Natural Products Phenols as Novel Antithrombotic Agents

Wenjing Zhou* and Ruihua Guo*a,b,c

* College of Food Science and Technology, Shanghai Ocean University, Shanghai 201306, China
b Shanghai Engineering Research Center of Aquatic-Product Processing & Preservation, Shanghai 201306, China
c National Experimental Teaching Demonstration Center for Food Science and Engineering, Shanghai Ocean University, Shanghai 201306, China

Email: rhguo@shou.edu.cn (R. G.)

Introduction

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

Phenolic aglycon

In 1997, a phenolic aglycon, 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 (IC50 = 69 μM), adrenalin (IC50 = 102 μM), arachidonic acid (IC50 = 149 μM) and ADP (IC50 = 218 μM).

![Figure 1 The structures of compound 1.](image)

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 (IC50 = 2.0 and 12.2 μM). Hence, they offer a wider pattern on the studies of antiplatelet field.

Maltol

In 2007, maltol 3-O-β-gluco pyranoside 8 was isolated from Bark of Evodia triphila (Rutaceae).[37] The results indicated that it inhibited 50% platelet aggregation induced by collagen, ADP, and thrombin. As a result, maltol 3-O-β-gluco pyranoside is a significant bioactive substance.

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]
Minireview

(-)-viniferal inhibitor Phyllanthus urinaria. It was found to be a potent fibrinolytic naturally occurred (Figure 4). Corilagin compounds had inhibitions on the platelet aggregation induced (+)-vitisin A aggregation induced by AA (IC50 = 3.1 μM). Six tannin compounds-polyphenol, Corilagin C 9, vitisinols D 10, (-)-viniferal 11[38] ampelopsin C 12,[39] miyabenol A 13[40] (+)-vitisin A 14[41] and (+)-vitisin C 15[42] were isolated from the dried roots of Vitis thunbergii in 2004 (Figure 3). All of the compounds had inhibitions on the platelet aggregation induced by AA and 9,11-dioexy-11R,9R-epoxy-methanoprostaglandin F2α (U46619, TXA2 analogous). Huang et al. revealed that (+)-vitisin C 15 had the strongest inhibition on the platelet aggregation induced by AA (IC50 = 5.7 μM), and (-)-viniferal 11 had the strongest inhibition on the platelet aggregation induced by U46619 (IC50 = 3.1 μM).

Polyphenols

Seven polyphenols, vitisinols C 9, vitisinols D 10, (-)-viniferal 11[38] ampelopsin C 12,[39] miyabenol A 13[40] (+)-vitisin A 14[41] and (+)-vitisin C 15[42] 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-dioexy-11R,9R-epoxy-methanoprostaglandin F2α (U46619, TXA2 analogous). Huang et al. revealed that (+)-vitisin C 15 had the strongest inhibition on the platelet aggregation induced by AA (IC50 = 5.7 μM), and (-)-viniferal 11 had the strongest inhibition on the platelet aggregation induced by U46619 (IC50 = 3.1 μM).

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 on platelet aggregation induced by ADP without affecting 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 IC50 of 38.6 μg/mL.

Figure 2  The structures of compound 2–7.

Six tannin compounds-polyphenol, Corilagin 16, penta-O-galloyl-β-glucoside 17[43] pedunculagin 18,[43] tellimagrandin II 19[44] casuariin 20[45,46] 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 (IC50 = 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 (IC50 = 0.070 μM).

Figure 3  The structures of compound 8–14.

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 collagen 30.4% and 46.4% on the concentration of the dosages of 100 and 150 mg/kg.

**Phloroglucinols**

Three phloroglucinol dimers, sideroxylonal A (24), sideroxynal B (25) and Sideroxynal C (26), were isolated from the flowers of Eucalyptus albens in 1998 (Figure 5). The sideroxylonal A–C (24–26) test showed the inhibition of PAI-1 (IC50 = 3.3, 5.3 and 4.7 μM, respectively). Other phloroglucinols with PAI-1 activities, euglobal IA2 (27), euglobal IIC (28) and robustadial A (29) (IC50 = 138, 700 and 152 μM, 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 lidgesii, exhibiting strong inhibition of platelet aggregations. Compound 29 was acetylated with Ac2O to achieve compound 32. Compounds 30–32 showed the strong inhibition of platelet aggregations induced by AA (IC50 = 61.8, 37.2 and 11.2 μM, respectively). Compound 32 had a stronger activity than the other two compounds. Therefore, the natural products can act as good prodrugs for inhibition of platelet aggregations. In 1995, a novel phenolic imperanene 33 was isolated from Imperata cylindrica and it could inhibit at 6 × 10−6 M against rabbit platelet aggregation induced by thrombin.

![Figure 5](image-url) The structures of compound 23–37.

In 2002, few phenols were isolated including gemichalcone A (34), gemichalcone B (35) and cycloartocarpin (36). 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 completely. Dong et al. reported a curcumin derivative isolated from the root of gingers, hexahydrocurcumin (37), (5S)-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, phonic 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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