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Myxobacteria: Producers of Enormous Bioactive Secondary Metabolites

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ABSTRACT

Myxobacteria are of great interest due to their unique social lifestyle and as potential producer of many useful and novel bioactive secondary metabolites. Their abilities such as gliding motility, predation by producing antibiotics, lytic enzymes and formation of fruiting bodies and myxospores under nutrient deficient conditions makes them unique from other bacteria. In this review article, production of antibacterial, antifungal and agriculturally important metabolites by various myxobacterium strains are discussed. Some cytotoxic compounds produced by them are also discussed which makes them potential producers of cancer chemotherapeutics in near future.

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INTRODUCTION

Natural products from plants and microbes play an important role in the discovery and development of drugs against human infectious diseases (Cragg and Newman, 2013). Microbes produce primary metabolites such as amino acids, nucleotides, carbohydrates and lipids which are essential for their growth and metabolism. Secondary metabolites are usually produced in late growth phase by many strains of microbial species. They produce them for their own benefit which they used to survive under unfavourable conditions, to capture and kill their prey, to form symbiotic association with plants and animals or to protect themselves from predators. The main producers of secondary metabolites among bacteria include Actinomycetes, *Bacillus* and Pseudomonads (Gerth *et al.,* 2003). Over a decade, myxobacteria have emerged as an important alternative source for bioactive compounds (Reichenbach, 1984).

Myxobacteria are considered to be rich source of structurally diverse secondary metabolites possessing interesting biological activities (Herrmann *et al.,* 2017). They are rod-shaped, gram negative δ-proteobacteria possessing unique features like gliding, predation and fruiting body formation under starvation conditions (Kaur *et al.,* 2017). These soil dwelling bacteria possesses a unique multi-cellular social life style which distinguishes them from many other bacteria. Such as they produce myxospores under nutrient deficient conditions, they glide over solid surfaces and prey on other bacteria. They can live in wide range of habitats such as soil, marine environment, compost, cow dung etc. (Kaur *et al.,* 2017).

The myxobacteria belong to order Myxococcales, and suborders Cystobacterineae, Sorangiineae, and Nannocystineae. The most common members are *Myxococcus Xanthus, Sorangium cellulosum, Stigmatella aurantiaca, Myxococcus fulvus, Nannocystis exedens* etc. Most of the bioactive

secondary metabolites produced by myxobacteria possess antifungal, antibacterial and anticancer activities (Kim *et al.,* 2003). Lytic metabolites that induce cell lysis include antibiotics, cell wall degrading enzymes, nucleases, lipases and proteases. Due to their ability to produce such distinct secondary metabolites, they are also called as 'microbial factories' (Reichenbach, 2001). The aim of this review paper is to summarize the important secondary metabolites produced by different myxobacterial strains and their use to humans and plants.

Antibacterial/Antifungal agents

Myxobacterial metabolites are more effective towards many gram positive and few gram negative bacteria, as well as yeast and fungi. This anti-microbial activity is due to number of different mechanisms. There are various cell wall degrading enzymes produced by different myxobacteria members (Weissman and Müller, 2010). These include glucosaminidase, muramidase, amidase, peptidase etc. that are effective against many pathogenic bacteria such as *E. coli, Staphylococcous aureus, Bacillus subtilis, Micrococcus luteus* etc. Few important anti-microbial agents produced by different myxobacterial strains are listed below (Weissman and Müller, 2010; Wenzel and Müller, 2009; Thierbach and Reichenbach, 1981; Irschik *et al.,* 1988; Kaur *et al.,* 2017).

Thuggacin: It was isolated from myxobacterium *Sorangium cellulosum* and considered to be effective against isolates of *Mycobacterium tuberculosis* which causes tuberculosis in humans.

Etnangien: It is a macrolide antibiotic effective against many Gram-positive bacteria including mycobacteria and rifampicin-resistant strain of *Staphylococcus aureus*. It was isolated from the culture broth of *Sorangium cellulosum* strains. They work as inhibitors of eubacterial DNA polymerase.

Althiomycin: It was isolated from *Myxococcus xanthus* strain DK897. It is also produced by many *Streptomyces* species and believed to disrupt translation at the peptidyltransfer stage. It is a broad spectrum antibiotic effective against many infectious bacteria.

Myxovalargin: It was isolated from myxobacterium *Myxococcus fulvus* strain Mx f65 and acts by disrupting the binding of the aminoacyl-tRNA to the A site. It also damages the cell membrane of many bacteria.

Myxovirescin: It is a macrocyclic secondary metabolite produced by *Myxococcus xanthus*. It is a broad spectrum drug and acts by interfering with polymerization of the lipid-disaccharide-pentapeptide hence, blocking the cell wall synthesis in many bacteria. The other useful property of this bacterium is, it adheres to variety of surfaces such as rubber and dental tissues and may be used for the treatment of plaque, gingivitis and also catheter-associated urinary tract infections.

Myxalamids: It is produced by *Myxococcus xanthus* strain Mx X12 and is effective against many Gram positive bacteria, molds and yeast. It acts as an inhibitor of electron transfer in the electron transport chain.

Myxothiazol: This antibiotic is produced by *Myxococcus fulvus* and it acts as an inhibitor of the mitochondrial cytochrome bc1 complex i.e. coenzyme Q - cytochrome c reductase.

Saframycin Mx1: It was produced by *Myxococcus xanthus* strain Mx x48. It is a strong inhibitor of Gram positive bacteria and halobacteria but less effective against Gram negative bacteria.

Ajudazol: It is produced by myxobacterium *Chondromyces crocatus* and it also acts as mitochondrial electron transport inhibitor. It is more effective against yeast and fungi.

Phenoxan: It was isolated from *Polyganium* sp. strain PI VO19. It is a powerful inhibitor of the eukaryotic respiratory chain at the site of complex I. It is effective against many fungal species.

Stigmatellin: It is also a potent antifungal agent which acts as the inhibitor of the quinol oxidation site of the cytochrome bc1 complex in mitochondria and the cytochrome b6f complex of thylakoid membranes. It is isolated from myxobacterium *Stigmatella aurantica*.

Cytotoxic compounds

The most important bioactivities exhibited by myxobacterial metabolites are their cytotoxicity towards mammalian cells. Due to this these compounds are used in cancer chemotherapy. Till date, many metabolites have been discovered which interfere with the eukaryotic cytoskeleton and may act as potential cancer chemotherapeutics.

Disorazol: It is a macrocyclic compound with two oxazol rings and was isolated from *Sorangium cellulosum* strain So ce12. It is effective against eukaryotic organisms as it inhibits the proliferation of different cancer cell lines and also acts as an antifungal agent (Elnakady *et al.,* 2004).

Epothilone: It is also produced by soil-dwelling myxobacterium *Sorangium cellulosum* and the principal mechanism of this class is inhibition of

microtubule function which is essential for cell division (Altmann et al., 2009).

Chondramide: It is a mixed non-ribosomal peptide/polyketide secondary metabolite produced by *Chondromyces crocatus* Cm c5. It exhibit strong cytotoxic activity against cancer cell lines especially, considered to be effective against breast cancer metastasis.

Chivosazol: It is also produced by *Sorangium cellulosum* strain So ce12 and possesses one oxazole ring in its structure. It is effective against yeast and at higher concentration also to filamentous fungi. It destroys the actin skeleton of eukaryotic cells, hence exhibits cytotoxic activity.

Rhizopodin: It is a macrocyclic lactone with an integrated oxazole ring and was isolated from *Myxococcus stipitatus*. It forms rhizopodia-like structures in animal cell cultures and found to be effective against cancer cell lines. It strongly affects the actin cytoskeleton at nanomolar concentrations (Weissman and Müller, 2010)

Tubulysin: It is a cytostatic compound isolated from the strains of myxobacteria *Archangium gephyra* and *Angiococcus disciformis*. Tubulysin A, being highly cytotoxic peptide possesses antimitotic activity which triggers apoptotic process by depleting cell microtubules. It arrests the cell cycle at G_2/M phase. Tubulysin A and B are ineffective against bacteria and yeast but show little antimicrobial activity against filamentous fungi. All the four tubulysins isolated from myxobacteria were effective in mammalian cell culture (Sasse *et al*., 2000; Khalil *et al*., 2006).

Agriculturally important compounds

Myxobacteria mainly possess bacteriolytic and cellulolytic activity due to presence of certain lytic enzymes. The bacteriolytic myxobacteria produce many agriculturally important antibiotics such as thiangazol, pyrrolnitrin etc. It is considered as a good antagonist of phytopathogens that destroy useful plants. The genera *Myxococcus, Corallococcus, Cystobacter, Archangium,* and *Stigmatella* are bacteriolytic myxobacteria that produce important antibiotics and may act as potential biocontrol agents. The antagonistic effects of six species of bacteriolytic myxobacteria, *Myxococcus coralloides, M. fulvus, M. stipitatus, M. flavescens, M. virescens,* and *M. xanthus,* were reported to be effective against several soil-borne phytopathogens. Among them, *M. coralloides* was considered effective for inhibiting the mycelial growth of the pathogens. Myxothiazol, isolated from *M. fulvus* when sprayed on diseased plants was found to be effective against rice blast and tomato Phytophthora blight (Bull *et al.,* 2002). Other such plant protectants are:

Thiangazol: It is a secondary metabolite isolated from *Polyangium* sp., strain PI3007 of myxobacterium. It shows many interesting biological effects such as antifungal, acaricidal and insecticidal activities, as well as HIV-1 inhibition (Kunze *et al.,* 1993).

Tartrolon: It was isolated from the culture broth of the myxobacterium, *Sorangium cellulosum*, strain So ce678 and is active against Gram-positive bacteria and mammalian cells (Irschik *et al.,* 1995).

Pyrrolnitrin: It is produced by myxobacterial species *Myxococcus fulvus*, *Corallococcus exiguous,* and *Cystobacter ferrugineus* and act as an important anti-fungal agent.

Ambruticin: This myxobacterial fungicide kills the yeast, *Hansenula anomala* and was isolated from *Sorangium cellulosum.* It is effective against plant pathogen *Botrytis cinerea* and works by interfering with the osmoregulation system of the susceptible fungi (Knauth and Reichenbach, 2000).

Soraphen: It was isolated from the culture broth of *Sorangium cellulosum* and found to be possessing antifungal activity. It is a potent plant diseases control agent as it is effective against many phytopathogenic fungi (Gerth *et al.,* 1994).

Other bioactive metabolites

Argyrin: It is an immunosuppressive agent isolated from the strains of myxobacterium *Archangium gephyra*. Argyrin B was considered to be a potential inhibitor of T-cell independent antibody formation by murine B cells. It is also effective against *Pseudomonas* sp. and possesses cytotoxic activity against mammalian cell cultures (Sasse *et al.,* 2002).

Aurachins: They are quinoline alkaloids found to be possessing antiplasmodial activity. They were isolated from the myxobacteria *Stigmatella aurantiaca* and *Stigmatella erecta*. Aurachin E is found to be most effective among them against malarial plasmodium (Höfle *et al.,* 2008).

Phenoxan, Phenalamide A1, and Thiangazole: These three were reported to be possessing antiviral activity against HIV-1 virus. These were isolated from strains of *Polyangium* sp. and *Myxococcus stipitatus* (Jurkiewicz *et al.,* 1992).

CONCLUSION

Till date, only few microorganisms are investigated as an efficient producer of natural bioactive molecules. The genome sequencing and metabolic profiling of myxobacterial strains makes it easier to go in depth of its secondary metabolite production mechanism. From the above literature, it is clear that they have antagonistic effect against many human, plant and animal pathogens.

Nowadays, People are exploring its anti-filarial, anti-malarial and antiviral activities. So, there is a need to explore more efficient methods for the extraction of these bioactive metabolites.

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