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Review Article

Pharmaceutical Chemistry for Novel drug discovery

# A Systematic Review On Synthesis And Anticancer Activity Of Podophyllotoxin From Podophyllum Peltatum L

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**Abstract:** The objective of this present review is to give a brief view about the use, synthesis and analysis of anticancer activity of podophyllo toxin from podophyllum peltatum L. PubMed, Elsevier, Google scholar search engine is utilized for collecting literatures which have detailed study of role, synthesis and potential therapeutic effects of podophyllotoxin from podophyllum peltatum L. Podophyllotoxin is an important chemical compound which is majorly obtained from plant source of podophyllum peltatum L and podophyllum hexandrum R .Podophyllum peltatum L is only plant have podophyllotoxins of around 68 percentage obtained from may to june at flowering stage. Phenyl alanine, cinnamic acid, ferulic acid were involved in the synthesis of podophyllotoxin. It binds and damages microtubule polymerization which leads to cell cycle arrest and concern DNA damage occurrs. Endoplasmic reticulum stress and autophagy was induced due to cell death by podophyllotoxin. Several investigations have been performed for biosynthesis, synthesis and anticancer activity according to literature. This review of research is an overview of anticancer activity of podophyllotoxin from Podophyllum peltatum L. The research will find an alternative way to satisfy pharmaceutical demand of podophyllotoxin.

**Keywords:** *Podophyllum peltatum* L, Antitumor activity, Podophyllotoxin, Phenyl alanine, Cinnamic acid, ferulic acid.

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## 1. INTRODUCTION

Podophyllum peltatum L is a medicinal plant which belongs to Berberidaceae family. A rhizome of podophyllum peltatum L contains several lignans which possess anticancer activity. Its most potential cytotoxic active constituent is podophyllotoxin and this podophyllotoxin is starting material for synthesis of anticancer agents like etoposide(figure-2) and teniposide(figure-3). Aryltetralin lignan is a chemical compound which is closely related to podophyllotoxin and aryltetralin also have anticancer activity.

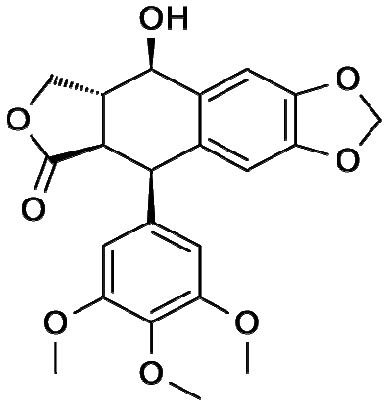


**Fig 1. Structure of Podophyllotoxin**

### *1.1 Derivatives of podophyllotoxin*

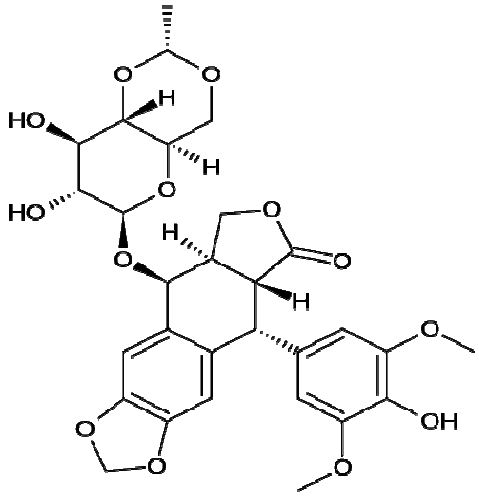


**Fig 2. Structure of etoposide**

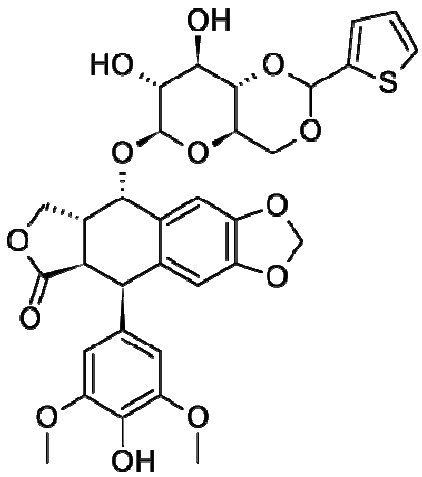


**Fig 3. Structure of teniposide**

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### *1.2 Uses of podophyllotoxin*

It is the best well known lignan among hundreds of best lignin. Podophyllotoxin and its derivatives are used as a medicament over 250 years. Podophyllotoxin is an antidote for snake bites believed by Native Americans. It is used as poison, as local antifungal, as anthelmintics[1]. In western countries, podophyllotoxin used as laxative medicine in 19th century. In 1940 podophyllum resins used to treat skin lesions like condylomas and warts particularly alcoholic extract of podophyllum to treat venereal warts[2]. Currently podophyllum used to treatment for condyloma acuminate and also cathartic herbal preparations. It has been used for treatment of genetal infections like noncervical human papilloma virus[3].

### *1.3 Source of Podophyllotoxin*

The important natural source of podophyllotoxin were derived from plants such as podophyllum species, Jeffersonia, Linun, Diphylleia, Catharanthus, Teucrium, Thymus, Nepeta, Juniper, Polygala, Anthriscusetc can produce podophyllotoxin[4].

### *1.4 Mechanism of action*

Podophyllotoxin destabilizes the microtubules of the cells by binding with tubulin and thus preventing the cell division[5]. Podophyllotoxin binds and damage microtubule polymerization which leads to cell cycle arrest and concern DNA damage occurred. Endoplasmic Reticulum stress and autophagy was induced due to cell death by podophyllotoxin[6]. The anticancer effect can be achieved by preventing of tubulin polymerization which induce cell cycle arrest at mitosis and impede the formation of the mitotic-spindles at microtubules. This action is compared with another control alkaloid, colchicines [7].

### *1.5 Biosynthetic pathways*

Khaled[7] illustrated as biosynthetic method of podophyllotoxin from phenyl alanine, ferulic acid and methylene dioxy substituted cinnamic acid which is a key method to synthesize other compounds which is showed in figure 4.

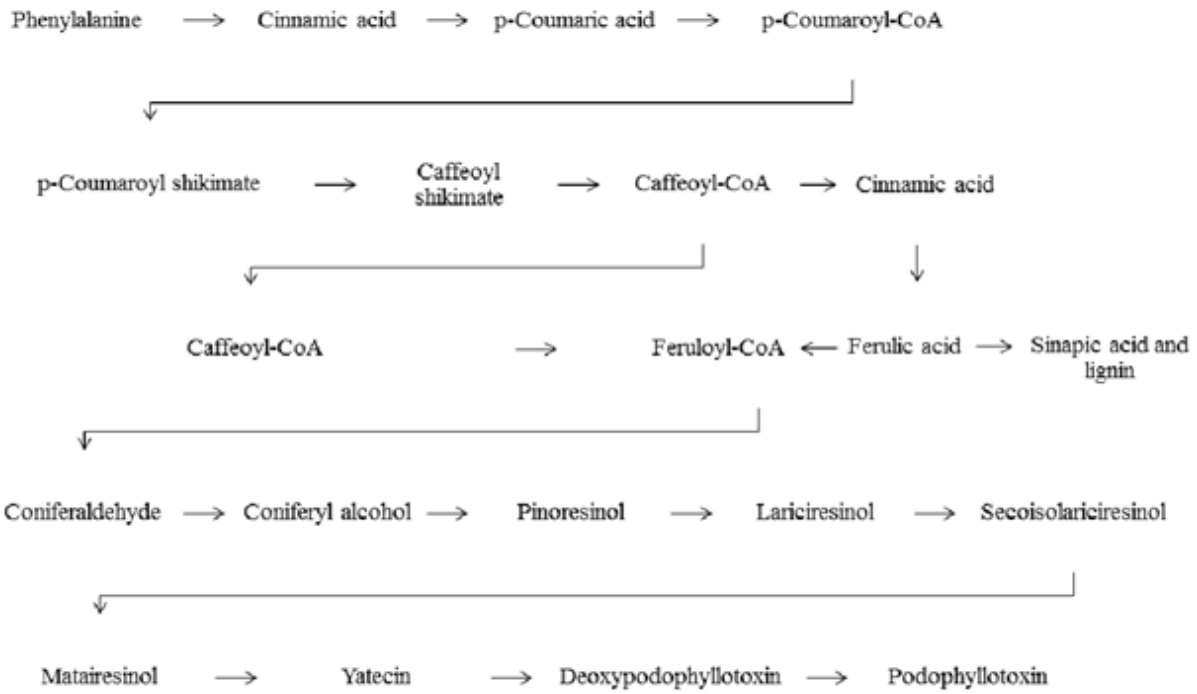


**Fig 4. Biosynthetic pathway of podophyllotoxin[7]**

Most pathways proposed that phenolic oxidative coupling of C6-C3 atoms via shikimic acid pathway (Figure no 5). This pathway illustrated synthetically from phenyl alanine to synthesize podophyllotoxins at $40^0$ to $60^0$ C. In synthetic pathway oxidative coupling happened in C6-C3 at normal room temperature.

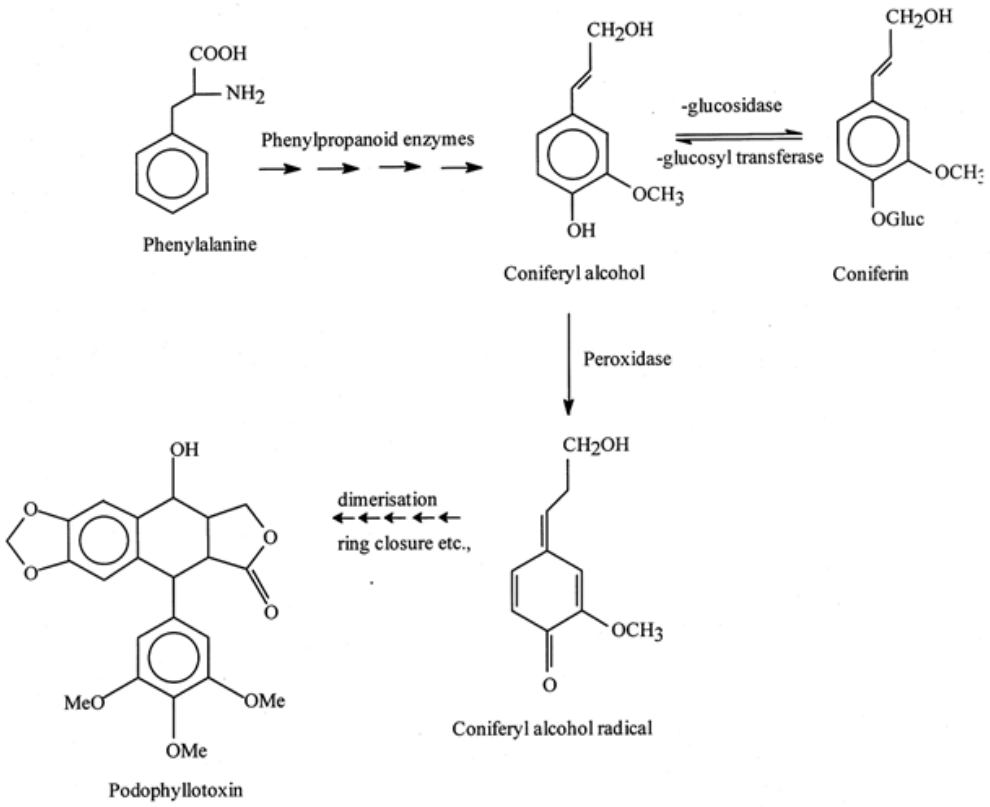


**Fig 5. Synthetic pathway of podophyllotoxin[8]**

### *1.6 Pharmacological activity of podophyllotoxin*

Several studies have been conducted by Jandaghi P and Noroozi M were revealed that possible natural products or plants help to cure several diseases like antiviral, anti cancer, antibacterial, antifungal etc[9]. Podophyllotoxin is suggested as an antiviral agent and active against human papilloma virus (HPV) in the treatment of condyloma acuminatum, fight against depression and treatment of venereal warts[10]. In another side *in vitro* pharmacological study of podophyllotoxin showed that it produce cytotoxicities against set of human cell lines like HeLa, HCT-8, A-549 and HL-60[11]. The scientist revealed podophyllotoxin did not have any organ toxicity in animal models[12].

### *1.7 Anticancer activity of podophyllotoxin*

Podophyllum peltatum L plant root was extracted and it contains podophyllotoxin which is used to treat cancer. Naturally synthesized podophyllotoxins was not active against cancer due to unactive podophyllotoxins but biotechnologically synthesized extract contains active podophyllotoxins which is used to treat cancer[13]. The entire plant extract also contains podophyllin which has antimitotic activity and used to treat ovarian cancer[14,15]. Podophyllotoxin are act against topoisomerase II enzyme than etoposide due to better binding to topoisomerase II enzyme. Podophyllotoxin bind with cell wall of cancer cell line and enter into the affected cancer cell and prevent microtubule polimerization which leads to bind topoisomerase II enzyme and slowly destroy it. So podophyllotoxin act as a topoisomerase II inhibitor. Huge number of cancers can be cured by this medication including neuroblastoma, hepatoma, testicular cancer, lung cancer[16]. Chemically synthesized 4β-1,2 ,3- triazole derivatives of podophyllotoxin exhibits anticancer activity by two podophyllotoxin C-4 position were linked together which give a novel dimeric podophyllotoxin derivatives. This novel derivatives against five human cancer cells including hepatoma- SMMC-7721, leukemia – HL-60, breast cancer-MCF-7, colon cancer-SW480, lung cancer by MTT assay method and cisplatin, etoposide were considered as reference standard during this study[17]. Common mechanism of action of podophyllotoxin is following in figure- 6

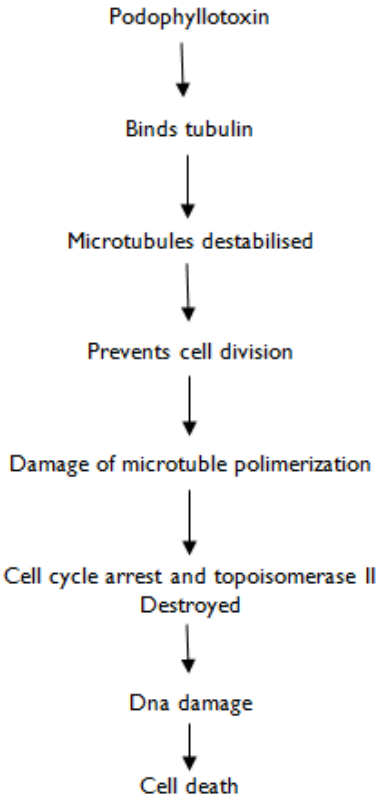


**Fig 6. Schematic diagram of mechanism of action – podophyllotoxin**

It is a naturally occuring antimitotic product which binds tubulin has colchichine. It has inhibitory action on cell growth led to develope anticancer derivatives like etopodide, teniposide and watersoluble prodrug like etoposide phosphate and its cytotoxic mechanism is inhibition of topoisomerase II, unlike inhibition of mitosis by lead compound[18].

## 2. CONCLUSION

Several investigations have been performed for synthesis, biosynthesis of podophyllotoxins from podophyllum peltatum L and evaluation of anticancer activity according to literature. This review is useful for overview of anticancer activity of podophyllotoxin from Podophyllumpeltatum L to find an alternative way to satisfy pharmaceutical demand of podophyllotoxin in the pharmaceutical industry for their future research.

## 3. CONFLICT OF INTEREST

Conflict of interest declared none

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