Plant-Derived Kavalactones and Their Bioactivities

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Kavalactones, mainly found in *Piper methysticum*, are a class of lactone compounds usually with an arylethylene-pyrone skeleton. Till now, fifty-one kavalactones have been isolated from the genera *Piper*, *Alpinia*, *Amomum*, *Polygala*, *Goniolthalamus*, and *Dumortiera*. The bioactivities of six kavalactones, kawain, 7,8-dihydrokawain, methysticin, dihydromethysticin, yangonin, and desmethoxyyangonin, have been studied extensively. This review aims to give an overview of kavalactones in the plants and their various bioactivities.

Keywords kavalactone, *Piper*, *Alpinia*, bioactivities

Introduction

Kavalactones, also called kavapyrones or styrylpyrones, are a class of lactones generally with an arylethylene-pyrone skeleton.^[1] They are mainly found in *Piper methysticum* G. Forst (kava: Piperaceae) and have once drawn researchers' attention due to their various bioactivities, especially for their anti-depress activities. Kava extract, containing large amount of kavalactones, had been commonly used as an anti-depressant until its ban in Europe in 2002, when several cases concerning alleged liver toxicity were reported. After that, culprits for causing hepatotoxicity were investigated.^[2-4] Kavalactones, as the main constituents of kava extract, were also tested for hepatotoxicity.^[5,6] However, there was lack of evidence that supported the alleged dangers related to kavalactones. With German court lifting ban on kava in 2014,^[7] the research on kavalactones might flourish again. Herein, we will summarize the kavalactones from the plants and their bioactivities.

Kavalactones isolated from plants

Kavalactones

Eighteen kavalactones (1–18), which were identified from kava roots, have already been covered in the review by Bilia *et al.*^[8] namely 11-hydroxy-12-methoxydihydrokawain (1), 7,8-dihydrokawain (2), dihydromethysticin (3), 5,6,7, 8-tetrahydroyangonin (4), 11,12-dimethoxy-5,6-dihydrokawain (5), 7,8-dihydro-5-hydroxykawain (6), kawain (7), methysticin (8), 5,6-dihydroyangonin (9), hydroxykawain (10), 5,6-dehydromethysticin (11), 7,8-dihydroyangonin (12), desmethoxyyangonin (13), yangonin (14), 11-methoxyyangonin (15), 10-methoxyyangonin (16), 11-hydroxyyangonin (17), and 11-methoxy-12-hydroxydehydrokawain (18). Among these kavalactones, compounds 2, 3, 7, 8, 13, 14 are the most abundant in the roots of *P. methysticum*.^[9] Compound 13 was also isolated from the genera *Alpinia* and *Amomum*.^[10-12] Chromatographic separation of the methylene chloride extract of *P. methysticum* roots yielded a new kavalactone 11-methoxy-5,6-dihydroyangonin (19).^[13] Dihydro-5,6-dehydrokawain (DDK, 20), a main constituent in the leaves of *Alpinia zerumbet*, was determined using GC-MS by Kuster

et al.^[14] Six kavalactones, 4-methoxy-6-(11,12-methylenedioxy-dihydrostyryl)-2-pyrone (21), 4-methoxy-6-(11,12-methylenedioxy-14-methoxy-dihydrostyryl)-2-pyrone (22), 4-methoxy-6-(11,12-methylenedioxy-10,14-dimethoxydihydrostyryl)-2-pyrone (23), 4-methoxy-6-(11,12-methylenedioxy-14-methoxystyryl)-2-pyrone (24), 4-methoxy-6-(11,12-methylenedioxy-styryl)-2-pyrone (25), and 4-methoxy-6-(11,12-dimethylstyryl)-2-pyrone (26) were isolated from the EtOAc-soluble fraction of the aqueous EtOH (1:4) extract of *Polygala sabulosa* (Polygalaceae).^[15] Matsuda *et al.* isolated 7,8-epoxyyangonin (27) from the extract of the roots of *P. methysticum*.^[16] (+)-Goniolthamin (28) and goniodiol (29), with no substituent on the ring of pyrone, were found in *Cryptocarya moschatam* (Lauraceae)^[17] and the genus *Goniolthalamus*.^[18] (+)-Altholactone (30), (+)-garvensintriol (31), (+)-etharvendiol (32), and (-)-etharvensin (33) were isolated from the stem bark of *Goniolthalamus arvensis*, and (+)-altholactone was identified as a major compound.^[19-21] Alkofahi *et al.* isolated goniotriol (34) from *Goniolthalamus giganteus* and settled its relative configuration by single X-ray diffraction.^[22] Three carboxylated-pyrone derivatives, Dumortins A–C (35–37), were isolated from *Dumortiera hirsuta*.^[23]

Kavalactone dimers

Diyangonins A–C (38, 39, 41), yangonindimers A–C (43–45), and three known analogues [(*rel-trans*-3-bis[6-(4-methoxy-2-pyronyl)]-*cis*-2,trans-4-diphenyl cyclobutane (40) 6,6'-(3,4-diphenylcyclobutane-1,2-diyl)bis(4-methoxy-2H-pyran-2-one) (42), aniba-dimer A (46)], were isolated from roots of *P. methysticum*.^[24,25] Kavalactone dimers (*r*-8,*c*-7',*t*-7-8,8'-11,12-dimethoxyphenyl-7,7'-di-[6-(4-methoxy-2-pyronyl)]-cyclobutane, 47) and (*rel*-(6*R*,7*S*,8*S*,5'*S*)-4'-methoxy-8-(11,12-dimethoxyphenyl)-7-[6-(4-methoxy-2-pyronyl)]-6-(*E*)-styryl-1'-oxabicyclo[4.2.0]octa-4'-en-2'-one, 48) were isolated from the trunk wood of *Aniba* species.^[26]

Hybrids of kavalactone and other types

Three hybrids, katsumadain A (49), katsumadain B (50), and katsumadain (51), which were fused by kavalactone and diarylheptanoid or terpene, have been isolated from the seeds of *Alpinia katsumadai*.^[27-29]

Figure 1 The structures of compounds 1–51.

Bioactivities of kavalactones

Among kavalactones derived from plants, the biological activities of compounds **3**, **7**, **8**, **18**, **19** have been investigated extensively.

Amomum, *Polygala*, *Goniiothalamus*, and *Dumortiera*, were mostly isolated from the roots of the plants. Their various bioactivities were investigated such as neuro-protective, anti-cancer, hepatoprotective, anti-osteoporosis, and anti-aging activity. After kava ban in Europe, attention on their toxicities^[37-40] instead of effective therapeutic activities was paid on kavalactones. However, as the ban being lifted from Germany, concerns about their therapeutic value might come back again. This review provides a basis for the future research in the field of kavalactones.

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