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Review

Medicinal uses, phytochemistry and pharmacology of the genus *Uncaria*

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ABSTRACT

Ethnopharmacological relevance: The genus *Uncaria* belongs to the family Rubiaceae, which mainly distributed in tropical regions, such as Southeast Asia, Africa and Southeast America. Their leaves and hooks have long been thought to have healing powers and are already being tested as a treatment for asthma, cancer, cirrhosis, diabetes, hypertension, stroke and rheumatism. The present review aims to provide systematically reorganized information on the ethnopharmacology, phytochemistry and pharmacology of the genus *Uncaria* to support for further therapeutic potential of this genus. To better understanding this genus, information on the stereo-chemistry and structure-activity relationships in indole alkaloids is also represented.

Material and methods: The literature study of this review is based on various databases search (SCIFinder, Science Direct, CNKI, Wiley online library, Spring Link, Web of Science, PubMed, Wanfang Data, Medalink, Google scholar, ACS, Tropicos, Council of Heads of Australasian Herbaria, The New York Botanical Garden, African Plants Database at Genera Botanical Garden, The Plant List and SEINet) and library search for Biological Abstract and some local books on ethnopharmacology.

Results: 19 species of the genus *Uncaria* are found to be important folk medicines in China, Malaysia, Phillippines, Africa and Southeast America, *etc*, and have been served for the treatment of asthma, rheumatism, hyperpyrexia, hypertension and headaches, *etc*. More than 200 compounds have been isolated from *Uncaria*, including indole alkaloids, triterpenes, flavonoids, phenols, phenylpropanoids, *etc*. As characteristic constituents, indole alkaloids have been considered as main efficacy component for hypertension, epilepsy, depressant, Parkinson's disease and Alzheimer's disease. In addition, pharmacokinetic and metabolism investigation reveal that the indole alkaloids are likely to be absorbed, metabolized and excreted at early time points. Moreover, the specific inhibition of CYP isozymes can regulate their hydroxylation metabolites at C-10 and C-11.

Conclusion: Preliminary investigations on pharmacological properties of the *Uncaria* species have enlightened their efficacious remedy for hypertension, asthma, cancer, diabetes, rheumatism and neurodegenerative diseases. To ensure the safety and effectiveness in clinical application, research on bioactive compounds, pharmacological mechanisms and toxicity of the genus *Uncaria* as well as the stereo-chemistry and structure-activity relationships of indole alkaloids seem very important.

Abbreviations: U1, *Uncaria acida* (Hunter) Roxb; *U2*, *Uncaria africana* G. Don; *U3*, *Uncaria attenuate* Korth; *U4*, *Uncaria barbata* Merr; *U5*, *Uncaria bernaysii* F. Muell; *U6*, *Uncaria borneensis* Havil; *U7*, *Uncaria callophylla* Blume ex Korth; *U8*, *Uncaria canescens* Korth; *U9*, *Uncaria cordata* (Lour.) Merr; *U10*, *Uncaria donisii* E. M. A. Petit; *U11*, *Uncaria elliptica* R. Br. ex G. Don; *U12*, *Uncaria florida* Vidal; *U13*, *Uncaria gambier* (Hunt). Roxb; *U14*, *Uncaria glabrata* DC～*Uncaria lanosa* var. *glabrata* (Blume.) Ridsb; *U15*, *Uncaria guianensis* (Aubl.) J. F. Gmel; *U16*, *Uncaria hirsute* Havil; *U17*, *Uncaria homomalla* Miq; *U18*, *Uncaria kunstleri* King; *U19*, *Uncaria laevigata* Wall. ex G. Don; *U20*, *Uncaria lanosa* Wallich var. *appendiculata* Ridsd; *U21*, *Uncaria longiflora* var. *pteropoda*; *U22*, *Uncaria macrophylla* Wall; *U23*, *Uncaria nervosa* Elmer; *U24*, *Uncaria orientalis* Guillaumin; *U25*, *Uncaria perrottetii* (A. Rich.) Merr; *U26*, *Uncaria rhynchophylla* (Miq.) Jacks; *U27*, *Uncaria roxburghiana* Korth; *U28*, *Uncaria scandens* (Smith) Hutch; *U29*, *Uncaria sessilifructus* Roxb; *U30*, *Uncaria sinensis* (Oliv.) Havil; *U31*, *Uncaria sterrophylla* Merr. & L. M. Perry; U32, Uncaria thwaitesii (Hook. f.) Alston; U33, Uncaria tomentosa (Willd. ex Schult.) DC; U34, Uncaria villosa; U35, Uncaria yunnanensis Hsia. C. C.; Aβ, beta-amyloid; ABTS, 2, 2'-azinobis (3-ethyl-benzthiazoline-6-sulfonic acid); AChE, acetylcholinesterase; AD, Alzheimer's disease; APPH, 2, 2-azo-bis (2-amidinopropane) dihydrochloride; AST, aspartate aminotransferase; Cy, cyclophosphamide; DPPH, 1, 1-diphenyl-2-picrylhydrazyl; DXR, doxorubicin; CD, circular dichroism; CE, Cotton effects; ET-1, endothelin-1; ERK, extracellular regulated protein kinases; γ-GABA, γ-aminobutyric acid; GSK-3β, glycogen synthase kinase-3β; HASMC, human aortic smooth muscle cells; 5-HT, 5-hydroxytroptamine; IFN-γ, interferon-γ; IL, interleukin; iNOS, inducible nitric oxide synthase; KA, kainic acid; LPS, lipopolysaccharide; MAO, monoamine oxidase; MAPKs, mitogen-activated protein kinases; MDA, malondialdehyde; MMP, matrix metalloproteinase; NE, norepinephrine; NF-κB, nuclear factor-κB; NO, nitric oxide; NMR, nuclear magnetic resonance; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; PDGF, platelet-derived growth factor; PLCγ1, phospholipase Cγ1; PRTC, peroxyl radical-trapping capacity; RBC, red blood cell; SOD, superoxide scavening activity; TEAC, trolox equivalent antioxidant capacity; TLR, toll-like receptor; TNF-α, tumor necrosisa factor-α; VSMCs, vascular smooth muscle cells

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Contents

1. Introduction

The genus *Uncaria*, belonging to the family Rubiaceae, contains approximately 34 species, which mainly distributed in tropical regions, such as Southeast Asia, Africa and Southeast America (Ridsdale, 1978). It is documented that about 14 species of *Uncaria* occur in Peninsular Malaysia and about 11 species found in China (Burkill, 1935; Ridsdale, 1978; Flora of China, 1999a). Mostly, the hooks of *Uncaria* species are applied to treat wounds and olcers, fever, asthma, rheumatism, hyperpyrexia, hypertension, headaches, gastrointestinal illness, and bacterial/fungal infections, *etc.* (Ahmed et al., 1978; Burkill, 1935; Heitzman et al., 2005; Keplinger et al., 1999; Phillipson et al., 1978; Tanahashi et al., 1997; Xu and Wu, 1981). The hooks of *Uncaria* are often prepared as a decoction and its leaves, roots and bark are also sometimes used (Phillipson et al., 1978; Risdale, 1978; Bridson and Verdcourt, 1988; Laus and Keplinger, 2003). Usually monotherapy treatments are administered but polyherbal treatments have also been described in some traditional herbal prescriptions. It is well known that Chinese traditional medicinal formulation, Diao-teng-san (Cho-Deung-San in Korean and Choto-san in Japanese), which is composed of 11 herbal ingredients, is effective in the treatment of vascular diseases, such as hypertension (Yang et al., 2002; Shimada et al., 2003), stroke (Shimada et al., 2003; Goto et al., 2001; Watanabe et al., 2003), vascular dementia (Itoh et al., 1999; Sanae et al., 2000) and atherosclerosis (Ha et al., 2004). In TCM, *U. rhynchophylla* is major component of Diao-teng-san for these bioactivities. In addtion, yokukansan is one of the traditional Japanese medicines called "kampo" medicines in Japan (Yi-Gan san in Chinese). It is composed of seven kinds of dried medicinal herbs. This medicine has been approved by the Ministry of Health, Labor, and Welfare of Japan as a remedy for neurosis, insomnia, and irritability in children. Recently, yokukansan is reported to improve behavioral and psychological symptoms of dementia such as hallucinations, agitation, and aggressiveness in patients with Alzheimer's disease, dementia with Lewy bodies, and other forms of senile dementia (Iwasaki et al., 2005a,2005b; Mizukami et al., 2009). Among the 7 ingredient herbs of yokukansan, *Uncaria* thorn is found to the highest potency in the treatment of neural degeneration diseases (Kawakami, et al., 2011).

As the medicinal uses of *Uncaria* species, a great deal of studies concerning the phytochemistry and pharmacology of *Uncaria* have been carried out. More than 200 chemical constituents, including indole alkaloids, triterpenes, flavonoids and phenylpropanoids, *etc*, have been isolated from the genus of *Uncaria*. Of these, indole alkaloids are regarded as the main bioactive constituents and are responsible for the broad spectrum of biological properties reported for *Uncaria* species (Heitzman et al., 2005; Zhou and Zhou, 2010). Furthermore, reports indicate that the tetracyclic oxindole alkaloids present in *Uncaria* mainly act on the central nervous system, whereas pentacyclic oxindole alkaloids affect the cellular immune system (Reinhard, 1999). Tetracyclic oxindole alkaloids, likely rhynchophylline **(32)** and isorhynchophylline **(40)** containing chiral carbon at C-7 position, are often characterized by rapid isomerization in aqueous solutions, which is dependent on temperature and pH (Guo and Gu, 1959; Liu et al., 2011; Laus et al., 1996; Sakakibara et al., 1999; Sutter and Wang, 1993). Protonation and decreasing polarity of the solvent have been suggested to slow the process of their isomerization (Keplinger et al., 1999).

Several reviews on the genus *Uncaria* have been reported. Phillipson et al. (1978) describes the collection of botanical, ethnobotanical and alkaloids information from the *Uncaria* species. Laus (2004) and Heitzman et al. (2005) highlight the structures and pharmacological activities of *Uncaria* since the year 1978. Due to the widely investigations on *Uncaria* have been demonstrated in the past ten years, this review, using various databases search and library search to provide constructive information on the ethnopharmacology, phytochemistry and pharmacology of the genus *Uncaria* as well as the stereo-chemistry and

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