UPDATES ON 4-HYDROXYDERRICIN AND XANTHOANGELOL OF ANGELICA PLANTS: EXTRACTION AND PHARMACOLOGICAL ACTIVITIES

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ABSTRACT

Two chalcones, e.g. 4-hydroxyderricin and xanthoangelol, have been proven in revealing many potential pharmacological activities, therefore their extraction method is critical because it influences the yield and, furthermore, its pharmacological activities. This review highlights the extraction method and various pharmacological activities of 4-hydroxyderricin and xanthoangelol from *Angelica keiskei* plants. The chalcone's diverse pharmacological activities are attributed to the flexible conformation of the opened-C ring and the moderate lipophilicity character on the A aromatic ring. The presence of a double bond in conjugation with carbonyl moiety is also important. However, further explorations need to be performed to obtain a remarkable yield of these particular prenylated-compounds and to understand their mechanisms of actions.

Keywords: *Angelica keiskei*, Chalcones, 4-Hydroxyderricin, Xanthoangelol

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INTRODUCTION

Chalcones (Fig-1a), are 1,3-diphenyl-2-propen-1-one flavonoids that may exist in *cis* and *trans* isomeric forms. In higher plants, chalcones are synthesized from malonyl CoA and cinnamic acid by chalcone synthase.¹ The molecular structure of these compounds consists of two aromatic rings which are linked by α , β -unsaturated ketone groups ($-\text{CO}-\text{CH}=\text{CH}-$), where various substituents are attached and form an almost linear or planar structure.²⁻³ Chalcones, which have been empirically used to treat many diseases, are contained in fruits, vegetables, and various plants.⁴ For example, the root and the stem of *Angelica keiskei* (ashitaba) contains yellow exudate, in which 2 major chalcones (4-hydroxyderricin and xanthoangelol) and flavonoid compound (cynaroside) are produced.⁵⁻⁶

The aim of this review article is to highlight the current updates in the extraction method and the pharmacological researches of 4-hydroxyderricin (4-HD) and xanthoangelol, natural chalcones of *Angelica* plants. The cited literature was selected in the publication period between January 2000 and March 2019.

EXPERIMENTAL

Briefly, a literature search in ScopeMed database using the keywords "4-hydroxyderricin" AND "xanthoangelol" AND "chalcones" AND "angelica" [in Title] resulted in 4 articles; in PubMed database using medical subject headings (MeSH) terms and the keywords "chalcones" [MeSH Terms] OR "chalcones" [All Fields] OR "chalcone" [MeSH Terms] OR "chalcone" [All Fields] AND "4-

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hydroxyderricin" [Supplementary Concept] OR "4-hydroxyderricin" [All Fields] OR "4 hydroxyderricin" [All Fields] AND "xanthoangelol" [Supplementary Concept] OR "xanthoangelol" [All Fields] AND "angelica" [MeSH Terms] OR "angelica" [All Fields] resulted in 28 articles; in Mendeley database using the keywords "4-hydroxyderricin" AND "xanthoangelol" AND "chalcones" AND "angelica" [in Papers] resulted in 63 articles; in GoogleScholar using the keywords "4-hydroxyderricin" AND "xanthoangelol" AND "chalcones" AND "angelica" [ranged between 2000-2019, include patents] resulted in 252 articles. Of those, articles excluded were: (1) published before year 2000; (2) Chalcones were not isolated from Angelica plants; (3) Review articles about chalcones; (4) Study for crops or others; (5) Duplicate articles found in different database; (6) Articles were not using English/Indonesian language; (7) Others.

Fig.-1: (a) Chalcone $C_{15}H_{12}O$ (ChemSpider ID 553346, <http://www.chemspider.com/Chemical-Structure.553346.html> accessed 01:47, Apr 10, 2019); (b) 4-hydroxyderricin $C_{21}H_{22}O_4$ (ChemSpider ID 4942973, <http://www.chemspider.com/Chemical-Structure.4942973.html>, accessed 01:36, Apr 10, 2019); (c) xanthoangelol $C_{25}H_{28}O_4$ (ChemSpider ID: 558181, <http://www.chemspider.com/Chemical-Structure.558181.html> accessed 01:50, Apr 10, 2019)

Extraction Method

Plants may contain secondary metabolites, which are distributed un-uniformly in the tissue, cellular and subcellular levels.⁷ Therefore, an important stage of analytical methods is the extraction step, as it greatly affects the type and quality of the analytical data.⁸ Medicinal plants study is usually initiated with the wet sortation of the specimen, the washing, the drying, and the grinding, prior to the extraction. The extraction itself is a separation method of active portions of the plant by using selective solvents through standard procedures.⁹ In this process, *dissolves like* is always employed in selecting the solvents. Polar solvents in aqueous mixtures containing methanol, ethanol, acetone, and ethyl acetate are often employed in extracting polyphenolic compounds from a plant matrix.¹⁰ All these stages are critical due to their effect on the outcomes (e.g. the yield and the content of phytoconstituents). Maceration, Reflux, and Soxhlet-extraction are commonly used in a laboratory-scale project. Recent extraction technique introduced microwave-assisted extraction (MAE), which is important for extracting valuable compounds from vegetal materials.¹¹⁻¹³ MAE is quite adaptable on both laboratory and industry scale.¹⁴

An invention about the extraction process (drying, pulverizing, hot-dip extracting with ethanol) for Angelica chalcones in stems to obtain a liquid extract, had been registered. The ethanol extract was dissolved in water and extracted with ethyl acetate under reduced pressure. The crude chalcones were subjected into macro-porous adsorption column for separation and purification by column chromatography on silica gel to obtain chalcones (CN102020544B CN Grant, 2010).¹⁵

Different solvents employed to extract the chalcones from different parts of Angelica plants and their resulted-outcomes were provided in Table-1.

Pharmacological Activities

Many pharmacological activities are possessed by chalcones, e.g. (1) Suppresses the differentiation of pre-adipocytes to adipocytes via AMP-activated protein kinase and mitogen-activated protein kinases pathways; (2) Inhibits MAO; (3) Antioxidant and inhibits α -glucosidase; (4) Stimulates GLUT4-

dependent glucose; (5) Induces apoptosis in neuroblastoma and leukemia cells; (6) Antitumor-promotion; (6) PTP1B inhibitor; (7) Inhibits influenza virus neuraminidase; etc. A summary of Angelica chalcones' pharmacological activities is provided in Table-2. Each Angelica chalcone demonstrates multiple pharmacological activities.

Table-1: Extraction Method of Chalcones in Angelica Plants

Angelica plant part	Solvent used for extraction	Chromatography system	Results	References
Dried stem exudate	A mixture of <i>n</i> -hexane-MeOH-H ₂ O (95:95:10, v/v/v)	Chromatographed over an octadecylsilane C18 column (2.5 cm i.d. x 50 cm; eluting solvent MeOH; flow rate 3.0 ml/min)	Xanthoangelol (yield = 2.4686%), xanthoangelol-F (yield = 0.7099%), xanthoangelol-H (yield = 0.0284%), isobavachalcone (yield = 0.1744%), 4-hydroxyderricin (yield = 1.4361%)	5
Dried stem exudate	A mixture of <i>n</i> -hexane-MeOH-H ₂ O (19:19:2, v/v/v)	Chromatographed over an octadecylsilane C18 column, continued with preparative HPLC	Xanthoangelol-I (yield = 0.0135%), xanthoangelol-J (yield = 0.0089%), deoxyxanthoangelol-H (yield = 0.0762%)	16
Dried stem exudate	Not described	Not described	Xanthoangelol (yield = 10.3%), xanthoangelol-F (yield = 2.44%), 4-hydroxyderricin (yield = 9.39%), isobavachalcone (yield = 0.134%), xanthoangelol-H (yield = 0.0049%), xanthoangelol-I (yield = 0.0152%)	17
Chopped stem	MeOH repeated twice, followed by fractionation using of <i>n</i> -hexane and EtOAc	Chromatographed over a silica gel column (1.5 cm i.d. x 85 cm) using 20-80% EtOAc in hexane	Xanthokeismin-A, xanthokeismin-B, xanthokeismin-C	18
Seeds	A mixture of <i>n</i> -hexane-MeOH-H ₂ O.	Chromatographed over an octadecylsilane C18 column using MeOH in H ₂ O gradient mixtures.	Ashitabaol-A (yield = 0.009%, colorless needles)	19
Dried root powder	EtOH 100 % for 30 min under gentle agitation; repeated twice.	Chromatographed over a cosmosil140 C18-OPN.	Xanthoangelol and 4-hydroxyderricin both with purity > 95%	20
Dried root powder	A mixture of <i>n</i> -hexane-MeOH-H ₂ O (19:19:2, v/v/v)	Chromatographed over a silica gel column using stepwise gradient elution with <i>n</i> -hexane-EtOAc (9:1→0:1; EtOAc-MeOH 1:0→1:4)	Xanthoangelol (yield = 0.0411%), 4-hydroxyderricin (yield = 0.0073%),	21
Dried root powder	EtOH at room temperature for 30 min; repeated twice	ODS chromatography successively eluting with 30, 40, 75, 100% EtOH. The 40 % EtOH elute	Xanthoangelol (yield = 0.72%)	22

		was subjected to silica gel chromatography and eluted with a gradient of CHCl ₃ -MeOH (50:1→5:1, v/v)		
Dried aerial parts	A mixture of MeOH-H ₂ O (7:3, v/v; 25 l) at 80°C for 4 h; repeated three times	Chromatographed over a silica gel column (Silica gel 60, 70-230 mesh) using stepwise gradient elution with hexane-dichloromethane (1:3), dichloromethane-MeOH (30:1), dichloromethane-MeOH (3:1)	Xanthoangelol (yield = 0.031%; 99% purity; yellow needles), 4-hydroxyderricin (yield = 0.004%; 98% purity; yellow powder)	23

Table-2: Pharmacological Activities of Angelica's Chalcones

Chalcone Compound	Angelica Plant Part	Biological Activities	References
Xanthoangelol	Herbs	(1) Suppresses melanoma-genesis by targeting BRAF and PI3K	24
		(2) Suppresses the differentiation of pre-adipocytes to adipocytes	25
		(3) Inhibits MAO	23
		(4) Antioxidant and inhibits α -glucosidase	26
	Stem exudate	(1) Antiplatelet activity <i>in vivo</i> in mouse	27
		(2) Stimulates GLUT4-dependent glucose	28
		(3) Attenuates protein and mRNA levels of inflammatory enzymes (iNOS and COX-2)	29
		(4) Reduces the serum LDL levels, total cholesterol and triglyceride contents in the liver rats	30
		(5) Induces apoptosis in neuroblastoma and leukemia cells	31
	Root	(1) Antitumor and antimetastatic activity	32
		(2) Inhibits platelet aggregation on rabbits which induced by collagen, platelet-activating factor, and phorbol 12-myristate 13-acetate	33
		(3) Induces adiponectin production in 3T3-L1 adipocytes	22
		(4) Antitumor and antimetastatic	34
	Stem	PTP1B inhibitor	35
Xanthoangelol-B	Root	Inhibits influenza virus neuraminidase	36
Xanthoangelol-D	Root	Could suppressed Nuclear Factor- κ B	37
	Stem	PTP1B inhibitor	35
Xanthoangelol-E, xanthoangelol-K, xanthoangelol-M	Stem	PTP1B inhibitor	35
Xanthoangelol-F	Root	Induces apoptotic cell death in human leukemia cells (HL60)	21
	Stem	(1) Cancer chemopreventive effects	5
		(2) PTP1B inhibitor	35
Xanthoangelol-G	Root	Inhibits influenza virus neuraminidase	36
Xanthoangelol-H/Jejuchalcone D	Root	Induces apoptotic cell death in human leukemia cells (HL60)	21
Xanthoangelol-I	Root	Induces apoptotic cell death in human leukemia cells	21

		(HL60)	
	Stem exudate	Cancer chemopreventive effects	16
Xanthoangelol-J	Stem exudate	Cancer chemopreventive effects	16
2''-Deoxy-xanthoangelol-H	Root	Induces apoptotic cell death in human leukemia cells (HL60)	21
4-Hydroxyderricin	Herbs	(1) Suppress melanoma-genesis by targeting BRAF and PI3K	24
		(2) Attenuates protein and mRNA levels of inflammatory enzymes (iNOS and COX-2)	29
		(3) Suppresses the differentiation of pre-adipocytes to adipocytes	25
		(4) Inhibits MAO	23
		(5) Antioxidant and inhibits α -glucosidase	26
	Stem exudate	(1) Stimulates GLUT4-dependent glucose	28
		(2) Suppresses nuclear translocation of NF- κ B.	29
	Root	(1) Antitumor and antimetastatic	32
		(2) Inhibits platelet aggregation on rabbits which induced by collagen, platelet-activating factor, and phorbol 12-myristate 13-acetate	33
		(3) Induces adiponectin production in 3T3-L1 adipocytes	22
		(4) Induces apoptotic cell death in human leukemia cells (HL60)	21
Isobavachalcone	Root	Induces apoptotic cell death in human leukemia cells (HL60)	21
	Herbs	Antioxidant and inhibits α -glucosidase	26
Water extract of <i>Angelica gigas</i> Nakai	Stem	Cancer chemopreventive effects	5
	Root	Promotes adipogenic differentiation	38

These diverse activities might be attributed to the flexible conformation of the backbone of the chalcone³⁸⁻³⁹; moreover, the long hydrocarbon bridge which attached to ring A of moderate hydrophobicity, contributes an important role for the pharmacological activity.⁴² The presence of a double bond in conjugation with carbonyl moiety of chalcones is also believed to be responsible for the pharmacological activities, as removal of this functionality makes them inactive.²⁴

CONCLUSION

In this review, the extraction method of *Angelica* chalcones and their pharmacological activities have been summarized. Xanthoangelol and 4-HD, two major chalcones, are found abundantly in the stem exudate of *Angelica* plants. The varieties of solvents and chromatographic system for separating the chalcones from different parts of the plant at least answered the reason for their different yields. These chalcones have been proven exerting various pharmacological activities due to their specific conformation structures. However, these pharmacological activities might also be influenced by the selected extraction method. Further considerable works need to be performed to obtain a remarkable yield of the chalcones and to perceive the working mechanisms of chalcones-prenylated substances.

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