Review Article

Bioactivities and Future Perspectives of Chaetoglobosins

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Chaetoglobosins belonging to cytochalasan alkaloids represent a large class of fungal secondary metabolites. To date, around 100 chaetoglobosins and their analogues have been isolated and identified over the years from a variety of fungi, mainly from the fungus Chaetomium globosum. Studies have found that chaetoglobosins possess a broad range of biological activities, including antitumor, antifungal, phytotoxic, fibrinolytic, antibacterial, nematicidal, anti-inflammatory, and anti-HIV activities. This review will comprehensively summarize the biological activities and mechanisms of action of nature-derived chaetoglobosins.

1. Introduction

Chaetoglobosins represent a large class of fungal secondary metabolites and belong to cytochalasan alkaloids, which contain a 10-(indol-3-yl) group, a macrocyclic ring, and a perhydropyroindolinolone moiety [1]. According to the chemical structure characteristics, they are divided into the subfamilies chaetoglobosin, penochalasin, prochaetoglobosin, armochaetoglasin, aureochaeglobosin, and oxuchaetoglobosin (Figure 1). To date, around 100 chaetoglobosins and their analogues have been isolated and identified over the years from a variety of fungi, including Chaetomium elatum [2], Chaetomium globosum [3], Phomopsis sp. [4], Botryosphaeria dothidea [5], and Chaetomium subaffine [6], mainly from the fungus Chaetomium globosum.

Increasing evidence has indicated that chaetoglobosins possess a broad range of biological activities, including antitumor [2], antifungal [3], phytotoxic [7], fibrinolytic [7], antibacterial [8], nematicidal [9], anti-inflammatory [10], and anti-HIV activities [11] (Table 1). Therefore, they have broad application prospects and attract researchers to further study. For better understanding and development of chaetoglobosins, we will review the biological activities and mechanisms of action of nature-derived chaetoglobosins.

2. Antitumor Activity

Cancer is the second leading cause of death throughout the world and is responsible for an estimated 9.6 million deaths in 2018. Studies have shown that lots of chaetoglobosines have potent antitumor activity in many types of tumor cell lines, such as HL60, A549, SMMC7721, and MCF-7 cell lines. There are three noteworthy characteristics of antitumor activity of chaetoglobosins: (1) chaetoglobosines had broad-spectrum antitumor activity. Compound 1 inhibited L929, KB3.1, PC-3, and HUVEC cell lines with the IC50 values of 1.6, 0.15, 0.42, and 0.78 μg/mL, respectively [9]. Ruan et al. also demonstrated that compound 36 showed potent cytotoxicity to HL60, A549, SMMC7721, MCF-7, and SW480 cell lines with the range of inhibition ratio at 51–96% for a concentration of 40 μmol/L [12]. In addition, compound 47 significantly inhibited growth of MDA-MB-435, SGC-7901, and A549 cell lines with IC50 values of 4.65, 5.32, and 8.73 μmol/L, respectively [54]. (2) Different chaetoglobosines had similar inhibitory activity on the same tumor cell lines. Compounds 4 and 7 had showed significant growth
Figure 1: Continued.
Figure 1: Chemical structures of chaetoglobosins.
### Table 1: Summary of bioactive chaetoglobosins.

| Number | Compounds | Activities | References |
|--------|-----------|------------|------------|
| 1      | Chaetoglobosin A | Antitumor | [1, 9, 12–17] |
|        |           | Antifungus | [1, 3, 18–20] |
|        |           | Antibacterial | [8, 19, 21] |
|        |           | Phytotoxicity | [12, 22] |
|        |           | Nematicidal | [9, 23, 24] |
|        |           | Fibrinolytic activity | [7] |
| 2      | 19-O-Acetylchaetoglobosin A | Antitumor | [9] |
| 3      | 20-Dihydrochaetoglobosin A | Nematicidal | [9] |
| 4      | Chaetoglobosin B | Antitumor | [2, 14, 15, 18] |
|        |           | Antibacterial | [12] |
| 5      | 19-O-Acetylchaetoglobosin B | — | [25] |
|        |           | Antitumor | [1, 2, 17, 26] |
|        |           | Antifungal | [1, 19] |
|        |           | Antibacterial | [27] |
|        |           | Phytotoxicity | [12, 22] |
|        |           | Antitumor | [2, 14, 15] |
| 6      | Chaetoglobosin C | Antitumor | [15, 18, 19] |
|        |           | Antifungal | [16] |
| 7      | Chaetoglobosin D | — | [25] |
| 8      | 19-O-Acetylchaetoglobosin D | Antitumor | [1, 14, 16, 17, 26, 28] |
| 9      | Chaetoglobosin E | Antifungal | [1, 18] |
|        |           | Phytotoxicity | [12] |
| 10     | Chaetoglobosin F | Phytotoxicity | [1, 12] |
|        |           | Immunosuppressive property | [29] |
| 11     | Chaetoglobosin Fa | Antitumor | [12] |
|        |           | Phytotoxicity | [12] |
|        |           | Antitumor | [12, 17, 26] |
| 12     | Chaetoglobosin F (ex) | Phytotoxicity | [12] |
|        |           | Antiinflammatory property | [30] |
| 13     | Chaetoglobosin G | Antifungal | [1, 31] |
|        |           | Antibacterial | [31] |
| 14     | Chaetoglobosin J | Antitumor | [15, 32] |
|        |           | Antifungal | [18, 33–39] |
| 15     | Chaetoglobosin K | Antitumor | [40, 41] |
| 16     | Chaetoglobosin M | Antitumor | [4, 41] |
| 17     | Chaetoglobosin N | — | [4] |
| 18     | Chaetoglobosin O | Antitumor | [14, 42] |
| 19     | Chaetoglobosin P | — | [43] |
| 20     | Chaetoglobosin Q | Antitumor | [15] |
| 21     | Chaetoglobosin R | Antifungal | [18, 20] |
| 22     | Chaetoglobosin S | — | [31] |
|        |           | Antitumor | [15] |
| 23     | Chaetoglobosin T | Antifungal | [20] |
|        |           | Antibacterial | [20, 27] |
| 24     | Chaetoglobosin U | Antitumor | [16] |
|        |           | Antifungal | [2, 12, 14, 17, 32, 44] |
| 25     | Chaetoglobosins V | Antifungal | [31] |
|        |           | Antibacterial | [27, 31] |
|        |           | Phytotoxicity | [12] |
| 26     | Chaetoglobosin V (b) | Antitumor | [12] |
|        |           | Antifungal | [31] |
| 27     | Chaetoglobosin W | Antitumor | [17] |
| 28     | Chaetoglobosin X | Antifungal | [45] |
| Number | Compounds                     | Activities                  | References |
|--------|------------------------------|-----------------------------|------------|
| 29     | Chaetoglobosin Y             | Antitumor                   | [28]       |
| 30     | Chaetoglobosin Z             | Antitumor                   | [14]       |
| 31     | Chaetoglobosin-510           | Antitumor                   | [46]       |
| 32     | Chaetoglobosin-540           | Antitumor                   | [46]       |
| 33     | Chaetoglobosin-542           | Antitumor                   | [46]       |
| 34     | Isochaetoglobosin D          | Antitumor                   | [2, 28]    |
| 35     | Isochaetoglobosin J          | —                            | [47]       |
| 36     | Yamchaetoglobosin A          | Antitumor                   | [10]       |
|        |                              | Anticoagulant activity      | [10]       |
| 37     | Penochalasin A               | Antitumor                   | [16, 48]   |
| 38     | Penochalasin B               | Antitumor                   | [48]       |
| 39     | Penochalasin C               | Antitumor                   | [26, 48]   |
| 40     | Penochalasin D               | Antitumor                   | [42]       |
| 41     | Penochalasin E               | Antitumor                   | [42]       |
| 42     | Penochalasin F               | Antitumor                   | [42]       |
| 43     | Penochalasin G               | Antitumor                   | [42]       |
| 44     | Penochalasin H               | Antitumor                   | [42]       |
| 45     | Penochalasin I               | Antifungal                  | [1]        |
|        |                              | Antibacterial               | [27]       |
| 46     | Penochalasin J               | Antitumor                   | [1]        |
|        |                              | Antifungal                  | [1]        |
| 47     | Penochalasin K               | Antitumor                   | [49]       |
|        |                              | Antifungal                  | [49]       |
| 48     | Prochaetoglobosin I          | Antibacterial               | [27]       |
| 49     | Isoprochaetoglobosin I       | Antitumor                   | [6, 15]    |
| 50     | Prochaetoglobosin II         | Antitumor                   | [2]        |
| 51     | Prochaetoglobosin III        | Antiamebic                  | [24]       |
| 52     | Prochaetoglobosin IIIed      | Antitumor                   | [2]        |
| 53     | Prochaetoglobosin IV         | —                           | [47]       |
| 54     | Trimethylated chaetoglobosin | —                           | [4]        |
| 55     | Armochaetoglasins A          | Antitumor                   | [50]       |
|        |                              | Antibacterial               | [27]       |
| 56     | Armochaetoglasin B           | Antitumor                   | [32, 51]   |
|        |                              | Antibacterial               | [27]       |
| 57     | Armochaetoglasin C           | Antitumor                   | [51]       |
|        |                              | Antibacterial               | [27]       |
| 58     | Armochaetoglasin D           | Antitumor                   | [51]       |
| 59     | Armochaetoglasin E           | Antitumor                   | [51]       |
| 60     | Armochaetoglasin F           | —                           | [51]       |
| 61     | Armochaetoglasin G           | Antitumor                   | [51]       |
| 62     | Armochaetoglasin H           | Antitumor                   | [51]       |
| 63     | Armochaetoglasin I           | Antifungal                  | [1]        |
| 64     | Armochaetoglasin J           | Antitumor                   | [51]       |
| 65     | Armochaetoglasin K           | Anti-HIV I                  | [11]       |
| 66     | Armochaetoglasin L           | Anti-HIV I                  | [11]       |
| 67     | Armochaetoglasin M           | Anti-HIV I                  | [11]       |
| 68     | Armochaetoglasin N           | Anti-HIV I                  | [11]       |
| 69     | Armochaetoglasin O           | Anti-HIV I                  | [11]       |
| 70     | Armochaetoglasin P           | Anti-HIV I                  | [11]       |
| 71     | Armochaetoglasin Q           | Anti-HIV I                  | [11]       |
| 72     | Armochaetoglasin R           | Anti-HIV I                  | [11]       |
| 73     | Armochaetoglasin S           | Antitumor                   | [50]       |
| 74     | 7-O-Acetylarmochaetoglobin S | Antitumor                   | [50]       |
| 75     | Armochaetoglasin T           | Antitumor                   | [50]       |
| 76     | Armochaetoglasin U           | Antitumor                   | [50]       |
| 77     | Armochaetoglasin V           | Antitumor                   | [50]       |
inhibitory activity against BC1 cell lines with \( IC_{50} \) values of 3.03 \( \mu \text{mol/L} \) and 7.2 \( \mu \text{mol/L} \), respectively, but both had no effect on cholangiocarcinoma cell lines (KKU-100 and KKH-OCA17) [2]. In study by Li et al., it also indicated that compounds 1, 10, 12, 13, 25, and 26 exhibited antitumor activity against HCT116 cell line with \( IC_{50} \) values of 3.15, 17.8, 4.43, 65.6, 29.5, and 18.4 \( \mu \text{mol/L} \), respectively. Furthermore, the structure-activity analysis showed that the cytotoxicity was closely related with the epoxide ring at C-6-C-7 or a double bond at C-6 [12]. (3) Some of chaetoglobosins had differential actions on distinct subtype cell lines of the same tumor. The study by Thohinung et al. showed that compound 13 inhibited the growth of cholangiocarcinoma KKH-100 cell (\( IC_{50} = 29.85 \mu \text{mol/L} \)), but had no inhibitory activity against the cholangiocarcinoma KKH-OCA17 cell line [2]. However, there are obvious disadvantages that are lack of animal experiments and the thorough study about structure-activity relationship. Therefore, further studies are needed to confirm the structure-activity relationship in order to better structural modification of lead compounds and obtain more effective drugs.

Currently, except for compound 15, antitumor mechanisms of action of other chaetoglobosins were not reported. Studies have indicated that various mechanisms are involved in the antitumor activities of compound 15 (Figure 2). Ali and colleagues found that compound 15 supressed Ras-induced malignant phenotype due to its dual inhibitory effect on both Akt and JNK signaling pathways. Furthermore, Akt’s two activation sites, T308 and S473, are known to be affected by treatment [54, 55]. Further study demonstrated that pretreatment with compound 15 decreased the phosphorylation at mTORC2 S2481, which phosphorylates Akt S473, comparable to Torin1, a known mTOR specific inhibitor. Therefore, it might be an mTOR inhibitor [33]. Moreover, administration of compound 15 to astroglial cell line can prevent and reverse the inhibition of lindane and dieldrin to gap junction-mediated communication, by stabilizing and reappearing the connexin 43 P2 phosphoform and activating the Akt/GSK-3β pathway [35–37]. Thus, we can infer that the mTOR/Akt/GSK-3β

| Number | Compounds          | Activities                  | References |
|--------|--------------------|-----------------------------|------------|
| 78     | Armochaetoglasin W | Antitumor                   | [50]       |
| 79     | Armochaetoglasin X | Antitumor                   | [50]       |
| 80     | Armochaetoglasin Y | Antitumor                   | [50]       |
| 81     | Armochaetoglasin Z | Antitumor                   | [50]       |
| 82     | Aureochaeglobosin A| Antitumor                   | [52]       |
| 83     | Aureochaeglobosin B| Antitumor                   | [52]       |
| 84     | Aureochaeglobosin C| Antitumor                   | [52]       |
| 85     | Oxichaetoglobosin A| Immunomodulatory activity   | [53]       |
| 86     | Oxichaetoglobosin B| Immunomodulatory activity   | [53]       |
| 87     | Oxichaetoglobosin C| Immunomodulatory activity   | [53]       |
| 88     | Oxichaetoglobosin D| Immunomodulatory activity   | [53]       |
| 89     | Oxichaetoglobosin E| Immunomodulatory activity   | [53]       |
| 90     | Oxichaetoglobosin F| Immunomodulatory activity   | [53]       |
| 91     | Oxichaetoglobosin G| Immunomodulatory activity   | [53]       |
| 92     | Oxichaetoglobosin H| Immunomodulatory activity   | [53]       |
| 93     | Oxichaetoglobosin I| Immunomodulatory activity   | [53]       |

**Table 1: Continued.**

**Figure 2: Antitumor mechanisms of action of compound 15.**
signaling pathway may play an important role in the anti-tumor action of compound 15. Besides, Li et al. demonstrated that compound 15 showed a more potent cytotoxic to cisplatin-resistant ovarian cancer OVCAR-3 and A2780/CP70 cell lines than normal ovarian IOSE-364 cell line, by enhancing the p53-dependent caspase-8 activation extrinsic apoptosis pathway and inducing G2 cell cycle arrest via cyclin B1 by increasing p53 expression and p38 phosphorylation. However, it is needed to note that compound 15 did not have effects on phospho-JNK and total JNK in inhibition of growth of OVCAR-3 and A2780/CP70 cells, which was different from mechanism of action in Ras-transformed epithelial and human carcinoma cells through inhibition of the JNK signaling pathway [34, 55]. We inferred that its antitumor mechanisms of action might be tumor type-dependent, which need to get the experiment certification further. In addition, compound 15 can effectively inhibit angiogenesis through downregulation of VEGF-binding HIF-1 [38].

3. Antifungal Activity

Fungi are the principal causal agents of plant diseases. Several studies had revealed that chaetoglobosins exhibited significantly inhibitory activity against plant pathogenic fungi. For example, compound 1 displayed significant growth inhibitory activity against the fungi Colletotrichum gloeosporioides [1], Fusarium sporotrichioides [3], Rhizopus stolonifer, Coniothyrium diploidiella [18], Setosphaeria turcica [56], Botrytis cinerea, Sclerotinia sclerotiorum [57], and Mucor miehei [13]. In a study by Zhang et al., it reported that compounds 6, 7, 9, 13, and 21 inhibited Rhizopus stolonifera and Coniothyrium diploidiella [18]. Compounds 13, 25, and 26 have also been reported to inhibit Alternaria solani [31]. In addition, Huang et al. found that compounds 6, 9, 10, 45, 46, and 63 displayed significant growth inhibitory activity against the fungi Colletotrichum musae, Penicillium italicum Wehme, Rhizoctonia solani, and Colletotrichum gloeosporioides. In comparison with other chaetoglobosins, compound 9 exhibited the highest antifungal activities. Based on the structure characteristics, we infer that C5-C6 double bond and C7-OH appear to greatly increase the antifungal potency [1]. Therefore, chaetoglobosins have a potential application value to control plant diseases.

4. Phytotoxic Activity

Chaetoglobosin exhibited significant inhibitory activity against many plant pathogenic fungi, indicating they might have a potential application value in agriculture. However, there are some literatures reported several chaetoglobosins showed phytotoxic activities. The study by Li et al. found that compounds 1, 9, 10, 12, 25 and 26 isolated from metabolites of Stenocarpella maydis showed remarkably the growth inhibition of radish (Raphanus sativus) seedlings with inhibitory rates of >60% at a concentration of 50 ppm. The configurations of C-17 and C-21 in compounds 25 and 26 are closely related with phytotoxicity potency [12]. In addition, compounds 1, 6 and 18 had also been reported inhibited the hypocotyl and root of Alfalfa seedings [27]. Therefore, the potential applications of chaetoglobosins in agriculture require comprehensive evaluation.

5. Antibacterial Effect

With antibacterial resistance becoming more and more serious, the search for new antibacterial agents is also urgent. Studies revealed that chaetoglobosins exhibited significant antibacterial activity against agricultural germs. Zhu et al. demonstrated that compound 17 is isolated from the solid culture of the mangrove endophytic fungus Penicillium chrysogenum V11, possessed significantly antibacterial against Colletotrichum gloeosporioides with the IC₅₀ value of 6.13 μmol/L [49]. Except for inhibition against agricultural germs, it also showed the effective on clinical pathogenic bacteria. Hu and his colleague found that compound 57 showed antibacterial activity against Klebsiella pneumoniae (MIC = 4.0 μg/mL) and ESBL-producing Escherichia coli ATCC 35218 (MIC = 16.0 μg/mL), wherein the inhibitory against Klebsiella pneumoniae was stronger than that of the clinically used antibiotic meropenem (MIC = 8 μg/mL), [27]. Thus, these studies further indicated that they may have a great potential application value in agriculture and clinical aspects.

6. Immunomodulatory Property

Dendritic cells (DCs), the most potent antigen-presenting cells, possess both immune sentinels and initiators of T-cell response. It is the major target in the modulation of excessive immune responses. Hua et al. confirmed that compound 10 inhibited the CpG-induced DCs maturation and function and suppressed TLR9 expression of CpG-induced DCs through many signaling pathways. In addition, It also inhibited CpG-induced activation of MAPKs (p38 and JNK, but not ERK) and the nuclear translocation of NF-κB and STAT1 (Figure 3) [29]. Therefore, compound 10 may have a great potential application in controlling DCs-associated autoimmune and/or inflammatory diseases.

7. Other Activities

In addition to the effects described above, studies showed that chaetoglobosins have some other activities, including fibrinolytic, anticoagulant, nematicidal, anti-HIV, and anti-inflammatory activities. Compound 1 was reported to inhibit J2 penetration and induce the production of urokinase in endothelial cells, associating with the elevation of fibrinolytic activity [7, 29]. Compound 36 showed anti-acetylcholinesterase activity and weak anticoagulant activity with PT at 16.8 s [10]. Mori et al. also found compounds 1 and 51 showed antiamebic activities in the cysteine-deprived medium, in comparable to in the cysteine-containing medium [24]. In addition, compounds 66, 67, 68, 71, and 72 showed significant anti-HIV activities, with EC₅₀ values ranging from 0.11 to 0.55 μmol/L and selectivity index values ranging from 12.33 to 75.42 [11]. Compound 12 could inhibit NF-κB and negatively regulated ERK1/2, p38, and
JNK1/2 phosphorylations to exert anti-inflammatory property [30]. Therefore, chaetoglobosins have a great application prospect.

8. Conclusion

Microbial metabolites are important sources of discovery for drug lead compounds. The researchers extracted around 100 chaetoglobosins from the fungi's secondary metabolites and found that they possessed a broad range of biological activities, such as antitumor, antifungal, phytotoxic, and anti-HIV activities. Therefore, they attract researchers to further study about antitumor and antimicrobial activities for better clinical application. However, it is needed to note that they have a dual role in agriculture, which is not only against plant-pathogenic fungi but also phytotoxic activities. Thus, the potential applications of chaetoglobosins in agriculture require comprehensive evaluation.

However, there are still some shortcomings in existing researches. Firstly, the research on chaetoglobosins remained in vitro, lack of in vivo animal experiments. Secondly, only a few chaetoglobosins have been elucidated about action mechanisms, but action mechanisms of most chaetoglobosins remained unclear. Thirdly, there was little research on the structure-activity relationship.

In conclusion, it is necessary to further evaluate their bioactivities in vitro experiments, their action mechanisms, and structure-activity relationship, thereby better and more comprehensive development and utilization of chaetoglobosins.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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