Review article

Botany, uses, phytochemistry and pharmacology of Vallaris: A short review

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1. Introduction

In the World Checklist of Selected Plant Families developed by the Royal Botanic Gardens at Kew, England, a total of 28 botanical names of Vallaris species have been listed under the family Apocynaceae of which only Vallaris glabra, Vallaris solanacea and Vallaris indecora are accepted names.1 In this short review, the current knowledge of the botany, uses, phytochemistry and pharmacology of V. glabra and V. solanacea is reviewed. No information is available in the literature on the chemical constituents and bioactivities of V. indecora. V. glabra (L.) Kuntze or bread flower is a woody climber with broadly elliptic leaves. Flowers are cup-like and white with a unique fragrance of leaves of pandan or newly cooked fragrant rice. The species is a popular ornamental plant in gardens of Southeast Asia. No uses of V. glabra in traditional medicine have been reported. From the leaves of V. glabra, cardiac glycosides, phenolic acids, fatty acids and triterpenes have been isolated. Essential oils extracted from flowers have been identified. The antiproliferative, antiplasmodial and antioxidant properties of V. glabra are reviewed. V. solanacea (Roth) Kuntze is a twining shrub up to 10 m tall. Leaves are elliptic and densely pubescent on both surfaces. Flowers are white or creamy, fragrant and borne in clusters. The species occurs naturally in forests of South and Southeast Asia. Traditionally, the milky latex of V. solanacea can be applied to treat ringworm and other skin infections, including sores, cuts and wounds. From leaves and seeds of V. solanacea, cardiac glycosides, fatty acids and triterpenes have been isolated. From the root bark, essential oils have been identified. Leaves and barks of V. solanacea have been reported to possess anticancer, antimicrobial, analgesic, anti-inflammatory, anti-diarrhoeal and cardiotonic properties, and display toxicity to brine shrimp but not to rats. V. indecora (Bail.) Tsiang & P.T. Li is a trailing shrub with elliptic or obovate leaves and pale yellow flowers. Occurring in China, the plant is used to treat worm diseases.
2. Phytochemistry

2.1. Cardiac glycosides

Bioassay-guided separation of \( V. \) \( glabra \) leaves has led to the isolation of two cardiac glycosides. One was identified as acoschimperoside P, 2'-acetate, a known compound first reported in seeds of \( V. \) \( solanacea \) and the other was new.

From seeds of \( V. \) \( solanacea \), glycosides of vallaroside, solanoside, vallarosolanoside, 16-deacetyl-16-anhydro-acoschimperoside P, mono-O-acetyl-acoschimperoside P, mono-O-acetyl-vallaroside and mono-O-acetyl-solanoside have been reported. O-Acetyl-solanoside was isolated from leaves of \( V. \) \( solanacea \). Subsequent chemical investigations reported \( \beta \)-sitosterol, \( \beta \)-amyrin, ursolic acid, vallaroside, solanoside, vallarosolanoside and acoschimperoside P from leaves. A new cardenolide glycoside of vallaroside and a known cardenolide glycoside of \( \beta \)-O-(\( \alpha \)-acofriosyl)-16-anhydrogitoxigenin, along with a new glycoside of benzyl 2-O-\( \beta \)-apiofuranosyl-(1 \( \rightarrow \) 2)-\( \beta \)-d-glucopyranosyl-2,6-dihydroxy-benzoate have also been isolated. Their molecular formulae were \( C_{22}H_{46}O_8 \), \( C_{30}H_{40}O_6 \) and \( C_{23}H_{36}O_{13} \) with molecular weights of 5973, 5710 and 5612, respectively. The known cardenolide glycoside was previously reported as 16-desacetyl-16-anhydro-acoschimperosid P.

2.2. Caffeoylquinic acids

From the MeOH leaf extract of \( V. \) \( glabra \), 3-O-caffeoylquinic acid (3-CQA) or neochlorogenic acid, 4-O-caffeoylquinic acid (4-CQA) or cryptochlorogenic acid, and 5-O-caffeoylquinic acid (5-CQA) or chlorogenic acid (CGA) were isolated. Caffeoylquinic acids are esters of caffeic and quinic acids. 3-CQA, 4-CQA and 5-CQA or CGA have the caffeoyl group attached to carbons 3, 4 and 5 of the quinic moiety, respectively. They have a similar molecular formula of \( C_{18}H_{18}O_9 \) and molecular weight of 354. The isolation of CQAs from leaves of \( V. \) \( glabra \) was the first for the genus \( Vallaris \). Earlier studies have documented the occurrence of CQAs in other Apocynaceae species. 3-CQA and 5-CQA have been isolated from stems and leaves of Catharanthus roseus, and 4-CQA from petals.

The content of 5-CQA or CGA in leaves of \( V. \) \( glabra \) (353 \( \pm \) 25 mg CGA/100 g) was two times higher than flowers of \( Lonicerajaponica \) or Japanese honeysuckle (173 \( \pm \) 13 mg CGA/100 g), the commercial source of CGA. The 3-CQA and 4-CQA content in leaves of \( V. \) \( glabra \) (370 \( \pm \) 15 mg CGA/100 g) was 16 times higher than flowers of \( L. \) \( japonica \) (23 \( \pm \) 2.2 mg CGA/100 g). Compared with other plants, the CGA content in leaves of \( V. \) \( glabra \) is significantly higher than leaves of \( Ettinergaelatior \) (torch ginger) and \( Ipomoeabatatas \) (sweet potato) with values of 294 \( \pm \) 25 and 115 \( \pm \) 16 mg CGA/100 g, respectively.

2.3. Other compounds

From the DCM leaf extract of \( V. \) \( glabra \), stearic acid (SA) and ursolic acid (UA) have been isolated. SA or octadecanoic acid, with molecular formula of \( C_{18}H_{36}O_2 \) and molecular weight of 284.5 is a saturated fatty acid with an 18-carbon chain. Ursolic acid is a pentacyclic triterpene acid with molecular formula of \( C_{30}H_{48}O_3 \) and molecular weight of 456.7.

SA isolated from leaves of \( V. \) \( glabra \) has been reported in other Apocynaceae species such as leaves and flowers of \( C. \) \( roseus \), and leaves of \( Alstoniaboonei \). In Apocynaceae, UA has been isolated from \( Alstoniascholaris \) and \( Plumeriarubra \). Widely found in plants, UA is a compound that possesses many biological activities such as antioxidative, anti-inflammatory, anticancer and hepatoprotective, as well as the ability to induce apoptosis.

A phytochemical study on flowers of \( V. \) \( glabra \) revealed the presence of monoterpenes, sesquiterpenes and acyclic monoterpane alcohols. Linalool (62%) was found to be the principal constituent. Of particular interest is the occurrence of 2-acetyl-1-pyrroline (2AP). The aromatic compound was first reported in cooked rice and in leaves of pandan. Using capillary GC, the content of 2AP in cooked rice and in leaves of pandan. Using capillary GC, the content of 2AP in

3. Pharmacology

3.1. Anticancer properties

Isolated from leaves of \( V. \) \( glabra \), acoschimperoside P, 2'-acetate was active in hedgehog (Hh) signalling inhibition. The cardiac
glycoside inhibited Hh/GLI-mediated transcriptional activity with an IC50 value of 2.3 μM. The compound also showed strong cytotoxicity against human pancreatic PANC1 (IC50 of 3.6 μM) and human prostate DU145 cancer cells (IC50 of 1.8 μM). The cytotoxic effect was associated with the ability of the compound to inhibit the Hh/GLI1 signalling pathway. The compound was found to inhibit the levels of GLI-related proteins of patched (PTCH) and B-cell lymphoma 2 (BCL-2) in PANC1 cells.

The antiproliferative activity of sequential extracts of different plant parts of V. glabra has been reported. DCM and DCM:MeOH leaf extracts, and DCM flower extract displayed broad-spectrum antiproliferative activity with effective inhibition of HT-29, MCF-7, MDA-MB-231 and SKOV-3 cancer cells (Table 1). Inhibition of stem extracts was more specific to MCF-7 and SKOV-3 cells with no activity against MDA-MB-231 cells. Against MCF-7 cells, the GI50 values of DCM extracts of stems and flowers (both 1.4 ± 0.2 μg/ml) were lower than that of the positive controls. DCM and DCM:MeOH extracts of leaves were comparable to tamoxifen. Hexane extracts of stems and flowers were more potent than tamoxifen and xanthorrhizol. Overall, the screening results showed that extracts from three different parts of V. glabra possessed effective antiproliferative activity. Other Apocynaceae species that displayed positive antiproliferative activity were Alstonia angustiloba, Calotropis gigantea, C. roseus, Nerium oleander and Plumeria obtusa.

MDA-MB-231 cancer cells treated with DCM leaf extract of V. glabra and stained with Hoechst 33342 dye showed that the extract had an apoptotic effect on the cells. Cells treated with DCM leaf extract at 12.5, 25.0 and 50.0 μg/ml displayed apoptotic morphology (Fig. 3).

MDA-MB-231 cancer cells were treated with concentrations varying from 1.6 to 25 μg/ml of DCM leaf extract of V. glabra. A histogram of fold-increase in caspase activity vs. concentration of DCM leaf extract is shown in Fig. 4. Based on caspase colorimetry, the apoptotic effect involved activation of caspase-8, -9 and -3, but not caspase-6. This indicates that the extract induced apoptosis through both the extrinsic (death-receptor) and intrinsic (mitochondrial) pathways. Caspase-8 and -9 are initiator caspases, while caspase-3 and -6 are effector caspases.

Of the isolates from leaves of V. solanacea, vallarisoside showed potent TRAIL-resistance-overcoming activity in human gastric adenocarcinoma (AGS) cells and cell growth-inhibitory activity against HeLa and SW480 cells.

### Table 1

Antiproliferative activity of sequential extracts of Vallaris glabra against four human cancer cell lines. \(^{22,23}\)

<table>
<thead>
<tr>
<th>Plant part</th>
<th>Sequential extract</th>
<th>Growth inhibition (GI50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaf</td>
<td></td>
<td>MCF-7</td>
</tr>
<tr>
<td></td>
<td>DCM</td>
<td>7.7 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>DCM:MeOH</td>
<td>7.0 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>MeOH</td>
<td>16 ± 2.1</td>
</tr>
<tr>
<td>Stem</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hexane</td>
<td>7.0 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>DCM</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>DCM:MeOH</td>
<td>3.9 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>MeOH</td>
<td>5.4 ± 1.6</td>
</tr>
<tr>
<td>Flower</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hexane</td>
<td>3.3 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>DCM</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>DCM:MeOH</td>
<td>4.6 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>MeOH</td>
<td>-</td>
</tr>
<tr>
<td>Xanthorrhizol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curcumin</td>
<td></td>
<td>11 ± 0.7</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
<td>4.1 ± 0.9</td>
</tr>
</tbody>
</table>

**GI50** (μg/ml) is the concentration which causes 50% reduction in cell growth and inhibition is not effective (-) if values >20 μg/ml. MCF-7 and MDA-MB-231 are human breast cancer cells, HeLa and SKOV-3 are human cervical cancer cells, HT-29 are human colon cancer cells and HepG2 are human liver cancer cells. Values of standard drugs of xanthorrhizol, curcumin and tamoxifen against MCF-7 and MDA-MB-231 were used as positive controls. Abbreviations: MeOH = methanol and DCM = dichloromethane.

### 3.2. Antimalarial properties

The antiplasmodial activity of leaf extracts of V. glabra has been reported. \(^{11,22}\) All hexane, DCM, DCM:MeOH and MeOH leaf extracts of V. glabra displayed effective antiplasmodial activity against...
chloroquine-resistant K1 strain of Plasmodium falciparum with EC50 values of 1.0, 0.8, 8.5 and 8.4 μg/ml, respectively. No activity was observed against chloroquine-sensitive 3D7 strain of P. falciparum. The selectivity index (SI) for antiplasmodial activity against K1 strain suggested that the extracts of V. glabra are potentially safe for use to treat malaria.

In general, EC50 values of leaf extracts against K1 strain of P. falciparum were much weaker than standard drugs of artemisinin and mefloquine. Other Apocynaceae species reported to have antiplasmodial activity were A. angustiloba, C. gigantea, Dyera costulata and Kopsia fruticosa.

3.3. Antioxidant properties

Out of methanol leaf extracts of six Apocynaceae species screened for antioxidant properties, V. glabra ranked second to D. costulata. Values of total phenolic content, free radical scavenging activity and caffeoylquinic acid content of V. glabra were 1300 ± 120 mg GAE/100 g, 1000 ± 100 mg AA/100 g and 380 ± 50 mg CGAE/100 g of samples (fresh weight).

3.4. Antimicrobial properties

At 40 μg/ml, the stem bark extract of V. solanacea has been demonstrated to inhibit the growth of Gram-positive bacteria of Staphylococcus aureus and Bacillus subtilis, Gram-negative bacteria of Salmonella typhi and Escherichia coli, and fungi of Candida albicans and Aspergillus niger. Petroleum ether, chloroform and ethanol extracts were tested using the agar well diffusion method. All solvent extracts yielded positive results with the petroleum ether extract exhibiting relatively higher zone of inhibition against S. typhi, E. coli, A. niger and C. albicans. Inhibition was comparable to that of standard drugs of ciprofloxacin and fluconazole (40 μg in 100 μl).

3.5. Analgesic properties

Ethanol extracts of leaves and stems of V. solanacea showed significant analgesic activity in acetic acid-induced writhing inhibition in mice. Writhing inhibition at a dose of 500 mg/kg body weight was 54%. At 250 mg/kg body weight, writhing inhibition was 23%. Ethanol bark extract of V. solanacea was also tested for analgesic activity. Writhing inhibition was 52% and 23% at doses of 500 and 250 mg/kg body weight, respectively.

3.6. Anti-inflammatory activity

Using the carrageenan-induced rat-paw oedema model, ethanol bark extract of V. solanacea significantly reduced the paw volume from 1 to 5 h. The extract showed highest effects at the third hour when the inhibition was 29% and 41% at doses of 200 and 400 mg/kg respectively.

3.7. Anti-diarrhoeal activity

The anti-diarrhoeal activity of ethanol bark extract of V. solanacea was demonstrated by castor oil-induced diarrhoea in mice. Results showed that 500 mg/kg body weight of extract significantly delayed the onset of diarrhoea episode to 1.1 h compared to 0.7 h of the control. The number of stools excreted by the animals (per group of 5) after 4 h was 1.3 and 3.6, respectively.

3.8. Cardiotonic activity

O-Acetyl-solanoside, a cardiac glycoside, isolated from leaves of V. solanacea was found to possess marked cardiotonic activity in cats and guinea pigs. Its therapeutic index is comparable to that of ouabain. The compound has a quick onset, medium duration of action, and shows consistent and dependable oral absorption with low cumulative toxicity.

3.9. Toxicity

A toxicity study of essential oil from the root bark of V. solanacea has been carried out on albino rats. Two groups of rats weighing 150–200 g were orally administered with the oil at doses of 3 ml/kg and 5 ml/kg body weight. None of the rats showed any toxicity effects of mortality after 12 h. The ethanol extract of leaves and stems of V. solanacea showed brine shrimp toxicity at LC50 of 80 μg/ml and LC90 of 320 μg/ml.

4. Conclusion

Of the two Vallaris species reviewed, the wide array of pharmacological properties of leaves and barks of V. solanacea confers its use in traditional medicine. Properties include antiproliferative, antimicrobial, analgesic, anti-inflammatory, anti-diarrhoeal and cardiotonic activities. The potent TRAIL-resistance-overcoming activity in AGS cancer cells and cell growth-inhibitory activity against HeLa and SW480 cells of vallarisisolide isolated from leaves of

![Fig. 4. Histogram of fold-increase in caspase-9, -8, -3 and -6 activity vs. concentrations of DCM leaf extract of Vallaris glabra.](image-url)

For each caspase, bars from left to right are extract concentrations at 1.56, 3.13, 6.25, 12.5 and 25.0 μg/ml.
V. solanacea deserve further research. V. glabra is a unique plant because it displayed both strong and broad-spectrum antiproliferative activity against HT-29, MCF-7, MDA-MB-231 and SKOV-3 cancer cells, and antiplasmodial activity against K1 strain of P. falciparum. Acoschimperoside P, 2’-acetate, a cardiac glycoside isolated from leaves of V. glabra inhibited Hh/GLI1 signalling pathway and showed strong cytotoxicity against PANC1 and DU145 cancer cells is noteworthy. The species would be of interest to the pharmaceutical industry as a potential candidate for anticancer and antimalarial drug discovery. With much higher CQA content in the pathway and showed strong cytotoxicity against PANC1 and DU145 isolated from leaves of V. glabra than flowers of L. japonica (the commercial source), the species can serve as a promising alternative source of CQA.

Conflicts of interest

All authors have none to declare.

References


