

## 25-Methoxyl-Dammarane-3 $\beta$ , 12 $\beta$ , 20-Triol, A Ginseng Saponin Derivative and an Anticancer Agent: *In Vitro* and *In Vivo* Activities, Molecular Mechanism of Action, Pharmacokinetics and Structural Modification

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### Abstract

25-Methoxyl-dammarane-3 $\beta$ ,12 $\beta$ ,20-triol (25-OCH<sub>3</sub>-PPD), a dammarane-type triterpene saponin isolated from *Panax notoginseng*, has shown strong antitumor effects in various human cancer cell lines, including prostate cancer, lung cancer, breast cancer, gastric cancer, colorectal cancer, pancreatic cancer, and hepatic fibrosis. This review focuses on the progress of research into 25-OCH<sub>3</sub>-PPD and its derivatives in cancer therapy, including *in vitro* and *in vivo* activities, structure-activity relationships, and the molecular mechanisms of action. In addition, we also summarized a method to evaluate the oral subchronic toxicity, improve oral bioavailability, and establish quality control standards for 25-OCH<sub>3</sub>-PPD. In this review, we have provided a detailed discussion of 25-OCH<sub>3</sub>-PPD and supplied a scientific reference for the research and development of 25-OCH<sub>3</sub>-PPD as a potential anticancer drug.

**Keywords:** 25-OCH<sub>3</sub>-PPD; Anticancer activities; Structure-activity relationships; Molecular mechanisms; Pharmacokinetics

### Introduction

Traditional Chinese Medicine (TCM) has been used in cancer therapies for a long history, resulting in fewer side effects compared with chemotherapy and radiation therapy. At present, approximately three-quarters of cancer clinical trials in progress in China are a combination of TCM therapy and traditional cancer treatment [1,2]. The major bioactive constituents with this important herbal activity are ginsenosides, which comprise mainly of dammarane-type saponin derivatives [3,4]. A large number dammarane-type triterpene glycosides has been isolated from the roots, leaves, stems, seeds, and berries of *Panax notoginseng*. Dammarane-type triterpenes have been classified into protopanaxadiols (PPDs) and protopanaxatriols (PPTs) [5,6]. Furthermore, structure-activity relationships have shown that the activities of PPDs were greater than those of PPTs. Aglycones have stronger activity compared with saponins and the presence of the sugar moieties reduces compound activity, in the order: monosaccharide glycoside>disaccharide glycoside>trisaccharide glycoside>tetrasaccharide glycoside [7-9].

A novel compound, 25-methoxyl-dammarane-3 $\beta$ , 12 $\beta$ , 20-triol (25-OCH<sub>3</sub>-PPD) (Figure 1), a tri-tetracyclic terpene dammarane aglycone of the protopanaxadiol-type, has potent anticancer activity [10]. It can inhibit the growth and proliferation of tumor cells and induce the differentiation and apoptosis of cancer cells. The cytotoxic effects of 25-OCH<sub>3</sub>-PPD have been reported in several human cancer cell lines, such as human prostate cancer, pancreatic cancer, lung cancer, gastric cancer, colorectal cancer, and breast cancer cells [11-17]. Of all known ginsenosides tested, 25-OCH<sub>3</sub>-PPD showed the most potent cytotoxic effects on cancer cells. In comparison with Rg<sub>3</sub>, a clinically used anticancer treatment in China, the half-maximal inhibitory concentration (IC<sub>50</sub>) demonstrated 10- to 100-fold stronger cytotoxicity in most cancer cell lines [10]. Numerous studies have shown that the anticancer activity of ginsenosides is related to the number of sugars associated with the core structure and the type of glycoside [18,19]. Additional studies have shown that a greater number of sugar moieties led to a gradual reduction in the anticancer effect. In order to further

study and make use of the active ingredient, the chemical properties, antitumor activity, structure-activity relationship, and molecular mechanisms of action of 25-OCH<sub>3</sub>-PPD and its derivatives were reviewed in this paper.

### Research Progress of 25-OCH<sub>3</sub>-PPD

#### Chemical and biological studies of 25-OCH<sub>3</sub>-PPD

A novel compound, 20(S)-25-methoxyl-dammarane-3 $\beta$ ,12 $\beta$ ,20-triol (20(S)-25-OCH<sub>3</sub>-PPD), was isolated from the total hydrolyzed saponins extracted from the leaves of *P. notoginseng* using conventional and reversed-phase silica gel chromatography. The identification of 20(S)-25-OCH<sub>3</sub>-PPD was based on the study of its physicochemical characteristics and NMR data. 20(S)-25-OCH<sub>3</sub>-PPD, recovered in the form of white needle-shaped crystals, has a molecular formula of C<sub>31</sub>H<sub>56</sub>O<sub>4</sub> and a molecular weight of 492 [10]. Because the C-20 of 20(S)-25-OCH<sub>3</sub>-PPD is chiral carbon atom, the compound has chiral isomers. Thus, 20(R)-25-methoxyl-dammarane-3 $\beta$ ,12 $\beta$ ,20-triol (20(R)-25-OCH<sub>3</sub>-PPD) was isolated from the total hydrolyzed saponins extracted from *P. ginseng* berry and elucidated by using a combination of 1D and 2D <sup>1</sup>H and <sup>13</sup>C NMR spectra and mass spectroscopy [19].

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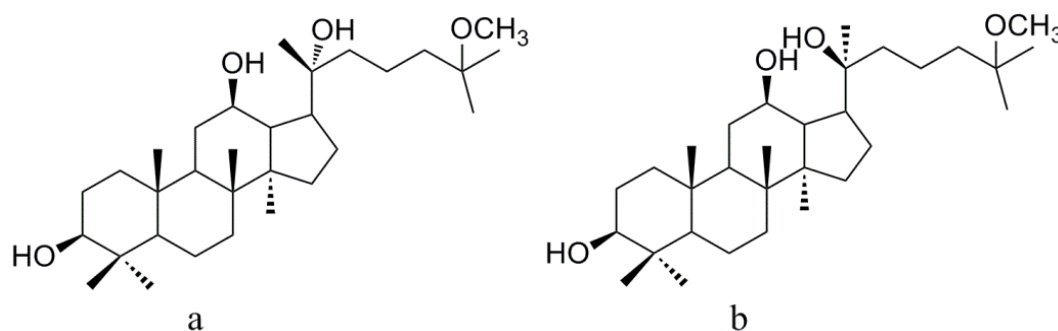
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The relative cytotoxicities of the compounds in Colon 205 and A549 cell lines were as follows: 20(R)-25-OCH<sub>3</sub>-PPD > 20(S)-25-OCH<sub>3</sub>-PPD > epimeric mixture of 25-OCH<sub>3</sub>-PPD. The IC<sub>50</sub> values of 20(R)-25-OCH<sub>3</sub>-PPD for most cell lines were similar to 20(S)-25-OCH<sub>3</sub>-PPD, which were 10- to 100-fold more cytotoxic than Rg<sub>3</sub>. However, 25-OCH<sub>3</sub>-PPD often becomes an epimeric mixture, which consists of 43% 25(S)-OCH<sub>3</sub>-PPD and 35% 25(R)-OCH<sub>3</sub>-PPD. A rapid separation method of the R-epimer of 25-OCH<sub>3</sub>-PPD from its epimeric mixture by crystallization-induced dynamic resolution (CIDR) was established. This method was helpful for the further study of 20(R)-25-OCH<sub>3</sub>-PPD and 20(S)-25-OCH<sub>3</sub>-PPD [19,20]. Furthermore, a rapid and selective UPLC-MS/MS method was invented for the simultaneous determination of the major constituent and related substances in the raw material of 25-OCH<sub>3</sub>-PPD. The method was successfully applied to establish a reasonable quality control standard for the raw material of 25-OCH<sub>3</sub>-PPD [21].

The anticancer effects of 25-OCH<sub>3</sub>-PPD have been reported in various human cancer cell lines (Table 1), including human colorectal cancer, lung cancer, pancreatic cancer, prostate cancer, and breast cancer

cells (Figure 2). The mechanism of the anticancer effect of 25-OCH<sub>3</sub>-PPD occurred through the inhibition of growth and proliferation and the induction of apoptosis in the cancer cells, which led to G1 cell cycle arrest in both PC3 and LNCaP cell lines. 25-OCH<sub>3</sub>-PPD was a potent therapeutic agent against both androgen-dependent and androgen-independent prostate cancer [11]. In addition, 25-OCH<sub>3</sub>-PPD also exerted potent cytotoxic activity on pancreatic and breast cancer cells, which was achieved by the inhibition of the MDM2 oncogene and associated pathways [11,16]. Meanwhile, 25-OCH<sub>3</sub>-PPD showed strong cytotoxicity in colon and lung cancers cells by targeting beta-catenin signaling [13-14]. Further research has shown that 25-OCH<sub>3</sub>-PPD concentration-dependently inhibited the lung cancer cell viability, had no effect on normal human lung epithelial cell activity, and increased the expression of p38 and the phosphorylation of ERK. The oral administration of 25-OCH<sub>3</sub>-PPD (10-40 mg/kg) showed a dose-dependent inhibition of xenograft tumors without affecting body weight, but reduced the expression of CD34 VEGF and MMP-9 in tumor tissue [15].

In addition, a mechanistic study revealed the potent antitumor

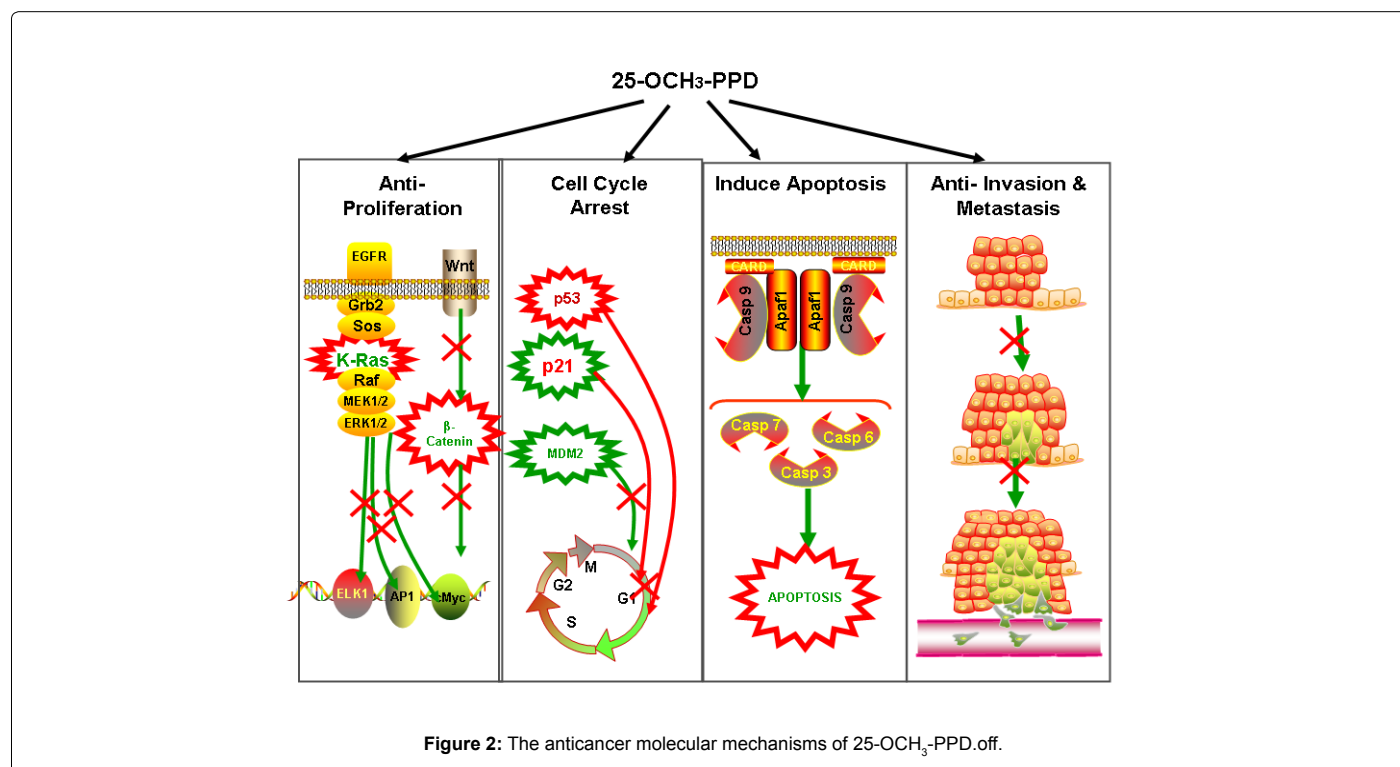


**Figure 1:** Structure of 20(S)-25-OCH<sub>3</sub>-PPD (a) and 20(R)-25-OCH<sub>3</sub>-PPD (b).

	Cell line	25-OCH <sub>3</sub> -PPD (μM)		
		IC <sub>20</sub>	IC <sub>50</sub>	IC <sub>80</sub>
Prostate cancer	LNCaP	5.4	12.0	26.6
	PC3	1.5	5.6	20.6
	IMR90-EEA	10.4	110.1	>500
	IMR90-EIA	6.2	275.7	>500
Pancreas cancer	Panc-1	1.2	7.8	51.6
	HPAC	0.9	5.8	36.6
Lung cancer	A549	0.66	4.88	35.86
	H358	4.48	19.12	81.7
	H838	3.37	13.39	53.29
	BEAS-2B	4.46	24.61	>100
Gastric cancer	BGC-823	-	22.15	-
	SGC-7901	-	32.40	-
	MKN-28	-	32.97	-
	GES-1	-	38.82	-
Colon cancer	SW480	-	7.29	-
Breast cancer	MCF7	-	6.98	-

**Note:** IC<sub>20</sub>, IC<sub>50</sub>, IC<sub>80</sub> are the concentrations that inhibit growth by 20, 50, and 80%, respectively, relative to the control. "-" were not determined.

**Table 1:** Antiproliferative activity of 25-OCH<sub>3</sub>-PPD in human tumor cells.



effects of 25-OCH<sub>3</sub>-PPD on gastric mucosa cells were related to the caspase signaling pathways [17]. Moreover, 25-OCH<sub>3</sub>-PPD induced the apoptosis of activated t-HSC/Cl-6 cells via c-FLIP-mediated NF- $\kappa$ B activation, which suggested a potential therapeutic action against hepatic fibrosis. The dose-response subchronic toxicity study showed that no mortality and treatment-related toxicity effects resulted from the continuous oral administration of 25-OCH<sub>3</sub>-PPD at any of the doses tested (150, 300, and 600 mg/kg) for 13 weeks [22].

### The pharmacokinetics of 25-OCH<sub>3</sub>-PPD

Dammarane triterpenoids generally exhibit poor bioavailability and short half-life. The pharmacokinetics of 25-OCH<sub>3</sub>-PPD epimers were studied after oral and intravenous administration in rats. The 25-O-demethylated metabolite appears as a pathway in the phase I metabolism of 25-OCH<sub>3</sub>-PPD in rats; it was shown that the absolute bioavailability of 25-OCH<sub>3</sub>-PPD was approximately 19.7% and the drug-time curve of 25-OCH<sub>3</sub>-PPD exhibited distinct double-peaks after oral administration. In addition, the apparent distribution volume and plasma clearance of 20(R)- and (S)-25-OCH<sub>3</sub>-PPD was significantly different [23,24]. The low oral bioavailability and rapid reduction of 25-OCH<sub>3</sub>-PPD in the blood indicated that formulation modification was required. The relative bioavailability of a self-microemulsifying drug delivery system (SMEDDS) was dramatically enhanced by an average of 9.8-fold compared with the suspension [25]. A nanoemulsion loaded with a 25-OCH<sub>3</sub>-PPD phospholipid complex was also developed. After the oral administration of the nanoemulsion and the suspension of 25-OCH<sub>3</sub>-PPD in rats, peak plasma concentration and area under the curve (0–24 h) of the nanoemulsion of 25-OCH<sub>3</sub>-PPD-phospholipid complex were 3.9- and 3.5-fold higher than those of free compound [26]. Furthermore, the molecular interactions between 25-OCH<sub>3</sub>-PPD and phospholipid 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) were investigated by using the Langmuir film balance technique. The interfacial stabilization of the 25-OCH<sub>3</sub>-PPD/DSPC system was fairly

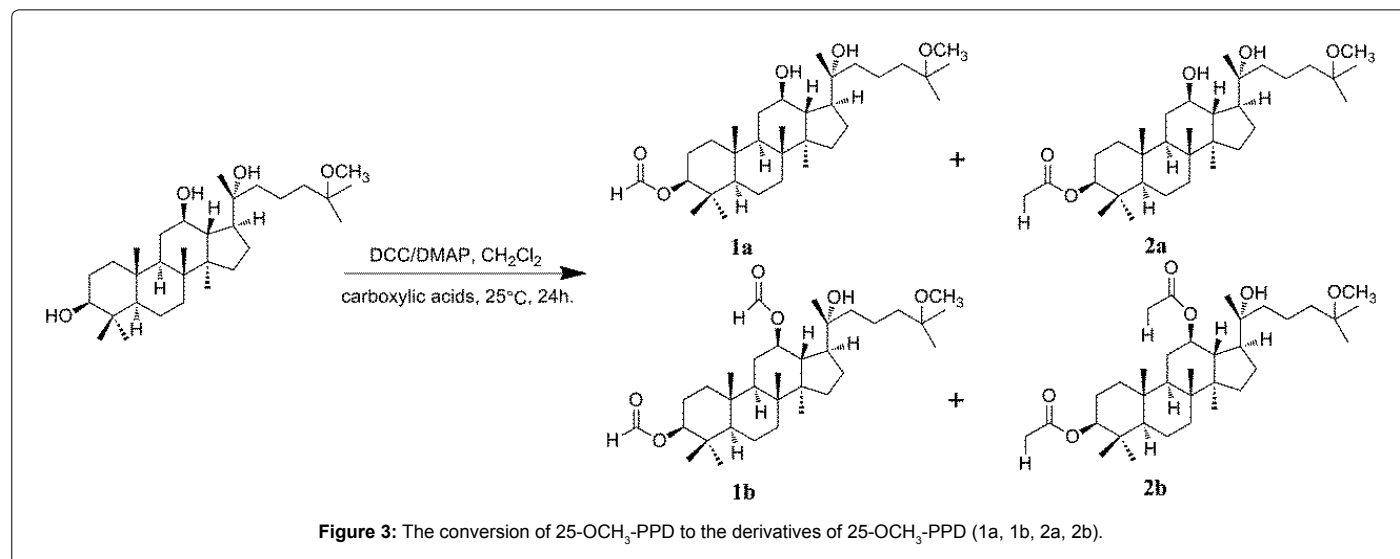
strong owing to hydrophobic interactions and this system had the capacity to load large amounts of 25-OCH<sub>3</sub>-PPD [27].

In addition, the metabolism of 25-OCH<sub>3</sub>-PPD in liver microsomes of human, monkey, dog, rat, and mice was identified, and showed that 25-OCH<sub>3</sub>-PPD was extensively metabolized in the aforementioned mammalian species. The catalytic oxidation and metabolism of CYP3A4 played an important role in the efficacy of 25-OCH<sub>3</sub>-PPD, especially in the C-20 hydroxyl group [28,29].

### The derivatives of 25-OCH<sub>3</sub>-PPD

There have been many studies on the antitumor effect of ginsenosides, which have included structural modifications, such as esterification, alkylation, catalytic hydrogenation, and oxidation. Pharmacokinetic studies have also indicated that ginsenoside fatty acid esters might be the antiproliferative active component *in vivo*. Thus, at present, the structural modification of 25-OCH<sub>3</sub>-PPD is mainly focused on esterification. The higher reactivity of positions 3 and 12 allows carboxylic acid to be used in CH<sub>2</sub>Cl<sub>2</sub> using *N,N*-dicyclohexylcarbodiimide (DCC) as a condensing agent with 25-OCH<sub>3</sub>-PPD as the starting material and 4-dimethylaminopyridine (DMAP) as a catalyst for selective esterification. Meanwhile, the simple ester derivatives of 25-OCH<sub>3</sub>-PPD, 1a, 1b, 2a, and 2b (Figure 3), showed stronger antiproliferative activities than 25-OCH<sub>3</sub>-PPD in the human lung cancer cell line A549, the human cervical cancer cell line HeLa, the human breast cancer line MCF-7, and the human colon cancer cell line HT-29. However, they produced no obvious effects on the human ovarian surface epithelial cells IOSE144. The results showed that the antiproliferative activity of the ester derivatives of 25-OCH<sub>3</sub>-PPD decreased with an increase in the length of the fatty acid carbon chain of the substitutions. Modification with short-chain fatty acids, such as acetic acid, resulted in potent antiproliferative activity [30].

### Conclusion



Since the discovery of 25-OCH<sub>3</sub>-PPD isolated from the total hydrolyzed saponins extracted from the leaves of *P. notoginseng*, research into its biological activity and the structure-activity relationships has produced many breakthroughs. 25-OCH<sub>3</sub>-PPD has demonstrated the strong cytotoxic effects in tumor cells and relatively non-toxic effects in normal cells. The simple ester derivatives of 25-OCH<sub>3</sub>-PPD showed stronger cytotoxic activity than 25-OCH<sub>3</sub>-PPD. This paper is the first review of the progress of the research into 25-OCH<sub>3</sub>-PPD and provides a scientific reference for the design of 25-OCH<sub>3</sub>-PPD as a potential anticancer agent.

However, further study of the structure-activity relationship and anticancer mechanism of these derivatives is necessary. Searches for the target of the antitumor effect of 25-OCH<sub>3</sub>-PPD were helpful for the discovery of the lead compounds. Computer-aided drug simulation is an advanced technology for the optimization and design of lead compounds. Thus, the use of computer-aided drug modeling techniques for the design of improved activity, bioavailability, and lower toxicity precursor compounds was feasible for further design and study of the antitumor activity of 25-OCH<sub>3</sub>-PPD derivatives. In addition, in order to screen the better lead compounds, the pharmacokinetic studies of the derivatives of 25-OCH<sub>3</sub>-PPD should also be considered.

#### Conflict of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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