Structural similarity-based approach to characterize crude drug components

Ai Muto
muto@kuier.kyoto-u.ac.jp

Minoru Kanehisa
kanehisa@kuier.kyoto-u.ac.jp

Bioinformatics Center, Institute for Chemical Research, Kyoto University, Gokasho, Uji, Kyoto 611-0011, Japan

Keywords: drug development, crude drugs, herbal medicine, structural similarity, KEGG

1 Introduction

Crude drugs are natural and unrefined substances used for cure of various diseases or improvement of nutritional status for human or animals. Various crude drugs have been used as folk remedies in the world, and many of top-selling drugs today are derived from such traditional remedies. Natural products are supposed to continue to be valuable sources for drug development, however, the mechanism of their drug-efficacy is still unclear for many crude drugs. One of the difficulties to elucidate the mechanism comes from synergy of components. Synergistic interactions are documented for constituents within a total extract of a single herb, and there have been reports of the total contents of an herbal product showing a significantly better effect than an equivalent dose of a single isolated active ingredient [3]. The first step to elucidate the synergistic effect is to characterize each component of crude drugs.

In this study, we show a new approach to characterize crude drug components. Our method is based on the assumption that two chemical compounds of similar chemical structure have similar activity in vivo, and uses structural similarity between crude drug component and approved drug for characterization.

2 Methods and Results

We used KEGG DRUG database (version 51.0 + update 2009/09/01) [2]. KEGG DRUG contains 9,079 drug information including all prescription drugs in Japan, all OTC (Over The Counter) drugs in Japan, most prescription drugs in USA, and many prescription drugs in Europe. 7,068 of them are with molecular structure and 278 are crude drugs. 202 of the crude drug entries have components information and most of the entries have descriptions of drug efficacy.

For each component of crude drugs, the structure similarity score with molecular structure of each approved drug was calculated using SIMCOMP [1], which compares two chemical structures of compounds using graph methods. According to these similarity scores, we obtained identical or very similar approved drugs. We determined SIMCOMP score (Tanimoto coefficient) = 0.7 for threshold. Then, we extracted the most similar approved drug for each component of crude drugs, and finally, we surveyed and compared their efficacy.

As a result of structure similarity calculation, we obtained the drugs whose structures are very similar to components of crude drugs. 161 of 202 crude drugs had at least one component that matched with any of approved drugs. For 58 crude drugs of them that has matched component, the efficacy also matched with the approved drugs and 25 of them had structurally identical components with matched drugs (Table 1), while 103 crude drugs showed no relationship with the efficacy of matched drugs.

Here we show an example of a crude drug and matched approved drugs. Phellodendron bark, a bitter stomachic and antidiarrheal crude drug, includes seven components. Six of them matched with approved drugs (Fig.1). Three of them are very similar each other, and each of them matched with berberine; one of well-known antidiarrheal drugs. Because chemical compounds of similar structure

<table>
<thead>
<tr>
<th>Total number of crude drugs</th>
<th>202</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% match with a drug of same efficacy</td>
<td>25</td>
</tr>
<tr>
<td>&gt;70% match with a drug of same efficacy</td>
<td>33</td>
</tr>
<tr>
<td>&lt;70% match with a drug of same efficacy</td>
<td>19</td>
</tr>
<tr>
<td>&gt;70% match with a drug of different efficacy</td>
<td>103</td>
</tr>
</tbody>
</table>
tend to have similar activity in vivo, it is possible that not only 100% matched compounds, but also the other similar compounds have the same antidiarrheal activity. Two of the other components are also similar each other, and both of them matched with glauicine; an antitussive drug. The other component; campesterol, matched with an antihyperlipidemic drug: beta-sitosterol. Each of the components matched with approved drug with a high similarity score. From the efficacy of similar drugs, we can guess the role of each component in a crude drug.

3 Discussions

After the calculation of structure search, many components of crude drugs were found to be identical with approved drugs. Natural products have been valuable sources for drug development for a long time, therefore most of matched drugs are supposed to be derived from the relevant crude drugs. On the other hand, we also obtained the components that didn’t match with any drug. Such components can be seed compounds of new drug development.

In addition, it was found that 80% of crude drugs contain a set of similar components. This new insight can be a clue to consider the synergistic effects of crude drugs. In some cases of antibiotic administration, an administration of multiple drugs with a little diversity may bring better effects for prevention of drug resistance than single drug.

Recently, new strategy to find drug seeds is awaited because development of new drugs is being stalled year by year. To consider synergy effects of mixed drug compounds will give us a new insight into drug efficacy.

Fig. 1 Components of Phellodendron bark and similar Drugs

References