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Research paper

Discovery and modelling studies of natural ingredients from *Gaultheria yunnanensis* (FRANCH.) against phosphodiesterase-4

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ABSTRACT

Phosphodiesterase-4 (PDE4) is an anti-inflammatory target for treatment of asthma and chronic obstructive pulmonary disease (COPD). Here, we report the isolation and characterization of 13 compounds (**G1-G13**) by bioassay-guided fractionation of the ethyl acetate extraction of *Gaultheria yunnanensis* (FRANCH.), one of which pentacyclic triterpene (**G1**) has never been reported. Four of them (**G1, G2, G4,** and **G5**) inhibit PDE4 with the IC_{50} values < 20 μM and **G1** is the most potent ingredient with an IC_{50} of 245 nM and moderate selectivity over other PDE families. Molecular dynamics simulations suggest that **G1** forms a hydrogen bond with Asn362, in addition to the hydrogen bond with Gln369 and π-π interactions with Phe372, which are commonly observed in the binding of most PDE4 inhibitors. The calculated binding free energies for the interactions of PDE4-**G1** and PDE4-**G2** are −19.4 and −18.8 kcal/mol, in consistence with the bioassay that G1 and **G2** have IC_{50} of 245 nM and 542 nM, respectively. The modelling results of these active compounds may aid the rational design of novel PDE4 inhibitors as anti-inflammatory agents.

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1. Introduction

Phosphodiesterases (PDEs) are a superfamily of enzymes that are responsible for hydrolysis of the intracellular second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) [1,2]. Posphodiesterase 4 (PDE4) specifically hydrolyze cAMP and is predominantly expressed in inflammatory and immune cells [3,4]. PDE4 inhibitors increase the intracellular cAMP level and activate in turn the protein kinases that tune activities of inflammatory cell and air-way smooth muscle, so as to be potential therapeutics for the treatment of inflammatory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and atopic dermatitis [5–8]. Although hundreds of PDE4 inhibitors are available, most of them show side effects such as nausea, emesis, and vasculopathy, limiting their therapeutic potential [9–11]. In comparison, biologically active natural products often have less severe side effects than synthetic compounds. Our previous studies showed that several compounds isolated from the Chinese herbs (*Morus alba* L., *Selaginella pulvinata,* and *Toddalia asiatica*) have affinity with PDE4 and anti-inflammatory activity [12–17], which provided a new strategy for the discovery of PDE4 inhibitors.

Gaultheria yunnanensis (FRANCH.), known as 'Tou Gu Cao' in traditional Chinese medicine (TCM), belongs to the Ericaceae family and is widely used as a folk medicine for the treatment of inflammatory diseases such as rheumatoid arthritis, chronic tracheitis, and swelling [18–20]. Previous investigations demonstrated that salicylate derivatives isolated from *G. yunnanensis* showed anti-inflammatory effects in animal and cell models *via* the regulation of NFκ-B signal pathway [21–24]. Inspired by our previous works and the concept that Chinese herbal medicine usually apply a multi-component and muti-target approach for the treatment of diseases, we speculated that several compounds isolated from *G. yunnanensis* (FRANCH.) may exert its anti-inflammatory effect *via* inhibiting PDE4.

The inhibitory activities of *G. yunnanensis* crude extracts against PDE4 were firstly evaluated, which showed moderate inhibition. 13 compounds were finally isolated from the ethyl acetate fraction in the further separation process, one new pentacyclic triterpene (**G1**) and 12 known compounds (**G2-G13**). Compounds **G1**, **G2**, **G4**, and

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G5 exhibited remarkable inhibitory activities against PDE4 with IC_{50} values less than 20 μM. The best two ingredients **G1** and **G2** (IC_{50} = 245 and 542 nM) showed stronger affinities than the positive control rolipram (1062 nM, a well-known PDE4 inhibitor). Molecular modelling of **G1** and **G2** to PDE4 was used to provide insight into the enzyme inhibition and structure activity relationship. The results indicated that hydrogen bond interactions of **G1** with Asn362 in PDE4 was observed in their binding pattern, in addition to the π-π interactions with Phe372 and hydrogen bond interactions with Gln369 which are commonly formed by most PDE4 inhibitors and their receptor.

2. Results and discussion

2.1. G1 and G2 are potent PDE4 inhibitors

All the isolated compounds (Fig. 1) were assayed for their inhibitory activities against PDE4D. Rolipram, a well-known PDE4 inhibitor, was used as the reference compound, having a comparable IC_{50} value of 1062 nM to that in literature (1 μM) [25]. Four compounds (**G1**, **G2**, **G4**, and **G5**) showed inhibitory activities with their IC_{50} values less than 20 μM (Table 1). Compounds **G1** and **G2** were the most potent PDE4 inhibitors with IC_{50} = 245 and 542 nM, respectively, which are more active than rolipram. The inhibitory curves of **G1**, **G2**, and rolipram were shown in Fig. 2. **G4** and **G5**

Table 1
Inhibitory affinities (IC_{50}, nM) of PDE4 inhibitors isolated from *G. yunnanensi*.

Compounds	IC_{50}	Compounds	IC_{50}
G1	245 ± 43	**G8**	>20 000
G2	542 ± 98	**G9**	>20 000
G3	>20 000	**G10**	>20 000
G4	6568 ± 367	**G11**	>20 000
G5	13 273 ± 1143	**G12**	>20 000
G6	>20 000	**G13**	>20 000
G7	>20 000	Rolipram	1062

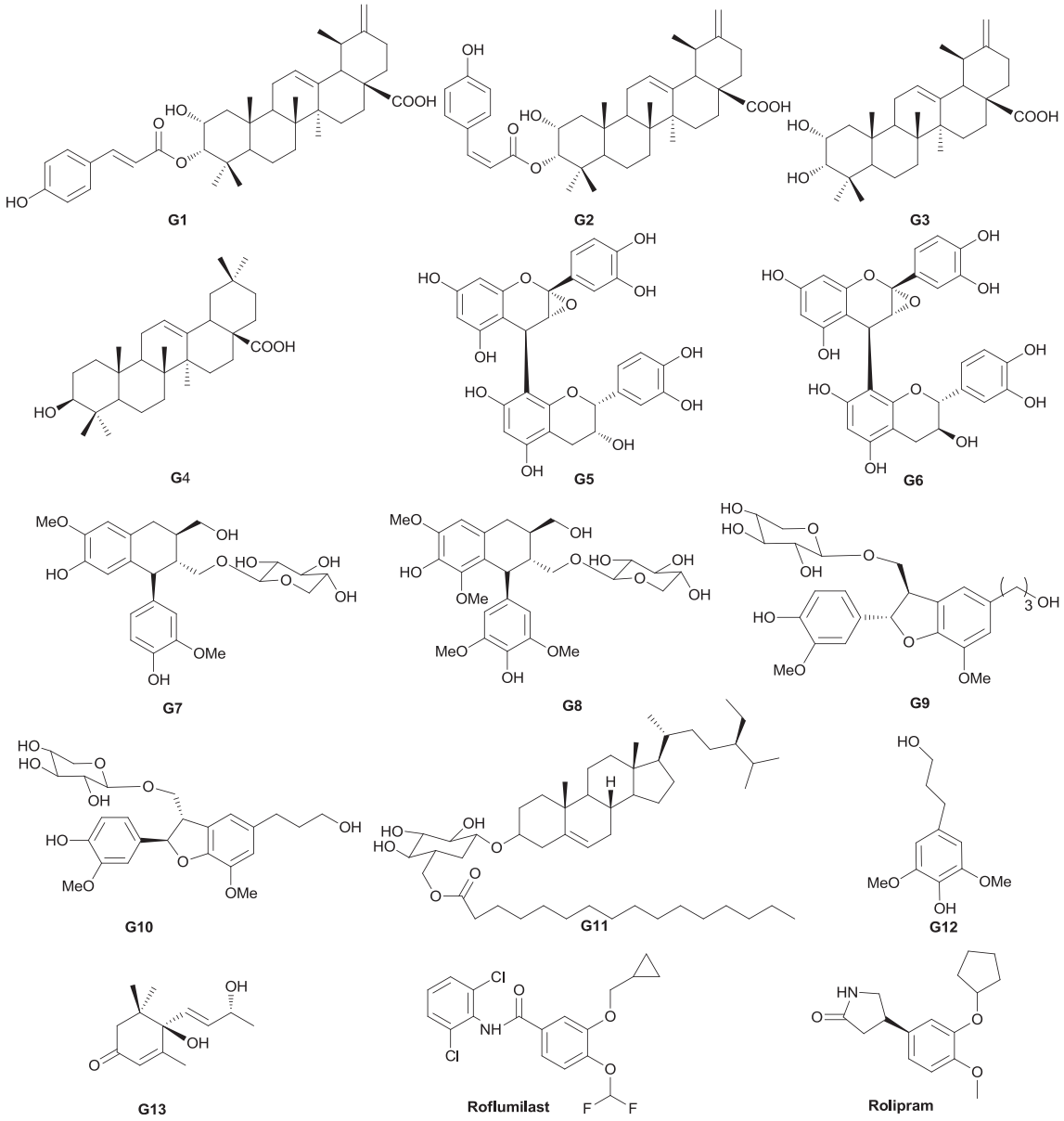

Fig. 1. 13 ingredients isolated from the EtOAc extract of *G. yunnanensi* and two well-known PDE4 inhibitors (roflumilast and rolipram).

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