.[16] The challenge in human pythiosis to several antifungal medications, such as polyenes, azoles, allylamines, and echinocandins, is the high effectiveness of treatment achieved from itraconazole. Itraconazole and terbinafine were a synergistic combination used to treat human pythiosis which caused a deeply invasive facial infection. Furthermore, the use of voriconazole and itraconazole was reported from Susaengrat et al[8] in vascular pythiosis in Thailand. This finding also reported that itraconazole is effective for all types of pythiosis infection, so this may guide to combine with other antibiotics such as chloramphenicol or tetracycline which may improve effectiveness. Brown et al[17] demonstrated radial growth assays for itraconazole, posaconazole, voriconazole, terbinafine, caspofungin, and mefenoxam against *P. insidiosum* and *Lagenidium* sp isolated from dogs.

That report revealed that the azoles had limited activity, whereas terbinafine and caspofungin caused significant, but minimal to moderate inhibition. In contrast, in our finding, itraconazole showed the most effectiveness for all strains of infection. This may be due to the limited success of pharmacological interventions against *P. insidiosum* in humans and animal isolates.[14] There were different drug susceptibility patterns between each clinical isolate used according to the virulence of each strain. The limitations of this study were the limited number of clinical isolates tested and no environmental strains or animal strains included. In this experiment, if there is no inhibition zone it does not mean that the drug has no activity to inhibit the growth of *P. insidiosum* because in this study only one concentration was tested. The result of antimicrobial screening used only commercial discs to test and had no report of MIC according to the limitation of zoospore production for broth microdilution assay was not allowed in our laboratory. With those limitations, we are still hopeful that chloramphenicol, tetracyclines, and itraconazole may offer new treatment options for human pythiosis in Thailand.

Conclusions

In conclusion chloramphenicol, tetracycline, and itraconazole exhibited the most efficiency in inhibiting mycelia growth of *P. insidiosum* while other antimicrobial drugs showed less effect. Since these 3 drugs exhibited a better response, further experiments should be carried out to evaluate for their MICs and use higher number of isolates. This could be applied for the effective treatment of pythiosis animals and humans in the future.

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การทดสอบความไวของเชื้อ *Pythium insidiosum* ต่อยาต้านจุลชีพด้วยวิธี Disc Diffusion

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บทนำ: โรค Pythiosis มีสาเหตุจากการติดเชื้อ *Pythium insidiosum* ซึ่งเป็น Fungus-like organism พบการติดเชื้อได้ทั้งในคนและสัตว์เลี้ยงลูกด้วยนม เชื้อมี Ergosterol ซึ่งเป็นองค์ประกอบที่เป็นเป้าหมายของยาต้านเชื้อรา Amphotericin B ในปริมาณน้อย ทำให้การรักษาด้วยยาชนิดนี้มีประสิทธิผลต่ำ

วัตถุประสงค์: เพื่อตรวจกรองความไวของยาต้านจุลชีพต่อเชื้อ *P. insidiosum* ที่แยกได้จากผู้ป่วยโรค Pythiosis ด้วยวิธี Disc diffusion

วิธีการศึกษา: การศึกษาความไวของยาต่อเชื้อ *P. insidiosum* จากผู้ป่วยโรค Pythiosis จำนวน 10 สายพันธุ์ ต่อยาต้านจุลชีพ 8 ชนิด (ยา Tetracycline, Oxacillin, Chloramphenicol, Cefotaxime, Vancomycin, Gentamycin, Meropenem และ Ciprofloxacin) และยาต้านเชื้อรา 2 ชนิด (ยา Itraconazole และ Aamphotericin B) ด้วยวิธี Disc diffusion

ผลการศึกษา: เชื้อ *P. insidiosum* จำนวน 6 สายพันธุ์ ไวต่อยาต้านจุลชีพโดยสายพันธุ์ที่แยกได้จากการติดเชื้อที่ผิวหนัง (SIMI 8569) มีความไวต่อยาต้านจุลชีพมากที่สุด จำนวน 6 ชนิด (ยา Chloramphenicol, Cefotaxime, Ciprofloxacin, Tetracycline, Oxacillin, และ Itraconazole) นอกจากนี้ยังพบเชื้ออีกจำนวน 4 สายพันธุ์ (M 29, SIMI 6666, SIMI 7873, และ SIMI 2989-42) ไม่สามารถยับยั้งการเจริญเติบโตได้ด้วยยาต้านจุลชีพทุกชนิดที่นำมาทดสอบ

สรุป: การตรวจกรองฤทธิ์ของยาปฏิชีวนะในการยับยั้งการเจริญของเชื้อ *P. insidiosum* พบว่า ยา Chloramphenicol, Tetracycline และ Itraconazole มีความไวต่อเชื้อได้ดีที่สุดซึ่งมีฤทธิ์ยับยั้งการเจริญเติบโตของสายราได้ร้อยละ 40 - 60 ของจำนวนเชื้อที่นำมาทดสอบ จึงสามารถใช้เป็นแนวทางในการศึกษาค่าความเข้มข้นของยาต้านเชื้อจุลชีพที่น้อยที่สุดที่สามารถยับยั้งการเจริญของเชื้อด้วยวิธี Broth dilution เพื่อเพิ่มประสิทธิภาพในการรักษาโรค Pythioisis ต่อไปในอนาคต

Keywords: เชื้อ *Pythium insidiosum* โรค Pythiosis ยาต้านจุลชีพ

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