A review on hydroxy anthraquinones from bacteria: crosstalk’s of structures and biological activities

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ABSTRACT
Anthraquinones (AQ), unveiling large structural diversity, among polyketides demonstrate a wide range of applications. The hydroxy anthraquinones (HAQ), a group of anthraquinone derivatives, are secondary metabolites produced by bacteria and eukaryotes. Plant-based HAQ are well-studied unlike bacterial HAQ and applied as herbal medicine for centuries. Bacteria are known to synthesize a wide variety of structurally diversified HAQ through polyketide pathways using polyketide synthases (I, II & III) principally through polyketide synthase-II. The actinobacteria especially the genus Streptomyces and Micromonospora represent a rich source of HAQ, however novel HAQ are reported from the rare actinobacteria genera (Salinospora, Actinoplanes, Amycolaptosis, Verrucosispora, Xenorhabdus, and Photorhabdus). Though several reviews are available on AQ produced by plants and fungi, however none on bacterial AQ. The current review focused on sources of bacterial HAQ and their structural diversity and biological activities along with toxicity and side effects.

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1. Introduction

Anthraquinones (AQ), an incredible group of natural compounds, are the largest group of natural pigments exhibiting remarkable applications in the fields of medicine, food, and dye industries since the ancient era. Anthraquinones have been distributed widely in plants, microorganisms, insects, and animals in either free or glycosidic form (Hegnauer 1959), however, the majority of them are isolated from plants followed by lichens and fungi (Duval et al. 2016). AQ from rhubarb and Aloe have been extensively used in folk medicine as Traditional Chinese Medicine (TCM) and Traditional Korean Medicine (TKM) since the ancient era (Li et al. 2019). Predominantly, the AQ are produced as secondary metabolites with a basic structure of 9,10-anthracenedione, a tricyclic aromatic organic compound (Bajaj 1999). In particular, hydroxy anthraquinones (HAQ) are described as derivatives of the 9,10-anthracenedione ring and renamed as mono-, di-, tri, up to octet based on the number of substitutions on the ring (Liu et al. 2008). Most of these HAQ are produced by plants belonging to the families of Rubiaceae, Rhamnaceae, Fabaceae, Polygonaceae, Bignoniaceae, Verbenaceae, Scrophulariaceae, and Liliaceae (Thomson 1987). Some of the HAQ especially rhein, emodin, aloe-emodin, physcion, and chrysophanol reveal significant pharmacological properties and have been used as laxatives and also as anti-cancer, anti-inflammatory, anti-arthritic, anti-fungal, anti-bacterial, anti-viral, anti-malarial, anti-oxidant, anti-diabetic, and hepatoprotective agents (Diaz et al. 2018). In addition, HAQ mainly unsubstituted 9, 10 anthracenedione derivatives show application potential as a dying agent due to the absorbance of visible light that imparts color to the compounds. Hence renowned interest has been created worldwide in HAQ as dyeing agents, food colorants, and pharmaceuticals.

Microbial HAQ, impart a bright color to bacteria and fungi (Gill 2001). As easily up-scalable organisms, the microorganisms draw the attention of researchers as a source of the HAQ. The compounds physcion, emodin, and chrysophanol, and subsequently catenarin, erythroglaucin, macrosporin, and questins have been frequently isolated
from fungi. These compounds mimic the close similarity with the plant-derived ones owing to endophytic interactions and genetic similarity of fungi with plants and animals (eukaryotes) in the assembly of many natural products (Strobel and Daisy 2003). Among the microbial world, actinobacteria are the renowned source of unique HAQ which are not reported earlier in plants. The present review emphasizes the HAQ derived from diversified bacterial sources especially actinobacteria along with an insight into their chemistry, structure–activity relationship (SAR) as well as biological properties.

2. Biosynthesis of HAQ

Polyketide synthases (PKS) are the multi-domain enzymes (PKS-I, II, and III) responsible for the synthesis of polyketides. PKS-III in plants (Crawford and Townsend 2010) and PKS-I in fungi (Flores-Sanchez and Verpoorte 2009) are responsible for HAQ production while PKS-II type is accountable for the synthesis of bacterial HAQ (Risdian et al. 2019). The plant-produced HAQ are either alizarin or emodin type. Structurally, the alizarin type is distinguished with one unsubstituted ring and produced by the shikimic acid pathway (chorismate/δ-succinylbenzoic acid) and creates great interest in the field of dyeing (carminic acid and Arpink redTM) (Dufossé 2014). Whereas, emodin types are characterized by OH-substitution on both rings and are formed by the polyketide pathway (Monks et al. 1992). However, microbes produce only emodin type of HAQ by using PKS-I (fungi) and PKS-II (bacteria) (Figure 1). Exceptionally, actinobacteria produce mainly emodin type and less extent alizarin type of HAQ, however, the biosynthetic pathway responsible for their synthesis is still unexplored (Balachandran et al. 2016). Furthermore, the HAQ isolated from actinobacteria were unique in structure, unlike plants and fungi owing to their altered mode of biosynthesis (Thomas 2001). It was noticed that, though the initial octaketide chain synthesis mechanism is identical in all organisms, further cyclization into HAQ is organism-specific. In fungi and other eukaryotes, octaketide cyclization is associated by two C2 units (acetyl CoA) (hence named as F-mode – ‘F’ represents fungi) while in bacteria is formed by three C2 units which are first exemplified in Streptomyces hence represented as S-mode which is

![Figure 1. Schematic representation of HAQ biosynthetic pathways among natural sources](image-url)
evidenced from the walkthrough of chrysophanol biosynthesis in *Streptomyces* (Bringmann et al. 2006) and *Penicillium islandicum* (Franck and Stange 1981) (Figure 1). Later on, the isomeric HAQ aloesaponarin-II has also been assumed to be synthesized by altered mode in plants and bacteria.

3. Microbial sources of HAQ

Fungi occupied a significant position as a source of HAQ among microbes owing to their rich biodiversity. Several other polyketides including naphthalenes, naphthoquinones, flavonoids, macrolides, polyeses, tetracyclines and tropolonones with remarkable bioactive profiles also reported from fungi apart from HAQ. Microbial strains with the potential to produce AQ have been an ingredient of the majority of traditional indigenous fermented foods and used as a health drink in China (Fuzhuan brick tea, Katsuobushi) (Fouillaud et al. 2018). Apart from fungi, actinobacteria have also been reported as a prolific producer of natural HAQ, followed by entomopathogenic bacteria (*Xenorhabdus* and *Photorhabdus* genus) (Bode 2009).

4. Actinobacteria as a source of HAQ

The phylum actinobacteria was reported as one of the largest phyla within the bacterial domain. The members of this phylum have been recognized as producers of novel bioactive secondary metabolites such as aminoglycosides, anthracyclines, glycopeptidases, beta-lactams, macrolides, nucleosides, peptides, polyeses, polyether, tetracyclines and polyketides (Berdy 2005). These compounds can be used as therapeutic enzymes, antibiotics, immunosuppressants, anti-tumor agents and vitamins (Wavve et al. 2001) to treat various ailments. Among them, antibiotics occupy a prominent position, in the medical, industrial and agricultural sectors (Barka et al. 2016). As the progenitors of diversified chemical molecules, actinobacteria from different natural habitats (terrestrial, marine and extreme environments) (Barka et al. 2016) have helped develop effective therapeutic compounds in an economically feasible way for the pharmaceutical industry (Williams et al. 1983). So far terrestrial actinobacteria are majorly exploited for bioactive principles. However, since past few years, the search is shifted to unique habitats such as a deep-sea ocean, (Fenical and Jensen 2006) symbiotic organisms associated with plants (Trujillo et al. 2015) or insects (Oh et al) for potent novel bioactive with unique structures resulting isolation of the novel HAQ, possessing significant biological activities. The mining of several research reports explored that the genus *Streptomyces* has been considered as one of the richest sources of novel HAQ (chromenequinones, enedymes, spartanamicins, and anthracyclines) among the actinobacterial group followed by *Micromonospora* (Hifnawy et al. 2020). Apart from AQ, HAQ are also isolated from terrestrial and marine actinobacteria as well as actinobacteria living as an endosymbiont of plants, insects, and sea animals belonging to genera *Salinospora, Amycoloptosis, Actinoplanes* and *Verrucosispora*, and so on.
4.1. Structures of HAQ from actinobacteria

Actinobacteria have been reported to produce different classes of AQ (anthracyclines and HAQ) with varying structures and functions. Structurally anthracyclines, anthraquinone-based fused tetracyclic ring structures (Malik and Müller 2016), consist of a linear tetracyclic ring with quinone-hydroquinone groups in rings B and C (Ex: daunorubicin produced by Streptomyces peucetius) (Pokhrel et al. 2016) unlike HAQ which consists of 9, 10-anthracenedione ring. Rarely, HAQ with a complex structure like anthraquinone-γ-pyrones, ericamycin, and enediyynes were also reported (Murphy et al. 2010; Rhea et al. 2012; Liang 2010). The aloesaponarin-II (1,8-dihydroxy anthraquinone) is the first HAQ isolated from mutant strains of Streptomyces coelicolor B22 and B159, (Rudd and Hopwood 1979) Streptomyces sp. GW32/698 & GW24/1694 and marine Streptomyces sp. M097 (Fotso et al; Cui et al. 2006). An elaborate table has been provided detailing the novel HAQ structures and their microbial source (Table 1).

4.2. Fused structures of HAQ from actinobacteria

Recently, Salinospora has been described as a fruitful genus of actinobacteria that can produce novel natural products including fused HAQ. Jensen et al. (2015) reported arenicolides, saliniketals, rifamycin, arenimycin, cyclomarins from the strains of marine S. arenicola (Jensen et al. 2015). Salinoquinones A-F, a class of anthraquinone-γ-pyrones, have been isolated from the marine S. arenicola strains indicating metabolic diversity among strains (Murphy et al. 2010). A new anthraquinone, 5-hydroxy ericamycin with potent antimicrobial activity, was extracted from the fermentation broth of the Actinoplanes sp. strain 4731 (Rhea et al. 2012).

Some of the enediyynes are considered as a class of fused anthraquinones of a 10 member group with sub-nanomolar inhibitory concentrations against a broad group of cancer cell lines. Genome mining study indicated that enediyynes are widely distributed in the genus Streptomyces (Liang 2010) and Micromonospora (Rudolf et al. 2016). The first compound dynemicin (DYN) was isolated from the culture broth of Micromonospora chersina sp. nov. No. M956-1 (Konishi et al. 1989) followed by uncialamycin (UCM) from Streptomyces uncialisin (Davies et al. 2005). Owing to the profound impact of these compounds on modern chemistry, biology, and medicine (Galm et al. 2005) new innovative methods have been introduced like high-throughput real-time PCR method to prioritize strains for natural-product discovery. This method can be used to identify strains that are highly likely to encode enediyne biosynthesis by genome sequencing, bioinformatics analysis, genetic manipulation followed by fermentation optimization to produce a higher titer of compounds than original strains. Until now, a total of 3400 strains from the actinomycetes strain collection at The Scripps research institute (TSRI) have been surveyed, out of which 81 potential enediyne producers were identified and discovered. Later on, the survey of 11,500 actinobacterial genomes in the NCBI and JGI genome database facilitated the characterization of Micromonospora yangpuensis DSM 45577 as a producer of a new anthraquinone-fused enediyne, yangpumicin A (YPM A) (Yan et al. 2017). Tiancimycin A (TNM A) is the one among them, isolated from Streptomyces sp. CB03234 (Yan et al. 2018).
| S. no | Source | IUPAC NAME | Common name | Structure | Biological activity | References |
|-------|--------|------------|-------------|-----------|---------------------|------------|
| 1     | *Streptomyces coelicolor* B22, B159, *Streptomyces sp.* GW32/698, *Streptomyces sp.* GW24/1694, *Streptomyces sp.* M097 | 3,8-Dihydroxy-1-methyl anthraquinone | Aloesaponarin-II | Anti-bacterial and anti-protozoal | Cui et al. (2006); Fotso et al.; Rudd and Hopwood (1979); Abdissa et al. (2017) |
| 2     | *Streptomyces sp.* M097, *Streptomyces lividans* K4-114 | 1,6-dihydroxy-8-hydroxy methyl anthraquinone | 9-hydroxyl Aloesaponarin-II | NS | Cui et al. (2006); Kalaitzis and Moore (2004) |
| 3     | *Streptomyces sp.* GW 24/1694 | 1-hydroxy-6-methoxy-8-methylanthraquinone | Methyl ether of Aloesaponarin-II | NS | Fotso et al. |
| 4     | *Streptomyces sp.* GW 32/698 | 1,8-dihydroxy-3-methylanthraquinone | Chrysophanol | Anti-oxidant, Xanthine oxidase inhibition | Fotso et al.; Shi et al. (2014) |
| 5     | *Amycolatopsis thermoflava* SFMA 103 | 1-methoxy-3-methyl-8-hydroxyanthraquinone | 1-O-methyl chrysophanol | Cytotoxic, anti-diabetic, anti-oxidant, anti-microbial | Kumar et al. (2017); Chandrasekhar et al. (2021). |
| 6     | *Streptomyces sp.* GW 32/698 | 3,8-dihydroxy-1-methyl anthraquinone-2-carboxylic acid | – | NS | Fotso et al. |
| 7     | *Streptomyces griseonubiginosus*, *Streptomyces sp.* B 8000, FX-58, *Micromonospora rhodorangea* | 3,8-dihydroxy-1-propylanthraquinone-2-carboxylic acid | DHPAC | NS | Naruse et al. (1998); Poumale et al. (2006); Haung et al. (2006); Xue et al. (2009). |

(continued)
| S. no | Source | IUPAC NAME | Common name | Structure | Biological activity | References |
|-------|--------|------------|-------------|-----------|---------------------|------------|
| 8     | *Streptomyces* sp isolate B8000 *Micromonospora rhodorangea* | 3,8-dihydroxy-1-propylanthraquinone | DHPA | Anti-microbial | Poumale et al. (2006); Xue et al. (2009). |
|       |        |            |             | ![](structure.png) |                     |            |
| 9     | *Streptomyces* sp B 8000 | 8-hydroxy-3-methoxy-1-propylanthraquinone | – | Anti-microbial | Poumale et al. (2006) |
|       |        |            |             | ![](structure.png) |                     |            |
| 10    | *Streptomyces* sp FX-S8 | 1,8-dihydroxy-2-ethyl-3-methylanthaquinone | – | Cytotoxic | Haung et al. (2006) |
|       |        |            |             | ![](structure.png) |                     |            |
| 11    | *Streptomyces* sp FX-S8 | 1,6-dihydroxy-8-propylanthraquinone | – | NS | Haung et al. (2006) |
|       |        |            |             | ![](structure.png) |                     |            |
| 12    | *Micromonospora rhodorangea* | 2-ethyl-1,8-dihydroxy-3-methylanthraquinone | – | NS | Xue et al. (2009) |
|       |        |            |             | ![](structure.png) |                     |            |
| 13    | *Micromonospora rhodorangea* | 2-ethyl-1-hydroxy-8-methoxy-3-methyl-9,10-anthraquinone | – | NS | Xue et al. (2009) |
|       |        |            |             | ![](structure.png) |                     |            |
| 14    | *Streptomyces spinoverrucosus* | 5,8-dihydroxy-2,2,4-trimethyl-6-(3-methylbutyl)anthra[9,1-de]-[1,3]oxazin-7(2H)-one | Isolation artifact | NS | Hu et al. (2012) |
|       |        |            |             | ![](structure.png) |                     |            |

(continued)
| S. no | Source                          | IUPAC NAME                                      | Common name                  | Structure | Biological activity       | References                  |
|-------|---------------------------------|------------------------------------------------|-----------------------------|-----------|---------------------------|-----------------------------|
| 15    | *Xenorhabdus luminescens*       | 1,6-dihydroxy-4-methoxy-9,10-anthraquinone    | –                           | pH-sensitive indicator dye | Richardson et al. 1988      |
| 16    | *Photorhabdus luminescens*      | 3,8-dimethoxy-1-hydroxy-9,10-anthraquinone   | –                           | pH-sensitive indicator dye | Li et al. (1995)            |
| 17    | *Photorhabdus luminescens*      | 1,3-dimethoxy-8-hydroxy-9,10-anthraquinone   | –                           | pH-sensitive indicator dye | Li et al. (1995)            |
| 18    | *Photorhabdus temperate*        | 1,8-dihydroxy-3-methoxyanthracene-9,10-dione | 3-methoxy chrysazone       | Mosquitocidal activity    | Ahn et al. (2013)          |
| 19    | *Photorhabdus temperate*        | 1,3-dimethoxy-8-hydroxy-9,10-anthraquinone   | –                           | NS         | Ahn et al. (2013)         |

Alizarin type (Substitution on single ring)

| S. no | Source                          | IUPAC NAME                                      | Common name                  | Structure | Biological activity       | References                  |
|-------|---------------------------------|------------------------------------------------|-----------------------------|-----------|---------------------------|-----------------------------|
| 20    | *Streptomyces sp RAUACT-1*      | 1,4-dihydroxy-2-(3-hydroxy butyl)-9,10-anthrac | 9,10-anthrac                | Anti-microbial | Ravikumar et al. (2012)  |
| 21    | *Streptomyces galbus ERINLG-127*| 2,3-dihydroxy-9,10-anthraquinone           | –                           | Anti-microbial | Balachandran et al. (2014) |
| 22    | *Streptomyces olivochromogenes ERINLG-261*| 2-hydroxy-9,10-anthraquinone | –                           | Anti-microbial | Balachandran et al. (2016) |

(continued)
| S. no | Source | IUPAC NAME | Common name | Structure | Biological activity | References |
|-------|--------|------------|-------------|-----------|---------------------|------------|
| 1,5-dihydroxy anthraquinones | 23 | *Streptomyces* sp ERI-26 | 1,5,7-trihydroxy-3-hydroxy methyl anthraquinone | | Anti-microbial | Duraipandiyan et al. (2014) |
| 24 | *Streptomyces* sp ERI-26 | 6,6’-bis (1,5,7-trihydroxy-3-hydroxymethylanthraquinone) | | Anti-microbial | Duraipandiyan et al. (2016) |
| 1,3,5-trihydroxy anthraquinones | 25 | *Micromonospora lupine lupac* 08, *Streptomyces spinoverrucosus* Verrucospora SN26-14.1. | 1,3,5-trihydroxy-4-isopentyl-2-methylanthracene-9,10-dione | Lupinacidin A | Cytotoxic, Anti-invasive | Igarashi et al. (2011); Sottorff et al. (2019); Hu et al. (2012) |
| 26 | *Micromonospora lupine lupac* 08 | 1,3,5-trihydroxy-4-isopentyl-2-methylanthracene-9,10-dione | Lupinacidin B | Cytotoxic, Anti-invasive | Igarashi et al. (2011) |
| 27 | *Micromonospora lupine lupac* 08 | (S)-1,3,5-trihydroxy-2-methyl-4-(3-methylpentyl)anthracene-9,10-dione | Lupinacidin C | Cytotoxic, Anti-invasive | Igarashi et al. (2011) |
| 28 | *Streptomyces spinoverrucosus* | 1,4,5-trihydroxy-2-methylanthracene-9,10-dione | Islandicin | Cytotoxic | Hu et al. (2012) |
| Galvaquinones | 29 | *Streptomyces spinoverrucosus* | 1,8-dihydroxy-3-methyl-2-(4-methylpentanoyl)anthracene-9,10-dione | Galvaquinone A | NS | Hu et al. (2012) |

(continued)
Table 1. Continued.

| S. no | Source | IUPAC NAME | Common name | Structure | Biological activity | References |
|-------|--------|------------|-------------|-----------|---------------------|------------|
| 30    | Streptomyces spinoverrucosus | 1,4,5-trihydroxy-2-methyl-3-(4-methylpentanoyl)anthracene-9,10-dione | Galvaquinone B | ![Structure](image) | Cytotoxic, Epigenetics-modulatory activity | Sottorff et al. (2019) |
| 31    | Streptomyces spinoverrucosus | 1,3,5-trihydroxy-2-methyl-4-(3-methylbutanoyl)anthracene-9,10-dione | Galvaquinone C | ![Structure](image) | NS | Hu et al. (2012) |

**Salinoquinones**

| S. no | Source | IUPAC NAME | Common name | Structure | Biological activity | References |
|-------|--------|------------|-------------|-----------|---------------------|------------|
| 32    | Salinispora arenicola | 2-((2R,3R)-2-methyl-3-vinyloxiran-2-yl)-4H-naphtho[2,3-h]chromene-4,7,12-trione | Salinoquinone A | ![Structure](image) | Cytotoxic | Murphy et al. (2010) |
| 33    | ————do——— | 2-((2R,3R)-3-ethyl-2-methyloxiran-2-yl)-4H-naphtho[2,3-h]chromene-4,7,12-trione | Salinoquinone B | ![Structure](image) | NA | Murphy et al. (2010) |
| 34    | ————do——— | 2-((2S)-3-chloro-2-hydroxypent-4-en-2-yl)-4H-naphtho[2,3-h]chromene-4,7,12-trione | Salinoquinone C | ![Structure](image) | NA | Murphy et al. (2010) |
| 35    | ————do——— | (Z)-2-(pent-2-en-2-yl)-4H-naphtho[2,3-h]chromene-4,7,12-trione | Salinoquinone D | ![Structure](image) | NA | Murphy et al. (2010) |
| 36    | ————do——— | 2-((2R)-3-hydroxypent-4-en-2-yl)-4H-naphtho[2,3-h]chromene-4,7,12-trione | Salinoquinone E | ![Structure](image) | NA | Murphy et al. (2010) |
| S. no | Source | IUPAC NAME | Common name | Structure | Biological activity | References |
|-------|--------|------------|-------------|-----------|---------------------|------------|
| 37    | do     | \((S)-2-(2-hydroxypent-4-en-2-yl)4H-naphtho[2,3-h]chromene-4,7,12-trione\) | Salinoquinone F | NA | | Murphy et al. (2010) |
| 38    | Actinoplanes sp 4731 | (6S,7S)-5,6,10,15,16-pentahydroxy-7-methoxy-3,11-dimethyl-6,7-dihydrotetraceno[2,1-g]isoquinoline-1,9,14(2H)-trione | 5-hydroxy ericamycin | Anti-microbial | | Rhea et al. (2012) |
| 39    | Streptomyces sps CB03234 | Tiancymycin A | Cytotoxic | | | Yan et al. (2018) |
| 40    | Micromonospora yangpurensis DSM45577 | Yangpumicin A | Cytotoxic | | | Nicolaou et al. (2020) |
| 41    | Micromonospora chersina sp Nov.No.M956-1 | Dynemicin A | Cytotoxic, anti-microbial | | | Konishi et al. (1989) |
| 42    | Streptomyces uncialis | Uncialamycin | Cytotoxic, anti-microbial | | | Davis et al. (2005) |

Abbreviations: NA, No activity; NS, Not studied; DHPA, Dihydroxy propyl anthraquinone; DHPAC, Dihydroxy propyl anthraquinone carboxylate.
4.3. HAQ from entomopathogenic bacteria

Surprisingly, entomopathogenic bacteria, a diverse group of gram negative microbes associated with animals and insects, also produce a certain class of HAQ as secondary metabolites along with isopropyl stilbenes and ethyl stilbenes (Hu et al. 2006) using PKS-II pathway (Brachmann et al. 2007). These compounds also flourished as one of the substrates of pharmaceutical interesting natural product. One of the entomopathogenic bacteria, *Photorhabdus luminescens* sp. laumonidii strain TT01 was the first completely sequenced for genomic DNA (Duchaud et al. 2003). Analysis of this genome sequence revealed the close similarity with *Streptomyces* (Sieber and Marahiel 2005) indicating the capacity of these bacteria to produce several structurally diverse secondary metabolites including peptides, polyketides, and hybrids of both. Some of the reported structures of various HAQ isolated from the entomopathogenic bacteria were included in Table 1.

5. Biological activities

For several decades, AQ have been recognized as natural coloring agents as well as therapeutic compounds. In the recent past, the application of anthraquinone derivatives are continuously growing very broad especially in the pharmaceutical sector as anti-laxative, anti-cancer, anti-inflammatory, anti-arthritic, anti-fungal, anti-bacterial, anti-viral, anti-platelet, anti-diabetic, hepatoprotective, immuno-enhancing, xanthine oxidase inhibitory, neuro-protective and anti-tributary activities as well as for the treatment of malaria and multiple sclerosis (Malik and Müller 2016). However, their laxative property has been exploited in the treatment of acute pathological conditions including cerebral ischemia-reperfusion injury, and glutamate-induced neuronal damage. Unlike the HAQ derived from plants and fungal origin, most of the bacterially derived compounds were studied only for antimicrobial and cytotoxic activities and few of them are yet to be studied.

5.1. Antimicrobial activity

HAQ isolated from different species of actinobacteria has been studied for the *in vitro* antimicrobial potential of pure compounds. 5-Hydroxy ericamycin isolated from *Actinoplanes* sp. strain 4731 has shown potent antimicrobial activity, with the MIC value as low as 0.06 μg/ml, against several bacterial pathogens including many resistant strains (Rhea et al. 2012). However, 8-hydroxy-3-methoxy-1-propylanthraquinone and 3,8-dihydroxy-1-propyl anthraquinone from marine *Streptomyces* sp. B8000 showed moderate activity against *Staphylococcus aureus* and *Streptomyces viridochromogenes* at 40 μg/disk (Poumale et al. 2006). Similarly compounds, 1,5,7-trihydroxy-3-hydroxymethyl anthraquinone and 6,61-bis (1,5,7-trihydroxy-3-hydroxymethylanthraquinone), isolated from terrestrial *Streptomyces* sp. (ERI-26) revealed higher antimicrobial activity (Duraipandiyan et al. 2014).

The alizarin types of HAQ from plants have been effectively used in the dyeing industry for a long time. Interestingly, the bacterial alizarins exhibited strong antimicrobial activity against superbugs. For example, 2,3-dihydroxy-9,10-anthraquinone
from *Streptomyces galbus* ERINLG-127 showed good antimicrobial activity with significant MIC values of 12.5 μg/ml against *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Klebsiella pneumonia* (ESBL-3894), *K. pneumoniae* (ESBL-3971), and *Staphylococcus aureus* (MRSA) (Balachandran et al. 2014). Similarly, 2-hydroxy-9,10-anthraquinone isolated from *Streptomyces olivochromogenes* (ERINLG-261) was studied against MRSA strains of clinical isolates isolated from a patients urine sample and has shown potent antimicrobial activity (Balachandran et al. 2016). Furthermore, inhibitory effects by the novel compound 1,4-dihydroxy-2-(3-hydroxybutyl)-9,10- anthraquinone 9,10–anthrac extracted from the *Streptomyces sp*. RAUACT-1 was reported against antibiotic-resistant and fish bacterial pathogens (Ravikumar et al. 2012).

Surprisingly, besides the anti-tumor potential, the anti-bacterial potential of anthraquinone fused enediynes have been explored earlier. Uncialamycin exhibits potent *in vitro* antibacterial activity against gram-positive and gram-negative human pathogens, including *Burkholderia cepacia* (Davies et al. 2005) whereas dynemicin and its triacetate showed extremely strong activity against gram-positive bacteria (Konishi et al. 1989). In comparison to dynemicin and its triacetate, triacetate has exhibited good antimicrobial activity.

5.2. Cytotoxicity activity

The daunorubicin is the first antibiotic that belongs to a class of anthracyclines, has been used as an anticancer drug in clinical practice since its discovery in the 1960s from *Streptomyces perucetius* (Di Marco et al. 1963). So far six members of this class (daunorubicin, doxorubicin, epirubicin, idarubicin and valubicin) are approved by the Food and Drug Administration FDA, USA, for clinical use (Minotti et al. 2004). Similarly, 2,3-dihydroxy-9,10-anthraquinone from *Streptomyces galbus* ERINLG-127 depicted as a potential anti-cancer compound *in vitro* with 75.1% cytotoxicity against A549 cell line of lung adenocarcinoma at 100 μg/mL with an IC₅₀ value of 60 μg/mL (Balachandran et al., 2014). Whereas, Galvaquinone B has shown moderate cytotoxicity in Calu-3, H2887 cell lines of non-small-cell lung cancer (NSCLC) with an epigenetic modulatory activity at the concentration of 1.0 μM.

Lupinacidins, another group of HAQ, showed potent cytotoxic and anti-invasive effects on the proliferation of murine colon cancer cells, 26-L5. Among the group, lupinacidin C was found to be the most potent anti-invasive agent with an IC₅₀ value of 0.019 μg/mL (0.054 μM) in addition to cytotoxic property (Igarashi et al. 2011). However, lupinacidin A & B compounds revealed a dose-dependent inhibition of *in vitro* invasion of colon 26-L5 cells at IC₅₀ values of 0.07 μ g/ml and 0.3 μg/mL, respectively. Among different saliniquinones, saliniquinone A observed to be the potent inhibitor of the human colon adenocarcinoma cell line (HCT-116) with an IC₅₀ of 9.9 x 10⁻⁹ M (Murphy et al. 2010). Cell lines HL-60, BCTC-823, and MDA-MB-435 were inhibited by 1,8-dihydroxy-2-ethyl-3-methyl anthraquinone isolated from *Streptomyces sp.* FX-58 with the IC₅₀ ranging from 6.83 to 82.2, 56.59 μg/mL. Nicolaou et al. 2020 reported that tiancimycin A and its congeners, uncialamycin, yangpumicin A, and dynemicin are potent antitumor agents (Nicolaou et al. 2020) while Kumar et al. 2017 showed that 1-O-methyl chrysophanol (OMC) isolated from the *Amycoloptosis thermoflava* SFMA-103 is effective against lung cancer and lymphoblastic
leukemia cells with the IC₅₀ values of 10.3 and 16.98 μM, respectively. In silico binding analysis of 1-O-methyl chrysophanol (OMC) towards alpha-amylase as well as alpha-glucosidase revealed predicted binding energy of 188.81 and 70.53 KJ/mol, while in-vitro analysis demonstrated the IC₅₀ values of 3.4 mg/mL and 38.49 μg/mL, respectively suggesting the OMC could be the probable anti-diabetic agent (Chandrasekhar et al. 2021). Kumar et al. 2017 reported in vitro antioxidant potency for OMC against DPPH radicals with an EC₅₀ of 18.2 μg/ml indicating promising superoxide, nitric oxide radical scavenging activity as well as inhibition of lipid peroxidation. Ahn et al. 2013 surprisingly noticed larvicidal activity against Culex pipiens pallens for 3-methoxy chrysazin (isolated from symbiotic bacteria Photorhabdus temperate).

6. Structure–activity-relationship (SAR) studies

The therapeutic efficacy and biological activity of any chemical entity depend on its structure and arrangement of functional groups, so as HAQ whose therapeutic properties depends upon multiple groups present on its ring (Mondal et al. 2015), transduction of the spatial orientation (Shrestha et al. 2014) and formation of intermolecular hydrogen bonds along with the configuration, size, and type of the substitute. Teng et al. (2007) reported that chrysophanol accumulation was much greater in intestinal Caco-2 cells than that of emodin which was attributed to the higher hydroxyl group’s presence in chrysophanol. Similarly, the presence of the carboxyl, hydroxyl, and hydroxyl methyl polar groups at C3, C6 and C3 respectively, have been attributed to higher antibacterial potential to emodin, rhein, and aloe-emodin to that of physcion and chrysophanol. However, physcion and chrysophanol weak antibacterial activity attributed to polar methyl and weakly polar methoxyl groups despite hydroxyl groups at C1 and C8, in chrysophanol and physcion, respectively (Lu et al. 2011; Xiang et al. 2008). Similarly, the antimicrobial activity of 1,8-dihydroxy-2-methyl-3,7-dimethoxy anthraquinone, lucidin 3-O-β-primeveroside, 1,3-dihydroxy-2-methyl anthraquinone, lucidin-3-ethyl ether, lucidin-3-butyl ether, and damnacanthal extracted from Morinda angustifolia root extract was evaluated and explained in terms of SAR. This group suggested that the presence of carbonyl and two β-hydroxyls at a linear position in 1,8-dihydroxy-2-methyl-3,7-dimethoxy might be an important pharmacophore for the strong antimicrobial activity. In contrast, the presence of an aromatic group attached directly to the cationic anthraquinone scaffold of 4,9-dioxo-4,9-dihydro-1H-naphthol triazole-3-im salts (analogs of cationic AQ) exerted relatively weak antibacterial properties but showed stronger anticancer activities, especially against melanoma, colon cancer, non-small cell lung cancer, and central nervous system cancer (Shrestha et al. 2014).

Baqi et al. (2009) reported that concentration-dependent inhibition of E-NTPD ases by 1-amino-2-sulfo-4-aryl(alk)ylamino is attributed due to the presence of the 2-sulfonate groups whereas 2-methyl-substituted derivatives were inactive (Baqi et al. 2009). Johnson et al. (1997) reported that compounds with an anthraquinone skeleton and propyl amino side chains containing epoxides or halohydrins as the alkylating species have greater activity than similar compounds with naphthoquinone or quinone skeletons (Johnson et al. 1997). The authors suggest that hydroxy substitution on the planar skeleton in conjunction with alkylating side chains has the most potent cytotoxic
activity. A similar conclusion was arrived at by Igarashi et al. (2011) based on cytotoxic and anti-invasive activities of Lupinacidine A over Lupinacidine B against murine colon 26-L5 carcinoma cells.

7. Toxicity studies

Abnormal bilirubin metabolism and hyperbilirubinemia were noticed in rats upon oral administration of 70% ethanol extract of *Polygonum multiflorum*, leading to hepatotoxicity and carcinogenicity which is attributed to quinine assisted UGT1A1 inhibition of liver microsomes (RLM) system (Wang et al. 2015; 2016). SAR analysis indicated that spatial orientation of the cis-emodin dianthrones, trans-emodin dianthrones, and emodin-8-O-glc are involved in inhibitors of UGT1A1 (Wang et al. 2017). *P. multiflorum* Radix, especially emodin, chrysophanol, and physcion are hepatotoxic and causes disposition of endogenous bile acids (BAs) while exogenous deuterium-labeled taurocholate (d5-TCA), glycochenodeoxycholic acid (d4- GCDCA), and 5 (and 6)-carboxy-2,7’-dichlorofluorescein (CDF) result in direct inhibition of BA transporters or regulate expression of BA transporter enzymes in sandwich-cultured rat hepatocytes (SCRHs) (Kang et al. 2017). Ma et al., reported that the inhibition of anion transporter 1 (hOAT1) and hOAT3 by AQ lead to transporter-mediated drug-drug interactions in rats (Ma et al. 2015). Xie et al., demonstrated that HAQ are associated with primary rat hepatocytes and HepG2 cell cytotoxicity however intensity differs with the type of HAQ (chrysophanol was the lowest among rhein, emodin, aloe-emodin, and physcion) especially number of hydroxyl groups (Xie et al. 2019; Westendorf et al. 1990). In addition these, HAQ also cause genotoxic effects such as tumor induction (Mori et al. 1996) mutagenic activity, DNA double-strand breaks (Müller et al. 1996), inhibition of topoisomerase activity, non-covalent DNA intercalation, and nuclear localization (Li et al. 2010) through the generation of reactive oxygen species (ROSs) that leads to DNA damage (Zou and Elledge 2003) which is attributed to the number of hydroxyl groups present in HAQ moiety (Westendorf et al. 1990). In contrast, to plant-derived HAQ, the research on toxicity studies of bacterial-derived compounds was limited except on chrysophanol. Chandrasekhar et al., working with another HAQ, that is, OMC, reported hypoglycemia with no genotoxic effects when administered a fivefold increased therapeutic dose (1000 mg/kg) in rats.

8. Side effects

The long-term use of AQ/HAQ may lead to drug dependence associated with notable side effects such as hypokalemia, dehydration, kidney damage, miscarriage, melanosis coli in addition to its extensive pharmacological potential. There are also reports of abdominal cramps, gastrointestinal discomforts, vomiting, dermatitis, nausea, bloody diarrhea and dizziness in drug overdose (Hallmann 2000; Widjanarko et al. 2013).

9. Conclusion

Actinobacteria are the emerging source of AQ/HAQ. The HAQ isolated from actinobacteria is unique with novel substitutions to that of plant-derived compounds. The genus
Streptomyces has been considered as a rich source of HAQ among the group of actinobacteria. However, studies on the biological activities of the bacterial derived HAQ are in the infancy stage but a few compounds have been studied for antimicrobial, cytotoxic, antidiabetic, and epigenetic modulatory properties. Further detailed clinical evaluation could be justified for these compounds to be used as novel therapeutic compounds in the future.

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