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Quantitative structure–activity relationship of antifungal activity of rosin derivatives

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ABSTRACT

To develop new rosin-based wood preservatives with good antifungal activity, 24 rosin derivatives were synthesized, bioassay tested with *Trametes versicolor* and *Gloeophyllum trabeum*, and subjected to analysis of their quantitative structure–activity relationships (QSAR). A QSAR analysis using Ampac 9.2.1 and Codessa 2.7.16 software built two QSAR models of antifungal ratio for *T. versicolor* and *G. trabeum* with values of R^2 = 0.9740 and 0.9692, respectively. Based on the models, *tri-N*-(3-hydroabietoxy-2-hydroxy) propyl-triethyl ammonium chloride was designed and the bioassay test result proved its better inhibitory effect against the two selected fungi as expected.

With the improved awareness of environmental conservation, traditional wood preservatives such as sodium pentachlorophenol and chromate copper arsenate (CCA) have been completely banned in many countries.[1] Hence, many studies have used biological resources as raw materials for the development and creation of new nontoxic and environmentally friendly wood preservatives as alternatives to CCA and other toxic preservatives.[2–4] Rosin, a cheap and important natural raw material, has many excellent characteristics including being antifungal, moisture proof, insulating, conglutinating, emulsifying, and softening. Over the years, rosin was widely used in many fields such as the electronics, medicine, pesticide, and soap industries. In the wood preservation industry, it has been proven that rosin could contribute to improving wood decay resistance and had a certain effect on fixating copper within wood, thereby reducing the environmental impact of wood treated with copper-based preservatives.[5–9]

The major component of rosin is resin acids, which comprise 85–90% of its mass. There are many kinds of resin acids, and the structures of resin acids changed as temperature increasing. Figure 1 illustrates the structural transformation of abietic acid into levopimaric acid.[10] Resin acid molecules have two interesting reactive centers, namely a double bond and a carboxyl group, so they can be easily isomerized and susceptible to air oxidation. In addition, resin acids can be involved in Diels–Alder addition, disproportionation,[11] hydrogenation,[12] polymerization,[13] ammonolysis,[14] esterification,[15] salt formation,[16] and decarboxylation[17] reactions. Using these reactions, the rosin can be modified to prepare a series of rosin derivatives that can contribute to improving its usefulness. For example, after modification, various rosin derivatives have been used as curing agents,[18,19]coating materials,[20,21] tablets,[22] varnishes,[23] hardeners,[24] and fungicides.[25,26] Furthermore, dehydrogenated rosin (DHR) and hydrogenated rosin (HR) are widely used in medicine.[27,28]

Quaternary ammonium salt is a kind of cationic surfactant that has good hydrophilicity, adsorbability, and surfactivity characteristics. It also has low toxicity and efficient and broad-spectrum antifungal activity.[29,30] Chen et al. [31] reported that dehydroabietic quaternary ammonium salt polymers had satisfactory bioactivity and better efficacy as well as reduced residual toxicity, increased selectivity, and prolonged service time. However, the bioactivity decreased markedly relative to that of the monomer: the higher degree of quaternization within limits of 40–68%, the less bioactivity. A series of Diels–Alder adducts of resin acid with acrylic acid were synthesized and showed great antimicrobial activity against different kinds of bacteria by the filter paper method.[26,32] Furthermore, in our earlier study, rosin was used as a raw material to synthesize a series of rosin derivatives that were used as fungicides. The results showed that rosin derivatives had obvious antifungal resistance and that different structures had different inhibitory effect.[33–35] To reasonably modify the chemical structure of rosin,

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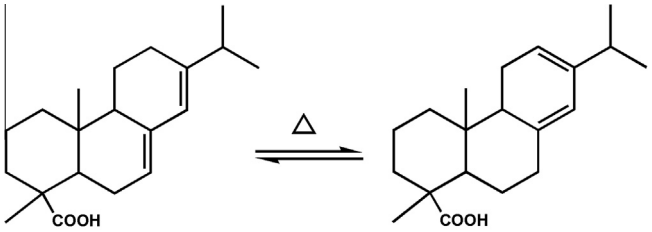

Figure 1. Structural transformation of abietic acid into levopimaric acid.

improve its biological activity, and obtain better antifungal activity, the relationship between the molecular structure of rosin derivatives and their biological activity requires elucidation.

In this study, the rosin was used as a raw material to synthesize a series of rosin derivatives, and the biological activity of these compounds against wood-decaying fungi were determined. Furthermore, their quantitative structure–activity relationships (QSAR) based on the molecular structure of rosin derivatives and their antifungal activity using Ampac and Codessa software was analyzed and some models were established. Based on the best models, a new compound with good activity was designed. This work can guide future synthetic work and contribute to new rosin development and utilization etc.

The main raw materials, rosin and dehydrogenated rosin, were of industrial grade and obtained from China. All other materials were analytical grade reagents.

A series of 24 rosin derivatives were synthesized according to the methods described elsewhere.[26,34,36–38] The molecular two-dimensional structures of these derivatives are summarized in Figure 2.

The antifungal activities of the rosin derivatives were determined using the paper disc method with the white-rot fungus *Trametes versicolor* and brown-rot fungus *Gloeophyllum trabeum* used as the test fungi. The raw materials and products were dissolved separately in 75% ethanol to obtain a molarity of 0.025 mmol/mL. The paper discs (8 mm) were then soaked in these solutions for 10 min and air-dried prior to use. Some discs dipped in 75% ethanol without chemicals served as controls, while others dipped in 0.025 mmol/mL dodecyl dimethyl benzyl ammonium chloride (1227) served as positive antifungal comparators. Meanwhile, potato dextrose agar (PDA) was decanted into petri dishes with actively growing mycelium of *T. versicolor* or *G. trabeum* as it was cooled but still liquid. After the PDA had set, all discs were placed onto the middle surface and the dishes were sealed. Each chemical was tested three times and all plates were incubated at 28 °C and 75% relative humidity for 3–5 days.[34] The antifungal activity expressed as antifungal ratio (AR) was calculated using the following equation:

$$\mathrm{AR} = (A/A_0) \times 100\% \quad (1)$$

where A_0 is the diameter of the inhibition zone of the comparator (1227) and A is the diameter of the inhibition zone in the presence of the tested chemicals (mm). Values of LogAR to different fungi were used to establish the QSAR models, respectively.

To further elucidate the relationship between antifungal activity and molecular structure, AMPAC Agui 9.2.1[39,40] was conducted for geometrical optimization and the data were imported into Codessa 2.7.16[41] to calculate the descriptors. The 'Best Multi-Linear Regression'[42] approach was used to calculate the QSAR and obtain a series of models. The optimum QSAR calculation model was identified using the 'breaking point' rule for determining the number of descriptors. The model was also validated by an internal validation and a leave-one-out approach.

In Codessa Pro, the descriptors are divided into six groups according to the molecular features reflected in their definition: constitutional, topological, geometrical, electrostatic, quantum-chemical, and thermodynamic. A wide range of structural information of the rosin derivative molecules was included in these descriptors.

Based on the descriptor information obtained through the computational analysis, a new compound with good bioactivity was designed, and its LogAR to *T. versicolor* or *G. trabeum* was predicted by using the QSAR models obtained, respectively. The compound was prepared and its antifungal activity was tested as described in section 2.2.

The results from the experimental antifungal activity of 24 Rosin derivatives (Fig. 2) are shown in Table 1.

The different structures of the rosin derivatives had different antifungal abilities. Among the 24 rosin compounds, most of them had obvious antifungal ability against both test fungi, but they were not all as efficient as 1227 with its inhibition ability against *T. versicolor* and *G. trabeum*, which were 30 mm and 22 mm, respectively. All the values of activity ratio (AR) are less than 100. Among them, compounds 15, 16, 19, 20, 22, and 23 exhibited good antifungal effects. In particular, under this experimental condition, compounds 19 and 20 showed the best antifungal activity. These two compounds have a double equivalent of a quaternary ammonium group. As reported, compounds with a quaternary ammonium group had good bactericidal ability.[43,44] This result showed that rosin quaternary ammonium salts had a satisfactory antifungal ability against both wood decay fungi, which is consistent with that reported elsewhere. Moreover, compared with commercially available fungicide 1227, the inhibitory ability of compounds 19 (*bis*-N-(3-hydroabietoxy-2-hydroxy) propyl-trimethyl ammonium chloride) and 20 (*bis*-N-(3-hydroabietoxy-2-hydroxy) propyl-triethyl ammonium chloride) is not far behind, especially against *G. trabeum*. This result suggested that the quaternary ammonium group plays an important role against *G. trabeum*.

Using the best multiple linear regression method encoded in Codessa Pro, up to 10 multilinear models were obtained for both test fungi. A simple ('breaking point') rule was used to decide the optimum number of descriptors by considering the improvement of R^2 by the addition of a further descriptor to the model. The selection of the optimum number of descriptors is presented in Figure 3. As shown in Figure 3, the breaking point occurs at three descriptors for both *T. versicolor* and *G. trabeum*. The values of these descriptors are listed in Table 1.

As shown in Table 2, the statistically best QSAR equations have the following statistical characteristics: $R^2 = 0.9740$, $F = 249.87$, and $s^2 = 0.0007$ for the LogAR data of *T. versicolor* ($\mathrm{LogAR_w}$) and $R^2 = 0.9692$, $F = 210.03$, and $s^2 = 0.0007$ for the LogAR data of *G. trabeum* ($\mathrm{LogAR_b}$), respectively. Both models include three descriptors in descending order according to their statistical significance (t values). In Table 2, X and ΔX are the regression coefficients and their standard errors. The best linear regression equations are shown as Eqs. 2 and 3.

$$\begin{aligned}\mathrm{LogAR}_w = {} & (1.3558 \pm 1.2514 \times 10^{-2}) + (1.7724 \times 10^{-1} \\ & \pm 7.1178 \times 10^{-3}) \times \mathrm{d1} + (2.1589 \times 10^{1} \pm 1.8938) \\ & \times \mathrm{d2} - (1.5455 \times 10^{1} \pm 4.2321) \times \mathrm{d3} \end{aligned} \quad (2)$$

$$\begin{aligned}\mathrm{LogAR}_b = {} & (1.6686 \pm 1.7884 \times 10^{-2}) + (1.3924 \times 10^{-1} \\ & \pm 8.0981 \times 10^{-3}) \times \mathrm{d1} + (1.6715 \times 10^{-2} \\ & \pm 2.1964 \times 10^{-3}) \times \mathrm{d4} + (1.2466 \times 10^{-2} \\ & \pm 1.8042 \times 10^{-3}) \times \mathrm{d5} \end{aligned} \quad (3)$$