Journal of the Taiwan Institute of Chemical Engineers 42 (2011) 580–591

Contents lists available at ScienceDirect

Journal of the Taiwan Institute of Chemical Engineers

journal homepage: www.elsevier.com/locate/jtice

# Drug design for mPGES-1 from traditional Chinese medicine database: A screening, docking, QSAR, molecular dynamics, and pharmacophore mapping study

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ARTICLE INFO

*Article history:*
Received 23 July 2010
Received in revised form 15 November 2010
Accepted 26 November 2010
Available online 26 January 2011

*Keywords:*
Microsomal prostaglandin $E_2$ synthase 1 (mPGES-1)
Traditional Chinese medicine (TCM)
Docking
Molecular dynamics (MD)
Qualitative structure–activity relationship (QSAR)

ABSTRACT

To search for new anti-inflammatory that can replace the current COX-1 and COX-2 inhibitors, virtual screening by molecular docking of traditional Chinese medicine (TCM) molecules into microsomal prostaglandin $E_2$ synthase (mPGES-1) glutathione binding site was performed. To compare the top ranking derivatives with other mPGES-1 inhibitors, we constructed QSAR models using comparative molecular force field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). The CoMFA model had a non-cross-validated coefficient ($r^2$) and a cross-validated coefficient ($q^2$) of 0.960 and 0.597. The $r^2$ and $q^2$ for CoMSIA (S + H + D) was 0.931 and 0.719, respectively. The top three TCM derivatives all can map into the respective steric, hydrophobic and hydrogen bond donor force fields. The top ranking TCM molecules were taken for *de novo* design; the top three *de novo* products were further analyzed using molecular dynamics simulation and qualitative structure–activity relationship (QSAR) model. Derivative, 2-O-caffeoyl tartaric acid-Evo_2, glucogallin-Evo_1 and 4-O-feruloylquinic acid-Evo_7, all had conserved hydrogen bond networks to key residues Arg38 and Arg70 during the 20 ns molecular dynamics simulation. In addition, all derivative–protein complexes had total energy lower the control–protein complex. Combining the results from molecular dynamics simulation and CoMFA/CoMSIA, we suggest 2-O-caffeoyl tartaric acid-Evo_2, glucogallin-Evo_1 and 4-O-feruloylquinic acid-Evo_7 as potent mPGES-1 inhibitors.



## 1. Introduction

Prostaglandins, products of prostanoids synthesis, are autocrines that are produced in various parts of human body. Prostaglandin $E_2$ ($PGE_2$), the most abundant subtype of prostaglandins, is the product from the action of prostaglandin E synthases on prostaglandin $H_2$ (Hara *et al.*, 2010). To date, there are three known classes of prostaglandin E synthases, namely cytosolic PGE synthase (cPGES) and two membrane-bound synthases, mPGES-1 and mPGES-2 (Hara *et al.*, 2010). The mPGES-1 protein, unlike the other PGE synthases, is not constitutively expressed and can be induced in response to inflammatory stimuli.

In the past, non-steroidal anti-inflammatory drugs (NSAIDs) have been designed to target COX-1 and COX-1, the upstream enzyme for producing prostaglandin $H_2$. However, long-term suppression of prostanoid biosynthesis by using COX-1 and COX-2 inhibitors can have severe side effects, including gastrointestinal injury and renal irritation (Koeberle and Werz, 2009). Current evidences suggest that suppression of mPGES-1 activity can be considered as an alternative anti-inflammatory approach. Since mPGES-1 is functionally coupled to COX-2 and is also being responsible for excessive $PGE_2$, its inhibitions are, therefore, related to inflammation, pain, fever, atherosclerosis and tumorigenesis.

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doi:10.1016/j.jtice.2010.11.009

To develop novel anti-inflammatory agents, TCM Database@-Taiwan (http://tcm.cmu.edu.tw), the current world largest small molecule database on traditional Chinese medicine, was employed in docking. Natural compounds isolated from TCM are gaining attention in the last few, and studies have been done already on compounds, such as emodin or gallic acid and many more, to investigate their potential effects to cellular process (Chen, 2009d; Chen *et al*., 2010b; Lin *et al*., 2010; Liu *et al*., 2010; Lo *et al*., 2010). In addition to screening of TCM database, we used both structure-based and ligand-based approaches to further validate and support the bioactivity of the lead candidates. Both strategies have been implemented in drug researches in the past, and we have successfully used both techniques in designing anti-viral, anti-inflammatory, and anti-tumor agents (Chang *et al*., 2010; Chen, 2008, 2009a,b,c,e,f, 2010a,b; Chen and Chen, 2007, 2010; Chen *et al*., 2009a,b, 2010a; Huang *et al*., 2010a,b,c).

## 2. Materials and methods

### 2.1. Docking

A total of 20,000 traditional Chinese medicine compounds were downloaded from TCM Database@Taiwan (http://tcm.cmu.edu.tw) and docked into the glutathione binding site of mPGES-1. All the ligands were pre-treated with force field of CHARMm, and all the missing hydrogen were added. The protein model used for docking was downloaded from Protein Data Bank (PDB: 3DWW (Jegerschold *et al*., 2008)). The nature substrate for mPGES-1, glutathione (γ-L-glutamyl-L-cysteinyl-glycine), which co-crystallized with mPGES-1 by electron crystallography, was used as the control molecule. The binding location of glutathione found in the protein crystal was set as the docking site.

**Table 1**
TCM docking results. Only the top 10 candidates and controls are shown.

| Compound | DS | -PMF04 | Jain | Ludi1 | Ludi2 | Ludi 3 |
|---|---|---|---|---|---|---|
| 2-O-caffeoyl tartaric acid | 215.079 | 144.63 | 5.42 | 870 | 698 | 789 |
| Chicoric acid | 206.092 | 177.22 | 5.00 | 915 | 694 | 826 |
| Mumefural | 201.985 | 136.75 | 8.50 | 1028 | 822 | 799 |
| 2-O-feruloyl tartaric acid | 198.739 | 145.13 | 5.16 | 833 | 661 | 693 |
| Rosmarinic acid | 148.434 | 145.59 | 5.40 | 971 | 743 | 921 |
| Quinic acid | 143.961 | 106.56 | 1.49 | 557 | 487 | 475 |
| Genipinic acid | 142.772 | 110.31 | 2.53 | 530 | 467 | 651 |
| Digallic acid | 142.547 | 147.27 | 1.67 | 953 | 708 | 848 |
| 5-O-feruloylquinic acid | 142.462 | 149.26 | 6.90 | 1011 | 784 | 865 |
| 4-O-feruloylquinic acid | 140.488 | 142.14 | 7.45 | 946 | 746 | 878 |
| Glutathione | 66.787 | 127.28 | 6.39 | 564 | 447 | 412 |

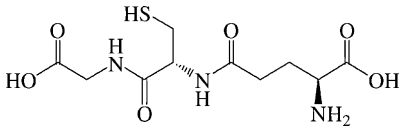
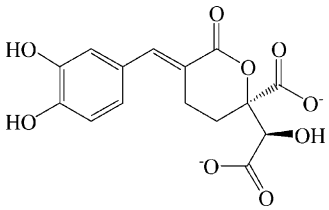
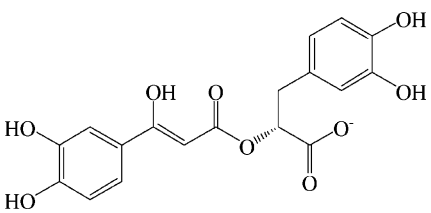
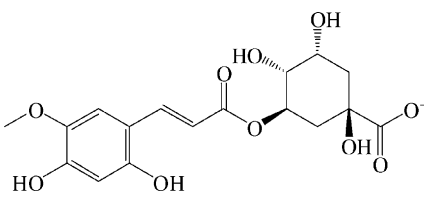
DS: Dock Score; PMF: Potential of Mean Force.

**Table 2**
Docking results for *de novo* products. The top 5 candidates are shown.

| Compound | DS | -PMF04 | Jain | Ludi1 | Ludi2 | Ludi3 |
|---|---|---|---|---|---|---|
| 2-O-caffeoyl tartaric acid-Evo_2 | 222.198 | 136.13 | 5.65 | 701 | 569 | 656 |
| Glucogallin-Evo_1 1 | 169.762 | 158.84 | 6.12 | 1062 | 795 | 974 |
| 4-O-feruloylquinic acid-Evo_7 | 167.056 | 152.93 | 8.01 | 999 | 783 | 919 |
| 1-Caffeoylquinic acid-Evo_3 | 165.916 | 150.93 | 5.90 | 774 | 591 | 674 |
| 4-O-feruloylquinic acid-Evo_5 | 159.929 | 160.19 | 7.34 | 1071 | 822 | 950 |
| Glutathione | 66.787 | 127.28 | 6.39 | 564 | 447 | 412 |

DS: Dock Score; PMF: Potential of Mean Force.

**Table 3**
Structures of glutathione, the top three derivatives and the parental compounds of the top three derivatives.

| Glutathione | 2-O-caffeoyl tartaric acid-Evo_2 |
|---|---|
|  |  |
| Glucogallin-Evo_1 | 4-O-feruloylquinic acid-Evo_7 |
|  |  |