Natural Products Phenols as Novel Antithrombotic Agents

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Thrombosis owns the highest incidence, and it is a serious threat to human health. Currently, the clinical antithrombotic drugs suffer from several drawbacks, causing allergic reactions or complications, etc. In recent years, small-molecule compounds isolated from natural products with antithrombotic activities in the field drug research on thrombus disease. In this review, we will focus on representative naturally occurring small molecule phenols with antithrombotic potency and potential for future therapeutic regimens to combat thrombosis disease.

Keywords phenols, thrombosis, antithrombotic activities, natural products, aglycon

Introduction

Thrombus is a severe health problem all over the world, especially in developing countries. It reduces the average life expectancy and changes the living habits.^[1,2] The current therapies (Heparin (ordinary heparin, low molecular weight heparin) and fondaparinux, and oral adjusted-dose vitamin K antagonists,^[3] aspirin, adenosine monophosphate receptor antagonist and platelet membrane glycoprotein antibody antagonist) are effective for the treatment of thrombosis patients clinically, however, they still remain unsatisfactory.^[3-12,13-15] Therefore, researchers are searching for small molecules with antithrombotic activities.^[16-25]

Natural products are divided into diverse chemical compounds isolated from varied biological sources such as plants, animals, marine organisms, microorganisms, minerals, and organic matters.^[26-29] In recent years, the research on natural products becomes a hot issue in drug research. The drug discovery from natural products possess several advantages such as timeliness, faster and better methods for bioassay screening, and compound isolation.^[30] Currently, naturally occurring phenols with antithrombotic activities have been reported in the recent literature or patents, which would provide many clues to find the novel agents. This progress holds a considerable promise to the development of alternative, highly effective and secure therapeutics agents and ultimately the eradication of thrombosis disease. In this paper, we reviewed phenols from natural products with antithrombotic activities.

Phenols

Phenol compounds exist widely in natural products. Because of the strong antioxidant activity,^[31] phenols can delay tumor occurrence and inhibit the formation of tumor.^[32] It possesses anti-platelet activities.^[33]

Phenolic aglycon

In 1997, a phenolic aglycom, resveratrol 3-O- β -D-glucopyranoside **1** (Figure 1), was isolated from the seeds of *Erythrophleum lasianthum* (Caesalpinioideae, Leguminosae), a South African plant.^[34] The test results *in vitro* on human platelet-rich plasma demonstrated that resveratrol possesses strong inhibition on platelet aggregation induced by collagen (IC_{50} = 69 μ M), adrenalin (IC_{50} = 102 μ M), arachidonic acid (IC_{50} = 149 μ M) and ADP (IC_{50} = 218 μ M).

Figure 1 The structures of compound 1.

m-Hydroquinone

Six hydroquinone constituents, resveratrol (**2**), (+)-catechin (**3**), (-)-catechin (**4**), (+)-epicatechin (**5**), (-)-epicatechin (**6**) and resorcinol (**7**), were isolated from the red wine in 2004 (Figure 2).^[35,36] All *m*-hydroquinone compounds had significant inhibition on peroxidase and cyclooxygenase reactions of COX-1. COX-1 exhibited a mechanism for antiplatelet agents. Compound **5** owns the strongest inhibition on peroxidase and cyclooxygenase reactions of COX-1 (IC_{50} = 2.0 and 12.2 μ M). Hence, they offer a wider pattern on the studies of antiplatelet field.

Maltol

In 2007, maltol 3-O- β -glucopyranoside **8** was isolated from Bark of *Evodiopanax innovans* (Araliaceae).^[37] The results indicated that it inhibited 50% platelet aggregation induced by collagen, ADP, and thrombin. As a result, maltol 3-O- β -glucopyranoside is a significant bioactive substance.

Figure 2 The structures of compound 2–7.

Polyphenols

Seven polyphenols, vitisinols C **9**, vitisinols D **10**, (-)-viniferol **11**,^[38] ampelopsin C **12**,^[39] miyabenol A **13**,^[40] (+)-vitisin A **14**,^[41] and (+)-vitisin C **15**^[72] were isolated from the dried roots of *Vitis thunbergii* in 2004 (Figure 3).^[42] All of the compounds had inhibitions on the platelet aggregation induced by AA and 9,11-dideoxy-11*R*,9*R*-epoxy-methanoprostaglandin $F_{2\alpha}$ (U46619, TXA_2 analogous). Huang *et al.* revealed that (+)-vitisin C **15** had the strongest inhibition on the platelet aggregation induced by AA (IC_{50} = 5.7 μ M), and (-)-viniferol **11** had the strongest inhibition on the platelet aggregation induced by U46619 (IC_{50} = 3.1 μ M).

Figure 3 The structures of compound 8–14.

Six tannin compounds-polyphenol, Corilagin **16**, penta-O-galloyl- β -glucoside **17**,^[43] pedunculagin **18**,^[44] tellimagrandin II **19**,^[44] casuarinin **20**^[44,45] and 5-desgalloylstachyurin **21**^[46] were naturally occurred (Figure 4). Corilagin **16** was isolated from *Phyllanthus urinaria*. It was found to be a potent fibrinolytic inhibitor^[47] in 2003. Corilagin decreased PAI-1 activity^[48] and

enhanced t-PA activity both in vitro and in vivo (IC_{50} = 39.7 mg/kg).^[49] Other five compounds were isolated from the plant of *Geum japonicum* in 1998.^[50] Among of them, compound **17** showed the most significant effect on prolonging the clotting times of rabbit plasma. By their effects on proteolytic activity of thrombin tested, compound **19** showed the most potent activity (IC_{50} = 0.070 μ M).

Phenolic acids

Tanshen is listed in the Chinese Pharmacopoeia and largely used in Chinese traditional treatment.^[51] Few phenolic acids are isolated from Tanshen with anticoagulant and antiplatelet aggregation activities.^[52] Salvianolic acid A **22** exhibited strong anticoagulant activities.^[53] Fan *et al.*^[54] revealed that Salvianolic acid A **22** had no effect coagulation parameter in rats. It was approved that salvianolic acid A **22** could inhibit platelet aggregation induced by ADP without affecting coagulation system. In the human platelet aggregation assay, salvianolic acid A **22** had a potent inhibition on platelet aggregation induced by ADP with IC_{50} of 38.6 μ g/mL.

Figure 4 The structures of compound 15–22.

Another phenolic acid, Rosmarinic acid, showed a mild antithrombotic effect.^[55] In 1993, Zou *et al.*^[56] revealed that Rosmarinic acid **23** could inhibit the thrombosis by 41.9% and 54.8% on the concentration of the dosages of 50 and 100

mg/kg. Meanwhile, it could also inhibit the platelet aggregation induced by collage 30.4% and 46.4% on the concentration of the dosages of 100 and 150 mg/kg.

Phloroglucinols

Three phloroglucinol dimers, sideroxylonals A (**24**), sideroxylonal B (**25**) and Sideroxylonal C (**26**), were isolated from the flowers of *Eucalyptus albens*^[57] in 1998 (Figure 5). The sideroxylonals A–C (**24–26**) test showed the inhibition of PAI-1 (IC_{50} = 3.3, 5.3 and 4.7 μ M, respectively). Other phloroglucinols with PAI-1 activities, euglobal IA2 (**27**),^[57] euglobal IIC (**28**)^[58] and robustadial A (**29**)^[59] (IC_{50} = 138, 700 and 152 μ M, respectively), were also isolated.

Others

There were other works on phenol compounds. In 1994, two phenol compounds, moscatilin **30** and moscatin **31**, were isolated from the stem of *Dendrobium Idigesii*,^[60] exhibiting strong inhibition of platelet aggregations. Compound **29** was acetylated with Ac_2O to achieve compound **32**. Compounds **30–32** showed the strong inhibition of platelet aggregations induced by AA (IC_{50} = 61.8, 37.2 and 11.2 μ M, respectively). Compound **32** had a stronger activity than the other two compounds. Therefore, the natural products can act as good pro-drugs for inhibition of platelet aggregations. In 1995, a novel phenolic imperanene **33** was isolated from *Imperata cylindrica*^[61] and it could inhibit at 6×10^{-4} M against rabbit platelet aggregation induced by thrombin.

completely. Dong *et al.*^[96] reported a curcumin derivative isolated from the root of gingers, hexahydrocurcumin (**37**), (5*S*)-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl) heptan-3-one. The platelet-rich human blood was tested to declare the antiplatelet aggregation. Hexahydrocurcumin was indicated to be a potent antiplatelet aggregation agent by experiment results.

Conclusions

This review summarized the small-molecule phenols antithrombotic active inhibitors. Phenols were characterized in phenolic aglycon, *m*-hydroquinone, maltol, polyphenols, phenolic acids, phloroglucinols. Their structural characteristics and antithrombotic properties (antiplatelet and anticoagulant therapies) were mainly discussed, which will provide valuable information for understanding the progress of antithrombotic activity investigation and developing new antithrombotic therapeutic agents.

Presently, due to drug high rate of bleeding, short half-life, and allergic reactions side-effects of current antithrombotic drugs, the search for novel drugs is mandatory. Therefore, many researchers pay more attention to small-molecule derived from natural resources.

Because of structural specificity, high activity and low toxicity of the natural products, they have been used as lead compounds for antithrombotic agents. Undoubtedly, natural products need to be investigated in more detail to obtain mechanistically and structurally novel and more potent derivatives and to explore their potential as novel adjuncts to established thrombosis disease.

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Figure 5 The structures of compound 23–37.

In 2002, few phenols were isolated including gemichalcone A (**34**), gemichalcone B (**35**) and cycloartocarpin (**36**).^[62] Compound **34** exhibited complete inhibition of platelet aggregation induced by AA. Compound **35** also showed significant antiplatelet aggregation activity. Meanwhile, compound **36** showed the inhibition toward AA and collagen

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