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Synthesis and Anti-Tumor Activity of Proanthocyanidins

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Recently proanthocyanidins have been paid much attention due to their significant biological activities and benefitical effects for health. Among the broad biological activities of proanthocyaidins, the author focused on the anti-tumor activity of proanthocyanidins including our work.

Since Konings and co-workers reported moderate cytotoxicity of proanthocyanidins to human tumour cell lines in 1994 [1], more than 50 papers have been reported. However, in most of cases, evaluation of antitumor activity was investigated using the mixture of proanthocyanidins such as "grape seeds extract". Thus the numbers of report of systematic structural activity relationship study (SAR) of proanthocyanidins against tumor cell lines are still limited. To solve this problem, synthesis of proanthocyanidins is necessary to obtain pure sample [2-5]. In this report, the author wishes to introduce the examples of synthesis and antitumor activity of proanthocyanidins with systematic SAR studies.

First example of synthesis and antitumor activity of the proanthocyandin is reported by Kozikowski and co-workers in 1999. They synthesized 3-*O*-galloyl-(2*R*,3*R*)-epicatechin-4β,8-[3-*O*-galloyl-(2*R*,3*R*)-epicatechin] and its antitumor activity against human breast cancer cell lines (Figure 1) [6].

In 2003, synthesis procyanidin oligomer was reported by Kozikowski et al. [7]. They synthesized epicatechin oligomers and each compound was separated by HPLC and isolated products were evaluated antitumor activity. They found that cytotoxic effects were associated with high degree level of oligomerization at the 100 μg/mL dose. No activity was observed for the epicatechin dimer, trimer and tetramer. They also reported that these results are based on the induction of cell cycle arrest in the G0/G1 phase (Scheme 1).

In 2013, the first synthesis of prodelphinidin B3 and C2 and their anti-tumor activity against human PC-3 prostate cancer cell lines was reported by Fujii et al. [8]. They achieved total synthesis of prodelphinidin B3 and C2using Lewis acid-mediated equimolar condensation of a catechin and/or catechin-gallocatechin nucleophile with gallocatechin electrophiles. In addition to achievement of the total synthesis, they examined antitumor activities against PC-3 prostate cancer cells and reported that the activity of prodelphinidin B3 and C2 was almost same as well-known epigallocatechin-gallate (EGCG). Theyreported that cytotoxic effects are clearly associated with the

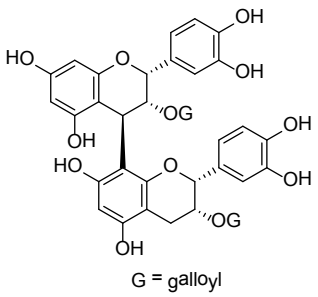
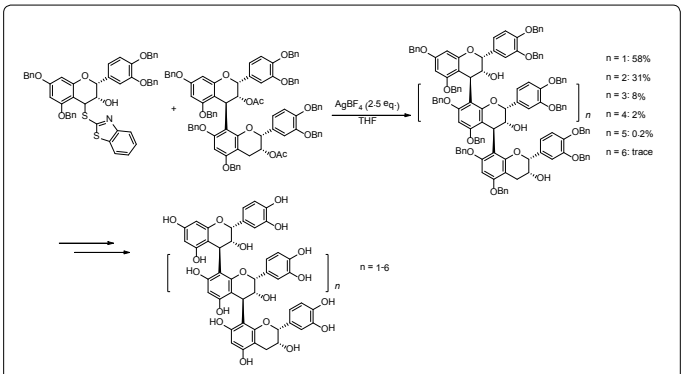


Figure 1: The structure of 3-*O*-galloyl-(2*R*,3*R*)-epicatechin-4β,8-[3-*O*-galloyl-(2*R*,3*R*)-epicatechin].



Scheme 1: Synthesis of epicatechin oligomers.

presence of the pyrogallol moiety of the B ring. Procyanidin B3 and C2 which lacked the pyrogallol moiety of the B ring did not show any activity. This activity of prodelphinidins might be due to cell cycle arrest at the G1/G0 phase and activating caspase-3 (Figure 2).

They also synthesize prodelphinidin B1, B2 and B4 [9]. They achieved synthesis of prodelphinidin B1, B2 and B4 via Lewis acid-mediated equimolar condensation of a gallocatechin and/or epigallocatechin nucleophile with gallocatechin and/or epigallocatechin electrophiles. They examined their antitumor activities against PC-3 prostate cancer cells. Prodelphinidin B1, B2, and B4 showed significant cytotoxic activity with IC_{50} values below 50 μM. The potencies seemed to be a little bit stronger than those of epigallocatechin-gallate (EGCG) and prodelphinidin B3 (Figure 3).

In addition to the prodelphinidins, Suda et al. [10] synthesized dimericcatechin and epicatechingallate and evaluated their antitumor activity against human prostate cancer cell lines. The results of antitumor activities showed significant cytotoxic activity but weaker than EGCG and prodelphinidins. This finding suggests that esterified pyrogallol moiety shows weaker activity compared to the compounds such as prodelphinidins (Figure 4).

Until now, the important structural factors of proanthocyanidins which show significant antitumor activity are as follows: 1) High degree oligomers show potent activity; 2) Proanthocyanidins which possess pyrogallol moiety show significant activity.

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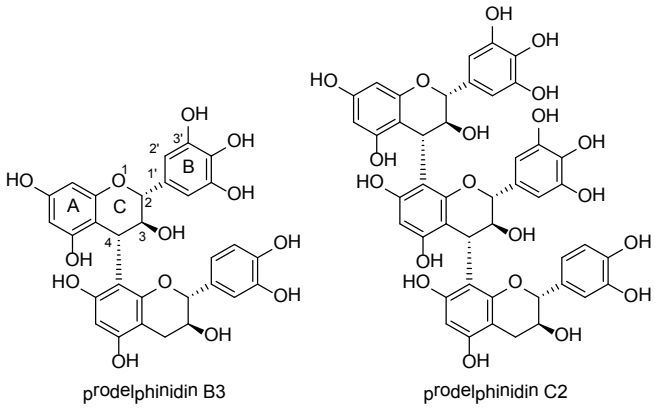
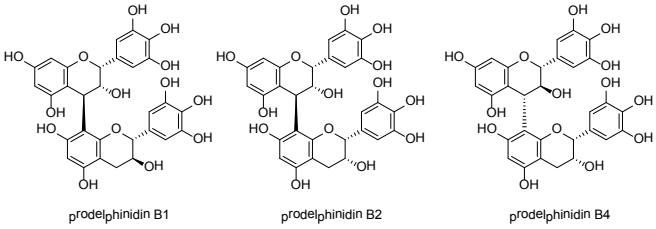


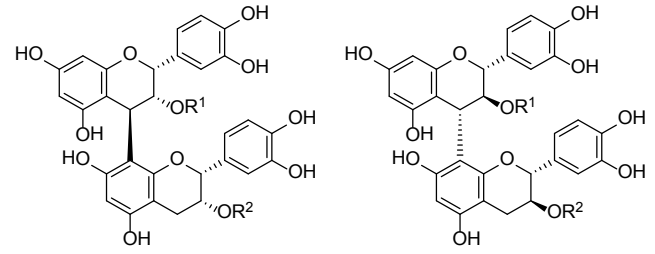
prodelphinidin B3 prodelphinidin C2

Figure 2: The structures of prodelphinidin B3 and C2.



prodelphinidin B1 prodelphinidin B2 prodelphinidin B4

Figure 3: The structures of prodelphinidin B1, B2 and B4.



R^1 = G (galloyl), R^2 = H
R^1 = H, R^2 = G
R^1 = R^2 = G

R^1 = G, R^2 = H
R^1 = H, R^2 = G
R^1 = R^2 = G

Figure4: The structures of dimeric catechin and epicatechin gallate.

Proanthocyanidins have been paid attention to the synthetic and biological researchers due to their unique structures and significant biological activities. Recent progress ofthe synthesis of proanthocyanidinsmade detailed biological studies possible. However, there is still much room to develop synthesis and biological activities especially for the highly polymerized proanthocyanidins. When synthetic methods of these complex molecules will be able to be developed, further useful biological activities and its mechanism of action will be disclosed.

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