Triterpenoids From *Alisma* Species: Phytochemistry, Structure Modification, and Bioactivities

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Plants from *Alisma* species belong to the genus of *Alisma* Linn. in *Alismataceae* family. The tubers of *A. orientale* (Sam.) Juzep, also known as *Ze Xie* in Chinese and *Takusha* in Japanese, have been used in traditional medicine for a long history. Triterpenoids are the main secondary metabolites isolated from *Alisma* species, and reported with various bioactive properties, including anticancer, lipid-regulating, anti-inflammatory, antibacterial, antiviral and diuretic activities. In this brief review, we aimed to summarize the phytochemical and pharmacological characteristics of triterpenoids found in *Alisma*, and discuss their structure modification to enhance cytotoxicity as well.

**Keywords**: triterpenoids, *Alisma*, structure, anticancer, lipid-regulation

**INTRODUCTION**

Plants from the genus of *Alisma* Linn. (*Alismataceae*) are widely distributed in temperate regions and subtropics of the northern hemisphere, belonging to 11 species. Six species were found in China and Asia, including *A. canaliculatum*, *A. gramineum*, *A. nanum*, *A. orientale*, *A. plantago-aquatica* and *A. lanceolatum* (*Flora of China Committee, 1992*). The tubers of *A. orientale*, known as *Ze Xie* in Chinese or *Takusha* in Japanese, have been used as diuretic and detumescent medications for a long history (*Chinese Pharmacopoeia Commission, 2015*). It is also used to treat obesity, diabetes and hyperlipidemia nowadays.

Phytochemical studies have revealed that triterpenoids are dominant components in tubers of *Alisma* plants. A total of 118 triterpenoids have been isolated and identified from *Alisma* species so far. Most of them contain protostane tetracyclic aglycones, whereas glycosides are rarely found in other plants. These triterpenoids have been considered as chemotaxonomic markers of the genus (*Zhao et al., 2007*). A small amount of other kinds of compounds have also been isolated from *A. orientale*, including diterpenoids, sesquiterpenoids, polysaccharides, phytosterols, amino acids, flavonoids and fatty acids (*Zhang et al., 2017*). The presence of triterpenoids attributes to the bioactivities of *A. orientale* (*Tian et al., 2014; Shu et al., 2016*), such as alisol A 24-acetate (2), and alisol B 23-acetate (47) (*Choi et al., 2019*).

Alisols have shown a series of biological activities, such as anticancer (*Law et al., 2010*), lipid-regulating (*Cang et al., 2017*), anti-inflammatory (*Kim et al., 2016*), antibacterial (*Jin et al., 2012*), antiviral (*Jiang et al., 2006*), and diuretic activities (*Zhang et al., 2017*). Since alisol B 23-acetate (47) exhibits a significant anti-tumor activity, structure-based modification on alisol B 23-acetate (47) gives a profound change of activity.

This paper aims to systematically review triterpenoids from *Alisma* species, involving their phytochemical characteristics, biosynthesis, bioactivities and structure modification.
TRITERPENOIDS

Starting from 1968, triterpenoids have been isolated from *Alisma* genus successively (Murata et al., 1968). All these compounds contain protostane tetracyclic skeleton with the structural characteristics of trans-fusions for A/B, B/C and C/D rings, α-methyl submitted at C-8, β-methyl at C-10, β-methyl at C-14 and side chain at C-17. At present there are 101 protostane triterpenoids, 12 nor-protostanes, and 5 seco-protostanes reported from *Alisma*. According to the changes of side chains submitted at C-17, protostane triterpenoids from *Alisma* are divided into four classes, including open aliphatic chains, epoxy aliphatic chains, spiro hydrocarbon at C-17, and epoxy at C-16, C-23 or C-16, C-24. The individual triterpenoids were detailed in Table 1.

Protostanes With Open Aliphatic Chains at C-17

Forty-five protostanes with open aliphatic chains at C-17 (1–45) have been identified as shown in Figure 1. Alisol A (1) is a representative compound of this type. Hydroxyl groups may substitute at C-29 (11) (Wang et al., 2017b), disubstitute at C-23/C-24 (19) and C-23/C-25 (43–45) (Nakajima et al., 1994; Peng et al., 2002b), or trisubstitute at C-23, C-24, and C-25 (41, 42). The hydroxyl group at C-23 or C-24 is easily acetylated. Moreover, double bond may form at C-25 and C-26 (38, 39) (Han et al., 2013), or C-25 may be substituted by carboxyl group (31) (Zhao et al., 2013).

Carbonyl groups substitute at C-16 (8, 9) (Zhao et al., 2015), disubstitute at C-7/C-16 (41) (Mai et al., 2015) or C-16/C-23 (21) (Yoshikawa et al., 1999), or substitute at C-24 (37) (Xu et al., 2012) or C-23 (23) (Yi et al., 2019). Hydroxymethyl groups substitute at C-16 (18) (Li et al., 2017) or disubstitute at C-16/C-25 (19).

Protostanes With Epoxy Aliphatic Chains at C-17

Thirty-six protostanes with epoxy aliphatic chains at C-17 (46–81) have been found in the genus of *Alisma* and their structures are listed in Figure 2. Alisol B 23-acetate (47) is a representative compound of this type. Epoxy group usually forms at C-24 and C-25 (46–73, 77–79, 81) (Fukuyama et al., 1988), and C-23 may be submitted by hydroxyl (66) or acetoxy group (67–71).

Except for epoxy ring, tetrahydrofuran ring from C-20 to C-24 (74, 75) and seven-membered peroxic ring from C-20 to C-25 (76) are also existed in the side chains at C-17.

Protostanes With Spiro Hydrocarbon at C-17

Eight protostanes with spiro hydrocarbon at C-17 (82–89) have been isolated from the genus of *Alisma* as shown in Figure 3. Oxaspiro-nonane moiety is generated between D ring and its side chain with C-17 as spiro hydrocarbon. Methyl group substituted at C-20 with α- (82) (Xin et al., 2016) or β- (85) (Jin et al., 2019) conformation. Alisol U (83) differs from alisol V (84) by forming an epoxy at C-24 and C-25.

PROSTANES WITH FUSED RING AT C-16 AND C-17

Twelve protostanes with fused-ring at C-16 and C-17 (90–101) have been isolated from *Alisma* as shown in Figure 4. Tetrahydropyranne ring is fused at C-16 and C-17 (90–98) (Yoshikawa et al., 1993; Peng and Lou, 2001; Hu et al., 2008a, b, Chen et al., 2018). Oxacycloheptane ring is fused at C-16 and C-17 (99–101). Alismanol J (101) differs from alismanketone B-23-acetate (99) by forming an oxygen bridge between C-16 and C-23.

Nor- and seco-protostanes

Twelve nor-protostanes (102–113) have been found in *Alisma*, including two dimethyl-protostanes (102, 103) and ten tetranorprotostanes (104–113). Among C-2 may be submitted by carbanyl group (109) (Mai et al., 2015). The configuration of C-17 is determined (107, 108) (Xin et al., 2018).

Only five seco-protostanes (114–118) have been known in *Alisma*, including two 13, 17-seco-protostanes (114, 115) (Matsuda et al., 1999; Wang et al., 2017a) and three 2, 3-seco-protostanes (116–118) (Yoshikawa et al., 1997). Their structures were detailed in Figure 5.

BIOSYNTHESIS

*Alisma* triterpenoids is commonly biosynthesized through mevalonic acid (MVA) pathway (Zhang et al., 2018) as shown in Figure 6. Three molecules of acetyl-CoA are catalyzed by enzymes to form mevalonate acid (MVA) (Vinokur et al., 2014). It is catalyzed by mevalonate pyrophosphate decarboxylase to produce isopentyl pyrophosphate (IPP), which reacts with dimethyllallyl pyrophosphate (DMAPP) to generate geranyl pyrophosphate (GPP) by farnesyl pyrophosphate synthase of A. orientale (AOFPS) (Peng et al., 2018). Squalene is synthesized by squalene synthase of A. orientale (AOSS) (Shen et al., 2013), which is then catalyzed by squalene epoxidase of A. orientale (AOSE) to produce 2,3-oxidosqualene and further to form protostane tetracyclic skeleton (Zhang et al., 2018). AOFPS and AOSS are rate-limiting enzymes in *Alisma* triterpenoids biosynthesis pathway (Zhou et al., 2018).

Fresh materials of *A. orientalis* are naturally rich in alisol B 23-acetate (47) (Zhu and Peng, 2006), which can convert into alisol A 24-acetate (2), alisol A (1), and alisol B (46) after processing at high temperature (Zheng et al., 2006). Other triterpenoids, such as alisol A (1) (Peng et al., 2002a) and their derivatives, were formed during the drying process (Yoshikawa et al., 1994).

BIOACTIVITIES

*A. orientale* is traditionally used to treat oliguria, edema, gonorrhea with turbid urine, leukorrhea, diarrhea, dizziness and hyperlipidemia (Chinese Pharmacopoeia Commission, 2015). Modern pharmacological studies have demonstrated its diuretic and lipid-lowering efficiency, together with anticancer, lipid-regulating, anti-inflammatory, antibacterial, antiviral activities.
### TABLE 1 | A total of 118 triterpenoids isolated and identified from Alisma genus.

| No. | Name | Skeleton structure | R₁ | R₂ | R₃ | R₄ | R₅ | R₆ | Double bond position | Source | References |
|-----|------|--------------------|-----|-----|-----|-----|-----|-----|----------------------|--------|------------|
| 1   | alisol A | A | βOH | H | βOH | βOH | OH | H | Δ₁³(17) | A. orientalis | Peng et al., 2002a |
| 2   | alisol A 24-acetate | A | βOH | H | βOH | βOAc | OH | H | Δ₁³(17) | A. orientalis | Peng et al., 2002a |
| 3   | alisol A 23-acetate | A | βOH | H | βOAc | βOH | OH | H | Δ₁³(17) | A. orientalis | Peng et al., 2002a |
| 4   | 11-deoxyalisol A | A | H | H | βOH | βOH | OH | H | Δ₁³(17) | A. orientalis | Peng et al., 2002b |
| 5   | 23-o-methyl alisol A | A | βOH | H | βOMe | βOH | OH | H | Δ₁³(17) | A. orientale | Nakajima et al., 1994 |
| 6   | 25-o-methoxy-alisol A | A | βOH | H | βOH | βOMe | H | Δ₁³(17) | A. orientale | Nakajima et al., 1994 |
| 7   | 16-oxo-alisol A | A | βOH | O | βOH | βOH | OH | H | Δ₁³(17) | A. orientale | Mai et al., 2015 |
| 8   | 16-oxo-alisol A 23-acetate | A | βOH | O | βOAc | βOH | OH | H | Δ₁³(17) | A. orientale | Mai et al., 2015 |
| 9   | 16-oxo-alisol A 24-acetate | A | βOH | O | βOAc | βOH | OH | H | Δ₁³(17) | A. orientale | Zhao et al., 2015 |
| 10  | 16-oxo-11-deoxy- alisol A | A | H | O | βOH | βOH | OH | H | Δ₁³(17) | A. orientale | Mai et al., 2015 |
| 11  | 5β,29-dihydroxy alisol A | A (5βOH) | βOH | H | βOH | βOH | OH | H | Δ₁³(17) | A. plantago-aquatica | Wang et al., 2017b |
| 12  | 25-o-butyl alisol A | A | βOH | H | βOH | βOH | OMe | H | Δ₁³(17) | A. orientalis | Zhang et al., 2017 |
| 13  | alisol E | A | βOH | H | βOH | βOH | OH | H | Δ₁³(17) | A. orientale | Yoshikawa et al., 1993 |
| 14  | alisol E 23-acetate | A | βOH | H | βOAc | αOH | OH | H | Δ₁³(17) | A. orientale | Yoshikawa et al., 1993 |
| 15  | alisol E 24-acetate | A | βOH | H | βOAc | αOH | OH | H | Δ₁³(17) | A. orientale | Yoshikawa et al., 1993 |
| 16  | 25-o-ethylalisol A | A | βOH | H | βOH | βOH | OH | OEt | H | Δ₁³(17) | A. orientale | Mai et al., 2015 |
| 17  | alisol H | A | H | O | O | H | OH | H | Δ₁³(17) | A. orientale | Yoshikawa et al., 1999 |
| 18  | 16β-methoxyalisol E | A | βOH | βOMe | βOH | αOH | OMe | H | Δ₁³(17) | A. orientale | Li et al., 2017 |
| 19  | 16β,25-dimethoxyalisol E | A | βOH | βOMe | βOH | αOH | OMe | H | Δ₁³(17) | A. orientale | Li et al., 2017 |
| 20  | 16β-hydroperoxyalisol E | A | βOH | βOOH | βOH | αOH | OH | H | Δ₁³(17) | A. orientale | Li et al., 2017 |
| 21  | 11,24-dihydroxy-alisol H | A | βOH | O | O | βOH | OH | H | Δ₁³(17) | A. orientale | Yoshikawa et al., 1999 |
| 22  | alisol T | A | βOH | βOMe | H | OH | H | OH | H | Δ₁³(17) | A. orientale | Li et al., 2017 |
| 23  | alismanin I | A | βOH | H | O | OH | H | H | Δ₁³(17) | A. orientale | Yi et al., 2019 |
| 24  | 15,16-dihydroalisol A. | A | βOH | H | βOH | βOH | OH | H | Δ₁³(17), Δ₁³(16) | A. orientale | Mai et al., 2015 |
| 25  | alismanol D | A | H | H | H | αOH | OH | H | Δ₁³(17), Δ₁³(15) | A. orientale | Mai et al., 2015 |
| 26  | 24-epi-alismanol D | A | H | H | H | βOH | OH | H | Δ₁³(17), Δ₁³(15) | A. oriental | Xin et al., 2018 |
| 27  | alismanol A | A | H | O | O | αOH | OH | H | Δ₁³(17), Δ₁³(15) | A. orientale | Mai et al., 2015 |
| 28  | alismanol C | A | H | O | βOAc | αOH | OH | H | Δ₁³(17), Δ₁³(15) | A. orientale | Mai et al., 2015 |
| 29  | 16-oxo-11-anhydro alisol A | A | H | O | βOH | βOH | OH | H | Δ₁³(17), Δ₁³(15) | A. oriental | Mai et al., 2015 |
| 30  | 16-oxo-11-anhydroalisol A | A | H | O | βOH | βOAc | OH | H | Δ₁³(17), Δ₁³(15) | A. oriental | Mai et al., 2015 |
| 31  | 3-oxo-11R,23-dihydroxy-24,24- dimethyl–26,27-dinorprotost-13(17)-en-25-oic-acid | A | βOH | O | H | βOH | COOH | H | Δ₁³(17) | A. orientale | Zhao et al., 2013 |
| 32  | alismanin B | A | βOH | O | H | βOH | H | H | Δ₁³(17) | A. orientale | Wang et al., 2017a |
| 33  | 25-anhydroalisol A | B | βOH | H | βOH | βOH | | | | A. orientalis | Peng et al., 2002a |
| 34  | 11-acetate-25-anhydroalisol A | B | βOAc | H | βOH | βOH | | | | A. orientalis | Peng et al., 2002a |
| 35  | 24-acetate-25-anhydroalisol A | B | βOH | H | βOH | βOAc | | | | A. orientalis | Peng et al., 2002a |
| 36  | 11-deoxy-25-anhydro-alisol E | B | H | H | βOH | αOH | | | | A. orientalis | Mai et al., 2015 |
| 37  | alisol X | B | βOH | H | H | O | | | | A. oriental | Xu et al., 2012 |
| 38  | 23-acetate-25-anhydroalisol E | B | H | H | βOAc | αOH | | | | A. oriental | Han et al., 2013 |
| 39  | 24-acetate-25-anhydroalisol E | B | H | H | βOH | αOH | | | | A. oriental | Han et al., 2013 |
| 40  | alismanol B | B | H | O | βOH | αOH | | | | A. oriental | Mai et al., 2015 |
| 41  | 7-oxo-16-oxo-11-anhydro alisol A | C | | | | | | | | A. oriental | Mai et al., 2015 |
| 42  | alismanol M | D | | | | | | | | A. oriental | Xin et al., 2016 |
| 43  | 13,17-epo-alisol A | E | μOH | αOH | | | | | | A. oriental | Peng et al., 2002b |
| 44  | 13,17-epoalisol A 24-acetate | E | μOH | αOAc | | | | | | A. oriental | Peng et al., 2002b |
| 45  | 11-deoxy-13,17-epoxy-alisol A | E | H | μOH | | | | | | A. oriental | Nakajima et al., 1994 |

(Continued)
| No. | Name                      | Skeleton structure | R₁   | R₂   | R₃  | R₄   | R₅   | R₆   | Double bond position | Source | References                  |
|-----|--------------------------|--------------------|------|------|-----|------|------|------|----------------------|--------|---------------------------|

**PROTOSTANES WITH EPOXY ALIPHATIC CHAINS AT C-17**

46  | alisol B                  | F                  | βO   | H    | H   | H    | aMe  | βOH  | Δ₁³(₁⁷)                | A. orientale | Nakajma et al., 1994    |
47  | alisol B 23-acetate       | F                  | βO   | H    | H   | H    | aMe  | βOAc | Δ₁³(₁⁷)               | A. orientale | Nakajma et al., 1994    |
48  | 11-deoxy-alisol B 23-acetate | F           | H     | H    | H    | H    | βMe  | βOAc | Δ₁³(₁⁷)             | A. orientale | Nakajma et al., 1994    |
49  | 11-deoxy-alisol B         | F                  | H     | H    | H    | H    | βMe  | βOH  | Δ₁³(₁⁷)             | A. orientale | Nakajma et al., 1994    |
50  | 16β-acetoxy alisol B      | F                  | βO   | H    | βOAc | H    | aMe  | βOH  | Δ₁³(₁⁷)             | A. oriental  | Cang et al., 2017       |
51  | 16α-acetoxy alisol B      | F                  | βO   | H    | aOAc | H    | aMe  | βOH  | Δ₁³(₁⁷)             | A. oriental  | Cang et al., 2017       |
52  | 16β-hydroxyalisol B 23-acetate | F              | βO   | H    | βOH  | H    | aMe  | βOAc | Δ₁³(₁⁷)             | A. oriental  | Peng and Lou, 2001      |
53  | 16β-methoxyalisol B 23-acetate | F            | βO   | H    | βOAc | H    | aMe  | βOAc | Δ₁³(₁⁷)             | A. oriental  | Jin et al., 2012        |
54  | 16β-ethoxy alisol B 23-acetate | F           | βO   | H    | βOEt | H    | aMe  | βOAc | Δ₁³(₁⁷)             | A. oriental  | Zhang et al., 2017      |
55  | alisol C                  | F                  | βO   | H    | O    | H    | aMe  | βOH  | Δ₁³(₁⁷)             | A. oriental | Nakajma et al., 1994    |
56  | 11-deoxy-alisol C 23-acetate | F              | H     | H    | O    | H    | aMe  | βOAc | Δ₁³(₁⁷)             | A. oriental | Nakajma et al., 1994    |
57  | 11-deoxy-alisol C         | F                  | H     | H    | O    | H    | aMe  | βOH  | Δ₁³(₁⁷)             | A. plantago-aquatica | Fukuyama et al., 1988 |
58  | 20-hydroxylalisol C       | F                  | βO   | H    | O    | OH   | aMe  | βOH  | Δ₁³(₁⁷)             | A. oriental | Mai et al., 2015        |
59  | alisol C 23-acetate       | F                  | βO   | H    | O    | OH   | aMe  | βOAc | Δ₁³(₁⁷)             | A. plantago-aquatica | Fukuyama et al., 1988 |
60  | alisol M 23-acetate       | F                  | βO   | βO   | H    | O    | aMe  | βOAc | Δ₁³(₁⁷)             | A. oriental | Li et al., 2017         |
61  | alisol N 23-acetate       | F                  | βO   | βO   | H    | H    | aMe  | βOAc | Δ₁³(₁⁷)             | A. oriental | Li et al., 2017         |
62  | 16β-hydroperoxyalisol B   | F                  | βO   | H    | βOH  | H    | aMe  | βOH  | Δ₁³(₁⁷)             | A. oriental | Li et al., 2017         |
63  | 16β-hydroperoxyalisol B 23-acetate | F          | βO   | H    | βOHN | H    | aMe  | βOH  | Δ₁³(₁⁷)             | A. oriental | Li et al., 2017         |
64  | alisol L                  | F                  | H     | H    | H    | O    | aMe  | βOH  | Δ₁¹₁(₂³),Δ₁³(₁⁷)    | A. oriental | Zhao et al., 2015       |
65  | alisol L 23-acetate       | F                  | H     | H    | O    | H    | aMe  | βOAc | Δ₁¹₁(₂³),Δ₁³(₁⁷)    | A. oriental | Yoshikawa et al., 1999  |
66  | 13β,17β-epoxy-alisol B    | G                  | βO   | βOH  |      |      |      |      |                    | A. oriental | Nakajma et al., 1994    |
67  | 13β,17β-epoxy-23-acetate-alisol B | G           | βO   | βOAc |      |      |      |      |                    | A. oriental | Jin et al., 2012        |
68  | 11-deoxy-13β,17β-epoxy-23-acetate-alisol B | G       | H     | βOAc |      |      |      |      |                    | A. oriental | Nakajma et al., 1994    |
69  | alisol D                  | G                  | βO   | H    | aOAc |      |      |      |                    | A. plantago-aquatica | Fukuyama et al., 1988 |
70  | alisol D 11-acetate       | G                  | βOAc | aOAc |      |      |      |      |                    | A. plantago-aquatica | Fukuyama et al., 1988 |
71  | 11-deoxyalisol D          | G                  | H    | aOAc |      |      |      |      |                    | A. oriental | Yoshikawa et al., 1999  |
72  | alisol J–23 acetate       | H                  |      |      |      |      |      |      |                    | A. oriental | Yoshikawa et al., 1999  |
73  | alisol K 23-acetate       | I                  |      |      |      |      |      |      |                    | A. oriental | Yoshikawa et al., 1999  |
74  | alismanol O               | J                  | H     |      |      |      |      |      |                    | A. oriental | Xin et al., 2016        |
75  | alismanol P               | J                  | αOH  |      |      |      |      |      |                    | A. oriental | Xin et al., 2016        |
76  | alisolide H               | K                  |      |      |      |      |      |      |                    | A. plantago-aquatica | Jin et al., 2019        |
77  | alisolide G               | L                  | O    | aOAc |      |      |      |      |                    | A. plantago-aquatica | Jin et al., 2019        |
78  | alisol Q 23-acetate       | L                  | E    | βOAc |      |      |      |      |                    | A. oriental | Jin et al., 2019        |
79  | alisol S 23-acetate       | L                  | βOH  | βOAc |      |      |      |      |                    | A. oriental | Jin et al., 2019        |
80  | alisolide I               | M                  |      |      |      |      |      |      |                    | A. plantago-aquatica | Jin et al., 2019        |
81  | alismaketone A-23-acetate | N                  |      |      |      |      |      |      |                    | A. oriental | Yoshikawa et al., 1997  |

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82  | alismanol Q               | O                  |      |      |      |      |      |      |                    | A. oriental | Xin et al., 2016        |
83  | alisol U                  | P                  |      |      |      |      |      |      |                    | A. oriental | Li et al., 2017         |
84  | alisol V                  | Q                  |      |      |      |      |      |      |                    | A. oriental | Li et al., 2017         |
85  | alisolide D               | R                  |      |      |      |      |      |      |                    | A. plantago-aquatica | Jin et al., 2019        |
**Anticancer Activities**

Recently, the experiments *in vitro* highlight that alisolides induce apoptosis and autophagy in human tumor cells, such as lung cancer (Wang et al., 2018), ovarian cancer (Zhang et al., 2016), and prostate cancer (Huang et al., 2006) cell lines. The cytotoxicities of alisol B 23-acetate (47), alisol A 23-acetate (59) and alisol A 24-acetate (2) are examined on several cells, B16-F10 melanoma cells, A549 lung adenocarcinoma cells, SK-OV3 ovarian cells, HT 1080 fibrosarcoma cells. The results show that alisol B 23-acetate (47), alisol C 23-acetate (59) and alisol A 24-acetate (2) have weaker inhibitory activities against all the tested cancer cells with ED50 values in the range of 10~20 µg/mL, while alisol B (46) exhibits significant effect on SK-OV3, B16-F10, and HT1080 with ED50 values of 7.5, 7.5, and 4.9 µg/mL, respectively (Lee et al., 2001).
Moreover, alisol F 24-acetate (93) and alisol B 23-acetate (47) are found inducing cell apoptosis via inhibiting P-glycoprotein mediation and reversing the multidrug resistance in cancer cell lines (Wang et al., 2004; Hyuga et al., 2012; Pan et al., 2016).

Alisol B (46) targets on Ca$^{2+}$-ATP enzymes in the sarcoplasmic reticulum or endoplasmic reticulum to induce autophagy of cancer cells (Law et al., 2010). This compound can also induce cell apoptosis by inhibiting the invasion and metastasis of SGC7901 cells (Xu et al., 2009). Alisol B 23-acetate (47) can inhibit the proliferation of PC-3 prostate cancer (Huang et al., 2006), and induce the apoptosis of lung cancer A549 and NCI-H292 cells through the mitochondrial caspase pathway (Wang et al., 2018). Alisol B 23-acetate (47)
obviously inhibits the proliferation, migration and invasion of ovarian cancer cell lines and induces accumulation of the G1 phase in a concentration-dependent manner. The protein levels of cleaved poly ADP-ribose polymerase (PARP) and the ratio of Bax/Bcl-2 are up-regulated, while the levels of CDK4, CDK6 and cyclin D1 are down-regulated after alisol B 23-acetate (47) treatment. Moreover, it can up-regulate the expression levels of IRE1α and Bip, and down regulate MMP-2 and MMP-9 in a dose- and time- dependent manner (Zhang et al., 2016). However, current studies of Alisma triterpenoids are limited into drug screening in vitro, and their anticancer activities need to be validated in vivo.

Lipid-Lowering Effects
One of A. orientale traditional effects is to treat hyperlipidemia. Studies have shown that the extracts of A. orientale tubers have potential effects on hyperlipidemia diseases (Park et al., 2014; Jang et al., 2015; Li et al., 2016; Miao et al., 2017). Alisol B 23-acetate (47) and alisol A 24-acetate (2) reduce the levels of TC and LDL-C in hyperlipidemia mice via inhibiting the activity of HMG-CoA reductase (Murata et al., 1970; Xu et al., 2016). According to the evaluations of alisols on inhibiting pancreatic lipase, the IC50 of alisol F 24-acetate (93) on pancreatic lipase was 45.5 µM (Cang et al., 2017). Studies results show that alisol B 23-acetate (47) can bound plasma protein (Xu et al., 2014). Alisol A (1), alisol A 24-acetate (2) and alisol B (46) can decrease TG level in plasma by improving lipoprotein lipase (LPL) activity (Xu et al., 2018). The effects of alisols with epoxy aliphatic chain at C-17 on LPL are stronger than those with an open aliphatic chain at C-17. Hydroxyl groups submitted at C-14, C-22, C-28, C-30, and an acetyl group at C-29 are necessary for lipid-regulation action of alisols.

Anti-inflammatory
Alisol B 23-acetate (47) prevents the production of NO in RAW264.7 cells by inhibiting iNOS mRNA expression.
FIGURE 5 | Chemical structures of the nor- and seco-protostanes.

(Kim et al., 1999). Alisol A 24-acetate (2) effectively alleviates liver steatosis by down-regulating SREBP-1c, ACC, FAS genes and up-regulating CPT1 and ACOX1 genes to activate AMPK signaling pathway and inhibit inflammatory cytokines TNF-α, IL-6 levels (Zeng et al., 2016). In addition, alisol B (46) and alisol B 23-acetate (47) significantly inhibit the production of leukotriene and the release of β-hexosaminidase in the concentrations of 1–10 mM (Lee et al., 2012).

Antibacterial
Alisol B (46), alisol B 23-acetate (47), alisol C 23-acetate (59), and alisol A 24-acetate (2) have significant bacteriostatic actions on four gram positive and four gram negative antibiotic resistant strains with the MICs ranged from 5 to 10 μg/ml (Jin et al., 2012). In addition, alisol A (1), 25-o-ethylalisol A (16), 11-deoxyalisol A (4), alisol E 24-acetate (15) and 25-anhydroalisol F (97) fight off gram-positive strains of bacillus subtilis and staphylococcus aureus with MICs ranged from 12.5 to 100 mg/ml (Ma et al., 2016).

Antiviral
Studies have shown that alisols from A. orientale exhibit obvious anti-hepatitis b virus effect (Jiang et al., 2006). Alisol F (92) and alisol F 24-acetate (93) significantly inhibit the secretion of HBV surface antigen with an IC50 value of 7.7 and 0.6 μM, and HBVe antigen secretion with an IC50 value of 5.1 and 8.5 μM, respectively. A series of derivatives of alisol A (1) obtained after structural modification also showed potential effect (Zhang et al., 2008, 2009).

STRUCTURE MODIFICATION
Alisol B 23-acetate can induce apoptosis and autophagy in cancer cell lines (Xu et al., 2015), and structure modification on alisol B 23-acetate (47) allows to obtain a diverse of derivatives (Lee et al., 2002). Alisol B 23-acetate (47) reacts with m-chloroper oxybenzoic acid (mCPBA) in CH2Cl2 at room temperature to gain 13β, 17β-epoxy-23-acetate-alisol B (67), and reacts with NH2OH.HCl in pyridine and MeOH to achieve amination at C-3. Deacetylation of alisol B 23-acetate (47) by NaOH yields alisol B (46). Although there is no significant difference of inhibition effect on B16-F10 and HT1080 cell lines between 13β, 17β-epoxy-23-acetate-alisol B (67) (ED50 values of 17 and 18 μg/ml) and alisol B 23-acetate (47) (ED50 values of 20 μg/ml, respectively), alisol B (46) (B16-F10 and HT1080 with ED50 values of 5.2 and 3.1 μg/ml), amination at C-3 of alisol B 23-acetate (47) (with ED50 values of 7.5 and 5.1 μg/ml) show exhibited greater activation against B16-F10 and HT1080 cancer cells. It indicates that deacetylation of C-23 and amination at
FIGURE 6 | Biosynthesis pathway of Alisma triterpenoids.
C-3 significantly enhance the inhibition effect on B16-F10 and HT1080 cell lines.

Four hydroxyl groups of alisol A (1) are usually the target sites for modification by reacting with acetic anhydride in N, N'-dicyclohexylcarbodiimide and 4-dimethylaminopyridine. Alisol A (1) can also dehydrate by SOCl₂ in the presence of anhydrous pyridine. The assessments of anti-hepatitis B virus (HBV) activities suggest alisol A (1) analogs with acetoxyl groups at C-11, C-23, C-24 or the epoxy ring at C-13 and C-17 increase the effects on HBV. Dehydration at C-25/C-26 enhances its sensitivity on HBV (Zhang et al., 2008, 2009).

Biotransformation of alisol A (1) also derives a series of active compound by several bacteria strains, such as C. elegans AS 3.2028 and P. janthinellum AS 3.510. Alisol A (1) can inhibit the proliferation of HCE-2 cells on the IC₅₀ of 99.65 ± 2.81 µM (Zhang et al., 2017). The activity screening results reveal hydroxylation at C-7 and C-12 increases the inhibiting effects of alisol A (1) on human carboxylesterase 2 (IC₅₀ values of 7.39 ± 1.21 and 3.73 ± 0.76 µM) and the acetyl group at C-23 or C-24 also increases its inhibition effect on HCE-2 cells (IC₅₀ values of 3.78 ± 0.21 and 6.11 ± 0.46 µM).

Taken together, epoxidation at C-13 and C-17, hydroxylation at C-23, C-7/C-12, amination at C-3, and dehydration at C-25/C-26 contribute to the activities of protostane tetracyclic skeleton of A. orientale, including anticancer activity, anti-hepatitis B virus, and the inhibiting activity on human carboxylesterase 2.

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CONCLUSION

The present work systematically summarized the information concerning the phytochemistry, bioactivities and structure modification of triterpenoids in Alisma species. To date, more than 100 protostane-type tetraterpenoids have been isolated and identified. Alisols are reported with anticancer, lipid-regulating, anti-inflammatory, antibacterial, and antiviral activities. Structure modification might contribute to the investigation of the therapeutic potential of alisols.

AUTHOR CONTRIBUTIONS

MJ designed the review and was responsible for the study conception. PW and MJ wrote the paper. PW, TS, and RS contributed to summarizing the phytochemistry and structure modification studies on triterpenoids. MH, RW, and JL contributed to summarizing the bioactivity studies on triterpenoids.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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