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Review

Corilagin, a promising medicinal herbal agent

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A R T I C L E I N F O

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A B S T R A C T

Corilagin, a gallotannin, is one of the major active components of many ethnopharmacological plants. It was isolated from *Caesalpinia coriaria* (Jacq.) Willd. (dividivi) by Schmidt in 1951 for the first time. In the past few decades, corilagin was reported to exhibit anti-tumor, anti-inflammatory and hepatoprotective activities, *etc*. However, little attention was paid to its pharmacological properties due to the complicated and inefficient extract method. In recent years, with the development of extraction technology corilagin was much easier to obtain than before. Thus, people return to pay attention to its anti-tumor, hepatoprotective, and anti-inflammatory activities, particularly as an anti-tumor agent candidate. Our research team had focused on the distribution, preparation and anti-tumor activity of corilagin since 2005. We found corilagin showed good anti-tumor activity on hepatocellular carcinoma and ovarian cancer. What's more, corilagin showed a low level of toxicity toward normal cells and tissues. Due to the extensive attention that corilagin has received, we present a systematic review of the pharmacological effects of corilagin. In this review, we summarized all the pharmacological effects of corilagin with a focus on the molecular mechanism of anti-tumor activity and show you how corilagin affected the signaling pathways of tumor cells as well as its physicochemical properties, distribution and preparation methods.

1. Introduction

Corilagin ($C_{27}H_{22}O_{18}$), as a gallotannin, is a major active component of many ethnopharmacological plants such as *Phyllanthus niruri* L., *P. emblica* L. and *P. urinaria* L., *etc*. Corilagin was first isolated in 1951 by Schmidt et al. [1] from divi-divi (*Caesalpinia coriaria* (Jacq.) Willd.). However, in the next 34 years, people were unaware of its bioactivity. It was not until 1985 Kakiuchi et al. [2] found corilagin could inhibit the activity of reverse transcriptase of RNA tumor viruses. This is the beginning of the research on the pharmacological activity of corilagin. In the past few decades, corilagin was reported to display several pharmacological activities, including anti-tumor [3], antioxidant [4], hepatoprotective [5], anti-inflammatory [6] activities, *etc*. In recently, much attention was drawn to its anti-tumor, hepatoprotective, and anti-inflammatory activities, particularly as an anti-tumor agent candidate. Due to the extensive attention that corilagin has received, there is a need for a systematic review of its pharmacological effects. We summarized all the pharmacological effects of corilagin with a focus on the molecular mechanism of anti-tumor activity and show you how corilagin affected the signaling pathways of tumor cells as well as its physicochemical properties, distribution and the methods for its preparation.

2. Methodology

We searched the online academic databases (PubMed, ACS, CNKI (China National Knowledge Infrastructure), Web of Science, Google Scholar) using corilagin as a keyword, and all available abstracts and full-text articles (mostly during the time span of 1951–2017) were gathered and analyzed. All of the scientific botanical names were confirmed using online databases (Flora of China, The Plant List and the Kew databases).

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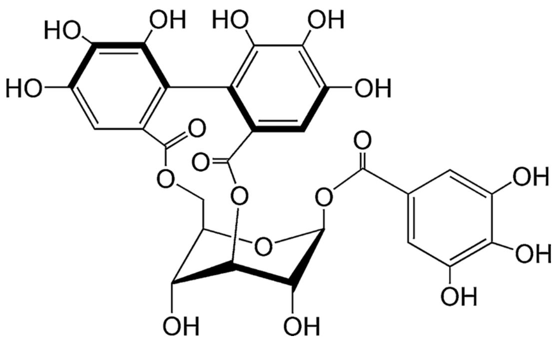

Fig. 1. Structure of corilagin.

3. Physicochemical properties

Corilagin (Fig. 1) is a gallotannin polyphenolic compound with a chemical formula of $C_{27}H_{22}O_{18}$ and molecular weight of 634.45 g/mol. Corilagin is an off-white acicular crystalline powder that easily dissolves in MeOH, EtOH, acetone and DMSO. We successfully isolated corilagin from *Phyllanthus niruri* L. and determined its molecular structure using NMR, obtaining the following data:

^{1}H NMR (400 MHz, DMSO): δ 6.20 (1H, d, J = 7.1 Hz, H-1), 3.87 (1H, t, J = 6.3 Hz, H-2), 4.58 (1H, br.s, H-3), 4.21(1H, overlap, H-4), 4.35 (1H, m, H-5), 4.24 (1H, overlap, H-6a), 3.94 (1H, t, J = 9.2 Hz, H-6b), 7.01(2H, s, H-2′, 6′), 6.55 (1H, s, H-6″), 6.49 (1H, s, H-6‴).

^{13}C NMR (400 MHz, DMSO): δ 92.7 (C-1), 72.1 (C-2), 78.0 (C-3), 62.6 (C-4), 76.8 (C-5), 64.4 (C-6), 119.2 (C-1′), 109.5 (C-2′, 6′), 146.0 (C-3′, 5′), 139.5 (C-4′), 165.3 (C-7′), 116.3 (C-1″), 124.4 (C-2″), 145.3 (C-3″), 136.0 (C-4″), 144.8 (C-5″), 107.4 (C-6″), 167.5 (C-7″), 116.0 (C-1‴), 123.6 (C-2‴), 145.2 (C-3‴), 135.9 (C-4‴), 144.4 (C-5‴), 106.6 (C-6‴), 167.2 (C-7‴).

4. Distribution

Our investigation revealed that to date, corilagin has been identified in 16 families and 50 species of plants (Table1). Corilagin is found mainly in the families Euphorbiaceae (20 species), Geraniaceae (10 species) and Combretaceae (7 species), and in species such as *P. niruri* L. [7], *P. emblica* L. [8], *P. urinaria* L. [9], *Geranium sibiricum* L. [4] and *Terminalia catappa* L. [5]. Corilagin is more likely to be isolated from the aerial parts of plants, including the leaves, flowers, fruits and seeds. We had determined the corilagin content of *P. urinaria* L., *P. tenellus* Roxb., *Acalypha australis* L., *Polygonum chinense* L., *Saururus chinensis* (Lour.) Bail., *Terminalia catappa* L., *Metacarpus longan* Lour. and *Punica granatum* L. We found that *P. niruri* L. and *Euphorbia longana* Lam. appeared to contain more corilagin than other tested plants (unpublished data). Thus, it is a good choice to isolate corilagin from *P. niruri* L. and *E. longana* Lam. To obtain sufficient corilagin to meet the needs of the future,we wish to find a plant that is highly rich in corilagin. Therefore, we will continue to evaluate the corilagin content of the remaining plants in Table 1 to find the plants with the highest corilagin content.

5. Preparation

The traditional methods for isolation of corilagin were organic solvent extraction; such as 50% ethanol or 50% acetone refluxing extraction assisted with ultrasound. In recent years, subcritical water extraction (SWE) showed the potential to extract polyphenolic compounds from plants compares to organic solvent extraction methods, results indicated that more corilagin was extracted through SWE than that of organic solvent extraction [52]. High pressure extraction (HPE) technique was a new method to extract polyphenols from plants. Prasad et al. [53] obtained higher corilagin content from *Dimocarpus longan* Lour. using the method of HPE than other extraction methods. Another specific and promising method to isolate corilagin were molecularly imprinted polymer (MIP), the molecularly imprinted polymer which was synthesized by using corilagin as template showed high affinity with corilagin [54]. Although the new methods were specific and efficient to extract corilagin from plants, the process was too complicated to be industrialized. Yamada et al. [55] reported the first total synthesis of corilagin in 2008. However, it is more efficient to obtain corilagin through traditional methods than total synthesis due to the low yield of total synthesis. We had isolated corilagin from *P. niruri* L. in 2005 through bio-activity guided separation of methanol phase and succeeded in applying a patent which is related to a sufficient method to isolate corilagin from *P. niruri* L. Thus, it is better to extract corilagin

Table 1
Plants distribution of corilagin.

Family	Plant	Part	Reference	Family	Plant	Part	Reference
Euphorbiaceae	*Phyllanthus amarus* Schumach. & Thonn.	Leaf	[10]		*G. wilfordii* Maxim.	Whole plant	[31]
	P. tenellus Roxb.	Whole plant	[11]		*Erodium cicutarium* L'Hér. ex Aiton	Aerial part	[32]
	P. emblica L.	Fruit	[8]		*E. stephanianum* Willd.	Aerial part	[33]
	P. muellerianus (Kuntze) Exell.	Leaf	[12]		*Pelargonium reniforme* Spreng.	Aerial part	[34]
	P. niruri L.	Leaf	[13]	Combretaceae	*Terminalia arjuna* (Roxb. ex DC.) Wight & Arn.	Fruit rind	[35]
	P. urinaria L.	Leaf	[14]		*T. bellirica* (Gaertn.) Roxb.	Fruit	[35]
	P. ussuriensis Rupr. et Maxim.	Aerial part	[15]		*T. catappa* L.	Leaf	[5]
	P. wightianus Müll.Arg.	Whole plant	[16]		*T. chebula* Retz.	Fruit rind	[35]
	Euphorbia longana Lam.	Seed, Peel	[17]		*T. citrina* (Gaertn.) Roxb.	Fruit rind	[36]
	E. pekinensis Rupr.	Aerial part	[18]		*T. macroptera* Guill. & Perr.	Leaf	[37]
	E. prostrata Aiton	Whole plant	[19]		*Lumnitzera racemosa* Willd.	Leaf	[38]
	Acalypha hispida Burm.f.	Leaf	[20]	Aceraceae	*Acer amoenum* Carrière	Leaf	[39]
	A. wilkesiana Müll.Arg.	Leaf	[20]		*A. nikoense* (Miq.) Maxim.	Leaf	[40]
	Alchornea glandulosa Poepp.	Leaf	[21]	Sapindaceae	*Dimocarpus longan* Lour.	Fruit rind	[41]
	Excoecaria agallocha L.	Whole plant	[22]		*Nephelium lappaceum* L.	Fruit rind	[42]
	Macaranga tanarius Müll.Arg.	Leaf	[23]	Asclepiadaceae	*Cynanchum paniculatum* (bunge) kitagawa	Whole plant	[43]
	Mallotus japonicus Müll.Arg.	Leaf	[24]	Burseraceae	*Canarium album* L.	Fruit	[44]
	Jatropha curcas L.	Leaf	[25]	Cunoniaceae	*Cunonia macrophylla* Brongn. & Gris	Leaf	[45]
	Sapium insigne (Royle) Benth.ex Hook.f.	Leaf	[26]	Leguminosae	*Caesalpinia coriaria* (Jacq.) Willd.	Whole plant	[1]
Geraniaceae	*Geranium bellum* Rose	Aerial part	[27]	Ericaceae	*Arctostaphylos uva-ursi* (L.) Spreng.	Leafy Shoot	[46]
	G. carolinianum L.	Aerial part	[28]	Guttiferae	*Caraipa densifolia* Mart.	Fruit	[47]
	G. pyrenaicum Burm.f.	Aerial part	[29]	Nymphaeaceae	*Nymphaea stellata* Willd.	Flower	[48]
	G. potentillifolium DC.	Aerial part	[27]	Polygonaceae	*Polygonum chinense* L.	Aerial part	[49]
	G. sibiricum L.	Aerial part	[4]	Rutaceae	*Zanthoxylum piperitum* (L.) DC.	Fruit	[50]
	G. thunbergii Siebold ex Lindl. & Paxton	Whole plant	[30]	Saururaceae	*Saururus chinensis* (Lour.) Bail.	Aerial part	[51]