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Myxococcus xanthus: A source of antimicrobials and natural bio-control agent

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Abstract
The predatory myxobacterium, *Myxococcus xanthus* was known for producing many potent antimicrobials in the cell extract and supernatant. Being a social soil bacterium in nature having unique life-style, it uses a frontal attack strategy for attacking its prey. It produces many secondary metabolites such as antibiotics and hydrolytic enzymes to kill and lyse the prey. Bacteriocins produced by them kills their prey and the lytic enzymes degrade and decompose cell contents of prey cell which makes it easy for absorption. The antibacterial produced by them not only kills host cells (paracides) but they also exhibits autolysis (autocides). There are many strains of *M. xanthus* known to be producing paracides and autocides such as Mx x12, DK1622, DM504/15 *etc*. The paracides produced by them are broad spectrum in nature effective against Gram negative and Gram positive bacteria, yeasts and molds, while autocides are ineffective against them.

Keywords: *Myxococcus xanthus,* predation, bacteriocins, paracides, autocides

1. Introduction
Myxococcus xanthus is a Gram-negative, gliding and soil dwelling bacterium which has a distinguished social behaviour. Myxobacterium belongs to phylum Proteobacteria, class Deltaprotobacteria and order Myxococcales. The most of myxobacteria are aerobic with exception of *Anaeromyxobacter* (Sanford *et al.,* 2002) [1]. *M. xanthus* plays significant role in soil ecology. The cells of bacteria contain type IV pili instead of flagella which enable movement on solid surface and not in liquid medium. The movement of bacterium is controlled by two types of movement systems: Adventurous and Social mobility systems (Berlman *et al.,* 2007) [2]. Myxobacterium is also well known for its complex life cycle, predation and multicellular behaviour. The life cycle of bacterium is comprises of vegetative swarming and fruiting body formation (Li *et al.,* 2003) [3]. The mechanisms of myxobacteria induced predation and multicellular behaviour are regulated by a variety of secondary metabolites produced by bacteria. In previous years, to understand these mechanisms the analysis of secondary metabolites produced by bacteria drawn the interest of researchers and interestingly about 20% of secondary metabolites are antibiotics (Shimkets *et al.,* 2006) [4]. The two α-pyrone antibiotics which are structurally different (myxopyronins and corallopyronins) were reported as potential antibacterial therapeutic agents (Sucipto *et al.,* 2017) [5]. Myxobacterium also reported to produce some of the most cytotoxic secondary metabolites (Bode *et al.,* 2006) [6]. One of such example of cytotoxic secondary metabolite is epothilone which is in clinical trial against cancer (Bode *et al.,* 2007) [7]. Myxovirescin is an antibiotic generally produced by bacterium during prey lysis with hydrolytic enzymes and extracellular outer-membrane vesicles (OMVs) (Kaene *et al.,* 2016) [8]. In *M. xanthus* about 8% of genome is dedicated to secondary metabolites formation. In genome, 18 gene clusters are specific for the production of polyketide antibiotics. In this bacterium, the number of genes for the antibiotic production is twice of *Streptomyces coelicolor* which is considered experimental model for antibiotic production (Goldman *et al.,* 2006) [9].

2. Antimicrobials from *M. xanthus* strains
M. xanthus possess large genome having 9.13 Mb of DNA that helps in secondary metabolism and degradative enzyme production **(**Goldman *et al.,* 2006) [9]. The ability of this bacterium to lyse both Gram negative and Gram positive species in a non-species specific manner makes it unique and clinically important for the production of novel chemical compounds.

The secondary metabolites produced by them for predation are likely to be important to know the origin of attack and defence mechanisms that may act as virulence factors in bacterium (Erken *et al.*, 2013) [10]. Some of the secondary metabolites produced by them are myxovirescin, myxalamid and cittilin compounds. They also secrete hydrolytic enzymes which they use to digest macromolecules of the prey. Low molecular weight antibacterial are of two categories *i.e.* paracides and autocides.

2.1 Paracides

This omnivore bacterium produces a huge number and variety of antibiotics. Paracides are a type of antibacterials which effect other microbes but does not have any effect on self-cells. Important paracides produced by them are as follows:

a) Myxovirescin A: One of the secondary metabolite produced by *M. xanthus* is TA (myxovirescin) which was first discovered by Rosenberg and colleagues in Israel (Rosenberg *et al.*, 1973) [11]. It is a broad spectrum antibiotic which kills other bacteria by interfering with polymerization of the lipid-disaccharide-pentapeptide thus, blocking cell wall synthesis (Zafriri *et al.*, 1981**)** [12]**.** This antibiotic has molecular formula $C_{35}H_{61}NO_8$ and molecular weight 623.872 g/mol having structure as shown in Fig. 1.

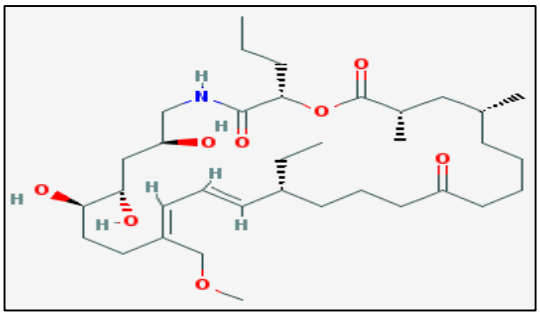

Fig 1: Structure of Myxovirescin A.
Source: https://pubchem.ncbi.nlm.nih.gov/compound/6450484

b) Myxalamids B: This antibiotic was extracted from cell mass and culture of this gliding bacterium, *M. xanthus* strain Mx x12. This antibiotic is effective against yeasts, molds and some Gram positive bacteria, while Gram negative bacteria were mostly resistant to it. This antibiotic producing strain was isolated from goat dung collected near Olympia, Greece in 1978 (Gerth *et al.*, 1982) [13]. This antibiotic is structurally analogue to piericidin A, which acts as an inhibitor of electron transport in the electron transport chain (Jansen *et al.*, 1983) [14]. The molecular formula of this antibiotic is $C_{25}H_{39}NO_3$ with molecular weight of 401.591 g/mol having structure as shown in Fig. 2.

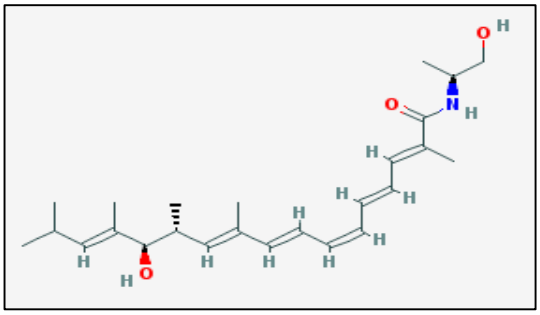

Fig 2: Structure of Myxolamid B.
Source: https://pubchem.ncbi.nlm.nih.gov/compound/Myxalamid_B

Other secondary metabolites produced by them are saframycin Mx1, althiomycin from strain DM504/15 and myxoprincomide, myxochromids, cittilins, siderophore myxochelin from strain DK1622 (Fig. 3)

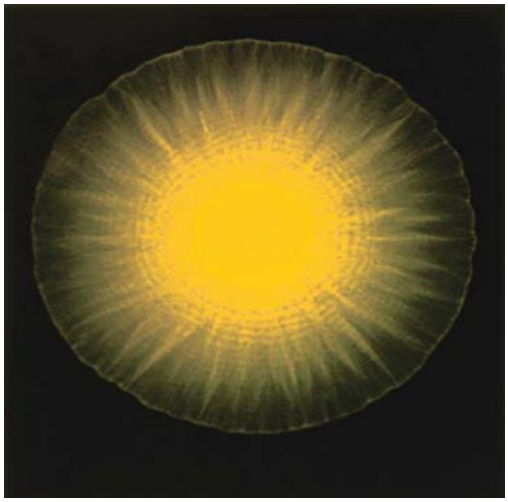

Fig 3: A swarm of *Myxococcus xanthus*, strain DK1622, on agar. (Jelsbak and Kaiser, 2005)[15]

2.2 Autocides: these are a type of antibacterial which effects self-cells. *M. xanthus* is known to be producing at least five different autocides (Varon *et al.*, 1986) [16]. AMI and AMV (phosphatidylethanolamine) are two major autocides produced by this bacterium. These autocides are specifically against *M. xanthus* and *M. fulvus*. All gram positive and gram negative bacteria are known to be resistant to these autocides. The bactericidal activity of AMV depends upon the targeted cell density, the more the cell density higher is the killing effect. The autolytic effect of AMI may be due to direct interaction with the cell membrane.

3. Conclusion

Having unique life-style of *Myxococcus xanthus*, it was found that it uses novel hunting strategy to kill and lyse its prey. Its novel mechanism of predation involves secretion of many antibiotics and lytic enzymes for lysing and nutrient absorption. Therefore, due to its novel predation mechanism, it is used as a natural biological control agent against many pathogenic microbes. Thus, it is an important bacterium from the public health of view point. There is a need for more advance understanding of its metabolic profile to know the quantitative degree of antimicrobial production.

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