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REVIEW ON PHARMACOLOGICAL ACTIVITIES OF *CINNAMOMUM RETICULATUM*

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ABSTRACT

This review describes the morphological, phytochemical and pharmacological properties of *Cinnamomum reticulatum* (Lauraceae). The plant is an evergreen tree and native to Taiwan. The present paper lists an overview the pharmacological action of potent compound called isoobtusilactone A isolated from *Cinnamomum reticulatum* and provides researchers with information for development of this herb.

Key words: Lauraceae, *Cinnamomum reticulatum*, Isoobtusilactone A.

INTRODUCTION

Cinnamomum species (Lauraceae) have been used in folk medicine for their sweating, antipyretic, and analgesic effects. *Cinnamomum reticulatum* Hayata (Lauraceae) is an evergreen tree, a tree native to Taiwan. Many novel compounds were extracted from the *C. reticulatum*. We have identified a series of new compounds including reticuol (1), isoreticulide (2), 4-hydrox-3-methoxyphenethyl derivatives (3-7), reticumanone (8), reticuone (9), cinnaretamine (10) and known compounds [1-4, 10]. No attention will be paid on how to isolate the compounds in this review. We will focus on describing pharmacological mechanism of action of isoobtusilactone A (IOA) (11) isolated from *C. reticulatum*.

PHARMACOLOGICAL ACTIVITIES

Cell cycle and apoptosis

Apoptosis refers to program cell death involving either the mitochondria or the activation of death receptors. Both pathways induce activation of caspase including initiator caspases (caspase-2,-8, -9 and -10) and effector

caspases (caspase-3, -6 and -7). The activation of caspase 3 will lead to apoptosis and DNA fragmentation.

Bax counteracts the antiapoptotic effects of Bcl-2. The translocation of Bax to mitochondria can alter the outer membrane permeability and activates the caspase cascade, leading to apoptotic death [9].

IOA (11) is a butanolide and displays anti-cancer activity [4-6]. Previous studies have demonstrated that IOA induces cancer cell program death including human breast cancer cell (MCF-7, MDA-MB-231), human hepatoma cell (Hep G2) and human non-small cell lung cancer (A549) [7]. IOA (11) alters Bax translocation to mitochondria resulted in releasing cytochrome c and activating the caspase cascade in Hep G2, MCF-7, MDA-MB-231, and A549 cell line. P53 is a tumor suppressor gene and known to cause cell-cycle arrest or induce apoptosis. Many mediators can control p53-mediated cell cycle arrest. In MCF-7 and MDA-MB-231 breast cancer cells, IOA caused a significant inhibition of cycle progression in G2/M phase and altered related cyclin-dependent kinase (CDK) and

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CDK inhibitor expression. In A549 cells, IOA (**11**) caused cell-cycle arrest in G0/G1 phase.

Reactive oxygen species (ROS) generation and apoptosis

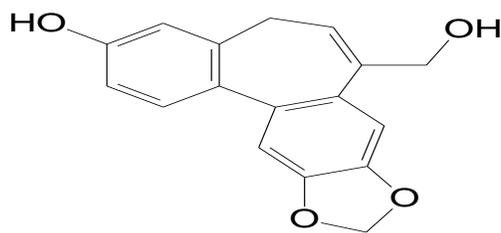
Mitochondria are considered as the main source of ROS. ROS are highly reactive oxygen free radicals are generated by multiple mechanisms. ROS can regulate by a number of cellular pathways and play a dual role in determining the fate of cell survival and death.

Previous studies have shown that IOA (**11**) results in a loss of mitochondria membrane potential and generate the ROS in Hep G2, MCF-7, MDA-MB-231, and A549 cell line. The effects can be blocked with different kinds of ROS scavenger *in vitro* study.

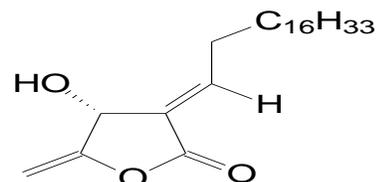
ROS signaling seems to be mediated in part by activation of the apoptosis signal-regulating kinase 1 (ASK1)/mitogen-activated protein kinase (MAPK) signaling pathway. ASK1 is a member of the MAPK kinase

kinase (MAPKKK) family and upstream activator of MAPK signaling cascades. MAPK signal pathway also plays an important role in oxidative stress-induced apoptosis. One study has demonstrated that IOA (**11**) induces cell growth inhibition in the MCF-7 and MDA-MB-231 cells through producing ROS and activation ASK1.

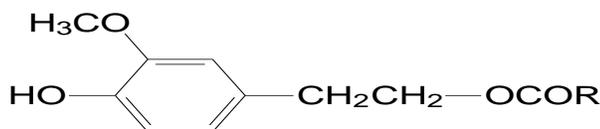
Tumor necrosis factor-related apoptosis-inducing factor ligand (TRAIL) cross-links with death receptor 4 (DR4) or DR5 leads the formation of death-inducing signaling complex [8]. Recently, one study has shown that co-incubation of TRAIL and IOA (**11**) significantly induces caspase-dependent apoptosis by up-regulation of C/EBP homologous protein (CHOP) and 5 (DR5) protein levels in Hep G2 [2]. Further, DR5 expression is associated with IOA (**11**) treatment accompanied by provoking intracellular ROS generation. Taken these results together, IOA (**11**) can generate ROS mediated cancer cells death.



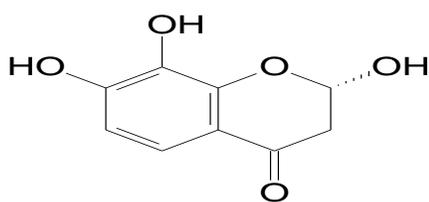
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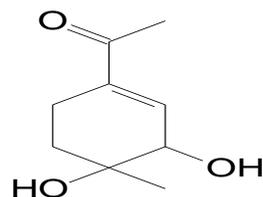
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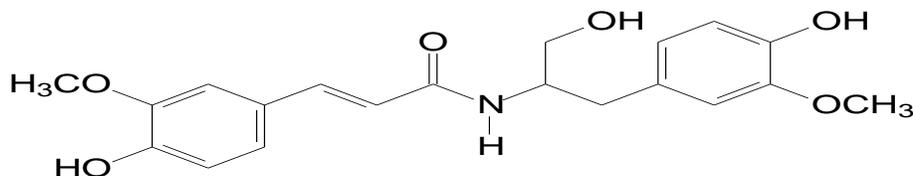
- 3** R = (CH₂)₂CH₃
- 4** R = (CH₂)₄CH₃
- 5** R = (CH₂)₁₃CH₃
- 6** R = (CH₂)₁₆CH₃
- 7** R = (CH₂)₁₉CH₃



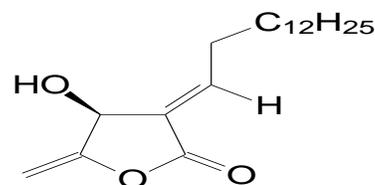
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CONCLUSION

The IOA (11) isolated from *C. reticulatum* has multiple pharmacological actions in inhibiting cancer cells growth. In general, IOA (11) inhibits cancer cells growth by mainly producing ROS mediated apoptosis. However, only one *in vivo* study demonstrated that IOA (11) inhibited

breast cancer growth in nude mice. In the future, *in vivo* studies should be conducted.

ACKNOWLEDGMENT

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