Flavonoids with Antithrombotic Activities: a Review

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Thrombus is a severe health problem all over the world, especially in developing countries. However, there is still no satisfactory antithrombotic therapeutic strategy. Currently, the clinical antithrombotic drugs suffer from several drawbacks such as high rate of bleedings and short half-life, causing allergic reactions or complications, *etc.* In recent years, small-molecule compounds isolated from natural products with antithrombotic activities become a hot issue in the field of drug research. In this review, we will focus on representative naturally occurring small molecule flavonoids with antithrombotic potency and potential for future therapeutic regimens to combat thrombosis disease.

Keywords thrombosis, small-molecule, antithrombotic activities, natural products, flavonoids

Introduction

The rapid development of economy improves the living conditions of human being, increases the average life expectancy, and changes the living habits.^[1,2] However, some serious diseases such as obesity and related diseases are threatening the whole society.^[2] Among them, thrombotic disease is the main factor of morbidity and mortality in the modern era,^[3-5] causing serious damages to human health and heavy economic burden for patients' family possibly.^[6-8] An estimated one in four people dies from causes related to thrombosis worldwide. Therefore, it is urgent to develop antithrombotic drugs with high efficiency, low toxicity, and low cost.^[9]

Antithrombotic drugs, including anticoagulant drugs and antiplatelet drugs,^[10,11] can dissolve fibrin clot or activate plasminogen into plasmin to cure thrombosis disease.^[12] Heparin (ordinary heparin, low molecular weight heparin) and fondaparinux, and oral adjusted-dose vitamin K antagonists,^[13] aspirin, adenosine monophosphate receptor antagonist and platelet membrane glycoprotein antibody antagonist^[14] have been approved by the FDA as treatments for thrombus. However, thrombolytic drugs aren't satisfactory^[15,16] due to several disadvantages^[17] such as too long half-life or too short-life, severe anaphylactic reaction, and lack of specificity.^[18] Especially, some drugs can cause complications^[19] with hemorrhage and limited therapeutic range.^[20-22] Only 1.8%–8.9% patients were treated by t-PA-based therapy.^[23,24] For example, heparin and vitamin K antagonists suffer from several drawbacks: heparins are involved in parenteral administration, vitamin K antagonists need frequent monitoring and dose adjustments, interactions with several medications, and dietary restrictions.^[25] Hence, researchers are searching for small molecules with antithrombotic activities.^[26-35]

Natural products are divided into diverse chemical compounds isolated from varied biological sources such as plants, animals, marine organisms, microorganisms, minerals, and organic matters.^[36-39] In recent years, the research on natural products becomes a hot issue in drug research. The drug discovery from natural products possesses several advantages such as timeliness, faster and better methods for bioassay screening, and compound isolation.^[40] Currently, naturally occurring flavonoids with antithrombotic activities have been identified

and appeared in the recent literature or patents. 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 summarized flavonoids from natural products with antithrombotic activities.

Flavonoids

Most flavonoids are isolated from natural materials with various skeletons such as flavonols, flavone aglycon, chalcones, prenylflavones, biflavones, *etc.* Flavonoids are reported with strong antioxidant activity,^[41] reducing blood-sugar effects,^[42] and improving blood circulation effects,^[43] decreasing cholesterol and benefit cardiovascular disease.^[44] Moreover, they exhibit fibrinolytic activities, anticoagulant activities, and antiplatelet activities.

Flavonols

Flavonol kaempferol (1) isolated from fruits of *Lagenaria siceraria*^[45] exhibited fibrinolytic activities on the fibrinolysis assay system (dissolve the plasma clot by 77.37%) in Figure 1, suggesting that kaempferol be a potent aspect for further fibrinolytic activities research on plasma clots *in vitro*.

Flavone aglycon

Luteolin (2) with flavones-C-glycoside was isolated from *Forosman Gentianaceous* plants.^[46] Luteolin displayed a potent platelet aggregation effect on platelet aggregation induced by arachidonic acid (AA) and collagen. In addition, it had also a significant effect on platelet aggregation induced by thrombin and platelet-activating factor (PAF) (IC₅₀=43.5 μM). Afifi^[47,48] reported luteolin possessed strong inhibition on collagen-induced platelet aggregation (IC₅₀=0.034 mg/mL). Simultaneously, luteolin-7-O-glucoside (3) and vitexin (4) presented strong inhibition of collagen-induced platelet aggregation (IC₅₀ of 0.046 and 0.021 mg/mL). Luteolin-7-O-glucoside belongs to flavones-O-glucoside, and vitexin belongs to flavones-C-glycoside.

6-Hydroxykaempferol 3,6,7-tri-O-glucoside (5) and 6-hydroxykaempferol 3,6-di-O-glucoside (6)^[49] extracted from the flower of

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Carthamus tinctorius L. exhibited significantly inhibitory potency on the collagen-induced platelet aggregation by testing the inhibition of platelet aggregation. The inhibition of compounds **5** and **6** were 3.9%–10.0% and 4.3%–19.3% at the concentration of 13–200 µg/mL, respectively. In addition, they also showed weak inhibition on the platelet aggregation induced by adenosine 5'-diphosphate (ADP). At the concentration of 200 µg/mL, the inhibition of compounds **5** and **6** were 2.7% and 0.4 %, respectively.

Five flavonoid glycosides, kaempferol 3-*O*- α -L-(2''*E*,4''*E*-di-*p*-coumaroyl)-rhamnoside (**7**), kaempferol 3-*O*- α -L-(3''*E*,4''*E*-di-*p*-coumaroyl)-rhamnoside (**8**), kaempferol 3-*O*- α -L-(4''-*E*-*p*-coumaroyl)-rhamnoside (**9**), afzelin (**10**) and quercitrin (**11**) were isolated from *Trogopterus faeces*^[50] and evaluated for antithrombotic activities by the thrombin time (TT) method assay. The lg(TT) prolongation (%) of compounds **7–11** increased from 1.05 to 2.31 μ g/mL linearly with the increase of the dosage from 7 to 70 μ g/mL. Among them, compounds **7–9** showed the significant antithrombotic activity. Two flavones diosmetin apiosyl-glucosides 5,7,4'-trihydroxy-falvone (apigenin) (**12**) (IC₅₀=0.036 mg/mL) and apigenin 7-*O*-glucoside (cosmosiin) (**13**) (IC₅₀=0.18 mg/mL) with antiplatelet aggregation activity were discovered from the aqueous extract of *Petroselinum crispum* (Mill) flat leaves specimens.^[51–53]

Figure 1 The structures of compounds **1–13**.

Chalcones

Ju *et al.*^[54] discovered two chalcones, 4-hydroxyderricin (**14**) and xanthoangelol (**15**) from *Ashitaba* roots (*Angelica keiskei* Koidz.) in Figure 2. Compounds **14** and **15** possessed inhibition of platelet aggregation induced by collagen and by PAF (IC₅₀=41.9, 46.1 μM; 41.9, 46.1 μM, respectively). Especially for xanthoangelol (**15**) could also inhibit the platelet aggregation induced by collagen and by PAF (IC₅₀=41.9 and 46.1 μM, respectively). As a result, the two compounds may be potential antithrombotic agents in the future.

Prenylflavones

In 1992, six prenylflavones from *Artocarpw commun*^[55-57] with the antiplatelet aggregation, cyclomorusin (**16**), artomunoxanthone (**17**), cyclomulberrin (**18**), dihydroisocy-cloartomunin (**19**), cyciocommunoi (**20**), and cyclocommunin (**21**) were discovered.^[58] Among the compounds, cyclomorusin (**16**) and artomunoxanthone (**17**) exhibited strongly inhibitory the platelet aggregation induced by PAF (IC₅₀=8.0 and 6.5 μM). Cyclomulberrin (**18**), dihydroisocycloar-tomunin (**19**), cyciocommunoi (**20**), and cyclocommunin (**21**) possessed inhibitory the platelet aggregation induced by AA and collagen, of which cyclocommunin (**21**) was the most potent compound on the antiplatelet activity induced by AA and collagen with IC₅₀ value 12.5 μM and 14.4 μM, respectively.

Two prenylflavones with the antiplatelet aggregation activities, yinyanghuo A (**22**) and yinyanghuo B (**23**), were isolated from the aerial part of *Epimedium sagittatum*,^[59] exhibiting significant inhibition of antiplatelet aggregation activity induced by AA ($IC_{50}=7.14$

and 1.67 μM). Cycloartocarpin A (**24**), cycloheterophyllin (**25**), broussoschalcone A (**26**), kazinol A (**27**), broussaurone A (**28**), and brousoflavonol F (**29**) showed inhibitory platelet aggregation induced by AA with IC_{50} values of 18.5, 10.9, 6.8, 11.4, 15.4 and 16.9 μM , respectively. Meanwhile, compounds **24**, **26**, **27** could inhibit the platelet aggregation induced by collagen strongly (IC_{50} of 23.7, 22.4 and 20.7 μM , respectively). Compound **27** exhibited the inhibition of platelet aggregation induced by PAF (IC_{50} =54.6 μM).

Figure 2 The structures of compounds **14**–**29**.

Biflavones

Two biflavones, hinokiflavone (**30**) and amentoflavone (**31**), were isolated from *Troglodytes faeces*^[49] and tested antithrombotic activity by the TT assay in Figure 3. The results showed that the lg(TT) prolongation (%) of compounds **30** and **31** were 1.08 and 1.09 with the same dosage of 50 µg/mL.

Others

Except for the above mentioned classifications, more flavonoides have been evaluated for their antithrombotic activity. Five flavonoides **32–36** with inhibition of the PAI-1 activities^[61] were discovered by the experiment on t-PA and PAI-1 production in cultured human umbilical vein endothelial cells (HUVECs). The results indicated that baicalein (**32**) inhibited the decrease of t-PA and the increase of PAI-1 activity efficiently ($IC_{50}=3.7\text{ }\mu\text{M}$). Besides this, wogonin (**33**), oroxylin A (**34**), skullcapflavone II (**35**), and 2',5',5',7-tetrahydroxy-6',8-dimethoxyflavone (**36**) had a relatively weaker inhibition for PAI-1 activity ($IC_{50}=105, 61, 110$, and $88\text{ }\mu\text{M}$, respectively). The results indicated that baicalein had potentials for the treatment of thrombus.

Tsai *et al.*^[62] reported isobavachalcone (**37**) and neobavaisoflavone (**38**) from the seeds of *Psoralea corylifolia* L., exhibiting inhibitory potency on platelet aggregation. Isobavachalcone (**37**) could inhibit the aggregation induced by arachidonic acid (AA) (IC₅₀=0.5 μM). Neobavaisoflavone (**38**) could inhibit the aggregation induced by AA and platelet-activating factor (IC₅₀=7.8 and 2.5 μM, respectively). Compared to the aspirin with 32.7 μM, neobavaisoflavone (**38**) with 7.8 μM exhibited significantly inhibitory potency on platelet aggregation. Baicalein (**37**) (IC₅₀=3.7 μM) inhibited the reduction of the t-PA activity and the elevation of the PAI-1 activity significantly. Furthermore, wogonin (**39**), oroxylin A (**40**), skullcapflavone II (**41**), and 2',5,5',7-tetrahydroxy-6',8-dimethoxyflavone (**42**) also showed inhibition of the increasing of PAI-1 activity induced by trypsin (IC₅₀=105, 61, 110 and 88 μM, respectively).

Ayanin (**43**) isolated from the root bark of *Melicope semecarpifolia*^[63] showed a weak inhibition of platelet aggregation induced by thrombin, collagen and PAF. The aggregation of aggregation induced by AA was 13.3%.

Figure 3 The structures of compounds 30–41.

Conclusions

This review summarized the small-molecule flavonoids antithrombotic active inhibitors. Flavonoids were characterized in flavonols, flavone aglycon, chalcones, prenylflavones, biflavones. 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.

Except these flavonoids as antithrombotic active inhibitors, some newly small molecular through fibrinolysis brings into play a similar role about thrombolysis. The mechanism of thrombolysis associated with (1) plasminogen regulator pathway; (2) single chain urokinase type plasminogen activator (sc-uPA) regulator pathway; (3) plasminogen activator inhibitor 1 (PAI-1) inhibitor pathway and (4) plasmin regulator pathway based on fibrinolytic features of the newly small molecular. The newly small molecules described act by utilizing or modulating such embedded mechanisms and do not affect the catalytic activity of the mature enzymes. These pathways whether discriminate flavonoids as zymogen modulators from inhibitors or activators that simply act on mature enzymes or enzyme, particularly those in the coagulation and fibrinolytic systems? Whether any other ways of mechanism? These are important attention in a future.

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References

- [1] Nicholson, C. D.; Lensing, A. W. *Expert Opin. Investig. Drugs* **2001**, *10*, 785.
- [2] Lee, Y. K.; Player, M. R. *Med. Res. Rev.* **2011**, *31*, 202.
- [3] Kong, Y.; Wang, Y.; Yang, W.; Xie, Z.; Li, Z. *J. Pharmacol. Sci.* **2015**, *127*, 462.
- [4] Mohammad H. N.; Abbas, M.; Mohammad Reza, O. *J. Hypertens.* **2000**, *18*, 1705.
- [5] Smith, S. C.; Rod, J.; Pearson, T. A.; Valentin, F.; Salim, Y.; Ole, F.; Wood, D. A.; Michael, A.; John, H.; Philip, H. *Circulation* **2004**, *109*, 3112.
- [6] Mozaffarian, D.; Benjamin, E. J.; Go, A. S.; Arnett, D. K.; Blaha, M. J.; Cushman, M.; Das, S. R.; de Ferranti, S.; Després, J. P.; Fullerton, H. J. *Circulation* **2016**, *131*, 29.
- [7] Beaglehole, R.; Bonita, R. *Lancet* **2008**, *372*, 1988.
- [8] Mathers, C. D.; Dejan, L. *Plos Med.* **2006**, *3*, 2011.
- [9] Ton, L.; Kamphuisen, P. W.; Northup, P. G.; Porte, R. J. *J. Hepatol.* **2013**, *59*, 358.
- [10] Pranav, S.; Bindra, V. K. *Indian J. Crit. Care Med.* **2010**, *14*, 188.
- [11] Mega, J. L.; Simon, T. P. *Lancet* **2015**, *386*, 281.
- [12] Alessi, M. C.; Juhan-Vague, I. *La Revue Du Praticien* **1999**, *49*, 1654.
- [13] Quinlan, D. J.; Eriksson, B. I. *Best Pract. Res. Clin. Haematol.* **2013**, *26*, 171.
- [14] Wei, X.; Yin, R. X.; Cardiology, D. O. *Med. Recapitulate* **2014**, *20*, 4520.
- [15] Xavier, A. R.; Siddiqui, A. M.; Kirmani, J. F.; Hanel, R. A.; Yahia, A. M.; Qureshi, A. I. *CNS Drugs* **2003**, *17*, 213.
- [16] Gross, P. L.; Weitz, J. I. *Clin. Pharmacol. Ther.* **2009**, *86*, 139.
- [17] Johannes, R.; Katus, H. A. *Expert Opin. Investig. Drugs* **2003**, *12*, 781.
- [18] Hsieh, F.; Hsu, C.; Huang, H.; Shiau, C. *FEBS J.* **2005**, *272*, 407.
- [19] Balasubramaniam, K.; Viswanathan, G. N.; Marshall, S. M.; Zaman, A. G. *Cardiol. Res. Pract.* **2012**, *2012*, 1.
- [20] Lees, K. R.; Bluhmki, E.; Kummer, R. V.; Brott, T. G.; Toni, D.; Grotta, J. C.; Albers, G. W.; Kaste, M.; Marler, J. R.; Hamilton, S. A. *Lancet* **2010**, *375*, 1695.
- [21] Peter, S.; Wardlaw, J. M.; Lindley, R. I.; Martin, D.; Geoff, C.; Gordon, M.; Karen, I.; Graham, V.; Anna, C.; Adam, K. *Lancet* **2012**, *379*, 2352.
- [22] Wardlaw, J. M.; Murray, V.; Berge, E.; Zoppo, G.; Sandercock, P.; Lindley, R. L.; Cohen, G. *Lancet* **2012**, *379*, 2364.
- [23] Dawn, K.; Lindsell, C. J.; Lawrence, B.; Walter, K.; Broderick, J. P. *Stroke* **2008**, *39*, 924.
- [24] Nadeau, J. O.; Shi, S. J.; Kapral, M. K.; Richards, J. A.; Silver, F. L.; Hill, M. D. *Can. J. Neurol. Sci.* **2005**, *32*, 433.
- [25] Arcelus, J. I.; Pere, D.; Del Carmen, F. C. M.; Ricardo, G.; David, J.; Sonia, J.; Lozano, F. S.; Manel, M.; Nieto, J. A.; Páramo, J. A. *Clin. Appl. Thromb.-Hemost.* **2014**, *21*, 297.
- [26] Friederich, P. W.; Levi, M.; Biemond, B. J.; Charlton, P.; Templeton, D.; Zonneveld, A. J.; Van, Bevan, P.; Pannekoek, H.; Cate, J. W. *Circulation* **1997**, *96*, 916.
- [27] Qiao, J. X.; Wang, T. C.; Réjean, R.; Carl, T.; Alexandre, L. H.; Schumacher, W. A.; Spronk, S. A.; Sheldon, H.; Gilles, B.; John, L. J. *Med. Chem.* **2013**, *56*, 9275.
- [28] Massimo, C.; Savitri, K.; Das, C. M.; Reuben, J. M.; William, S.; Jamileh, N.; Frederick, B.; Gascoyne, P. R. *Circ. Res.* **2012**, *111*, 920.
- [29] Louisa, D.; Sim, D. S.; Dilks, J. R.; Price, B.; Sarah, B.; Denker, B. M.; Georgios, K.; Athan, K.; Robert, F. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 2951.
- [30] Bullingham, A.; Strunin, L. *British J. Anaesthesia* **2009**, *339*, 622.
- [31] Abboud, M.; Needle, S.; Burns-Kurtis, C.; Valocik, R. P.; Amour, A.; Chan, C.; Brown, D.; Chaudry, L.; Zhou, P.; Patikis, A. *J. Cardiovascular Pharm.* **2008**, *52*, 66.
- [32] Eriksson, B. I.; Dahl, O. E.; Lassen, M. R.; Ward, D. P.; Rothlein, R.;

- Davis, G.; Turpie, A. G. *J. Throm. Haemost.* **2008**, *6*, 457.
- [33] Kolesnikov, A.; Rai, R.; Mordenti, J.; Liu, L.; Torkelson, S.; Shrader, W.; Leahy, E.; Hu, H.; Gjerstad, E.; Janc, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2243.
- [34] Srivastava, S.; Goswami, L. N.; Dikshit, D. K. *Med. Res. Rev.* **2005**, *25*, 66.
- [35] Rai, R.; Kolesnikov, A.; Yong, L.; Young, W. B.; Leahy, E.; Sprengeler, P. A.; Verner, E.; Shrader, W. D.; Burgess, H. J.; Sangalang, J. C. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1797.
- [36] Grover, J. K.; Yadav, S.; Vats, V. *J. Ethnopharmacol.* **2002**, *81*, 81.
- [37] Hansen, E.; Andersen, J. H. *Curr. Pharm. Biotechnol.* **2015**, *17*, 71.
- [38] Orlikova, B.; Legrand, N.; Panning, J.; Dicato, M.; Diederich, M. *Cancer Treat. Res.* **2014**, *159*, 123.
- [39] Sharma, S. B.; Gupta, R. *Mini Rev. Med. Chem.* **2015**, *15*, 52.
- [40] Tian, L.; Teng, X.; Zhong, C. *Gen. Chem.* **2015**, *1*, 22.
- [41] Valko, M.; Rhodes, C. J.; Moncol, J.; Izakovic, M.; Mazur, M. *Chem. Biol. Interact.* **2006**, *160*, 1.
- [42] Unnikrishnan, M. K.; Veerapur, V.; Nayak, Y.; Mudgal, P. P.; Mathew, G. *Polyphenols in Human Health & Disease* **2013**, *1*, 143.
- [43] Fan, L. L.; Zeng, G. Y.; Zhou, Y. P.; Zhang, L. Y.; Cheng, Y. S. *Chin. Med. J.* **1982**, *95*, 145.
- [44] Boyer, J.; Liu, R. H. *Nutr. J.* **2004**, *3*, 1.
- [45] Rajput, M. S.; Vineet, M.; Purti, A.; Chandrawanshi, H. K.; Urmila, P. *Nat. Prod. Res.* **2011**, *25*, 1870.
- [46] Lin, C. N.; Kuo, S. H.; Chung, M. I.; Ko, F. N.; Teng, C. M. *J. Nat. Prod.* **1997**, *60*, 851.
- [47] Afifi, F. U. *Nat. Prod. Res.* **2011**, *26*, 878.
- [48] Afifi, F.; Shervington, A.; Darwish, R. *Acta technologiae et legis medicamenti* **1997**, *8*, 105.
- [49] Iizuka, T.; Moriyama, N. H.; Taniguchi, A.; Hoshi, K. *Nat. Med.* **2005**, *59*, 241.
- [50] Nian, Y. Y.; Wei, W. T.; Jin, A. D. *Nat. Prod. Res.* **2010**, *24*, 1843.
- [51] Chaves, D. S.; Frattani, F. S.; Assafim, M.; Almeida, A. P.; Zingali, R. B.; Costa, S. S. *Nat. Prod. Commun.* **2011**, *6*, 961.
- [52] Beier, R. C.; Ivie, G. W.; Oertli, E. H. *Phytochemistry* **1994**, *36*, 869.
- [53] Yoshikawa, M.; Uemura, T.; Shimoda, H.; Kishi, A.; Kawahara, Y.; Matsuda, H. *Chem. Pharm. Bull.* **2000**, *48*, 1039.
- [54] Ju, S. D.; Oak, P. Y.; Cheng, G. Y.; Sung, E. L.; Young, H. P. *Nat. Prod. Res.* **2014**, *28*, 2312.
- [55] Lin, C. N.; Wen, L. S. *Phytochemistry* **1991**, *30*, 1669.
- [56] Shieh, W. L.; Lin, C. N. *Phytochemistry* **1992**, *31*, 364.
- [57] Chun, N. L.; Wen, L. S. *Phytochemistry* **1992**, *31*, 2922.
- [58] Lin, C. N.; Shieh, W. L.; Ko, F. N.; Teng, C. M. *Biochem. Pharm.* **1993**, *45*, 509.
- [59] Chun, N. L.; Wen, L. S. *Phytochemistry* **1992**, *31*, 2922.
- [60] Chen, C. C.; Huang, Y. L.; Sun, C. M.; Shen, C. C. *J. Nat. Prod.* **1996**, *59*, 412.
- [61] Kimura, Y.; Okuda, H.; Ogita, Z. *J. Nat. Prod.* **1997**, *60*, 598.
- [62] Tsai, W. J.; Hsin, W. C.; Chen, C. C. *J. Nat. Prod.* **1996**, *59*, 671.
- [63] Chen, I. S.; Chen, H. F.; Cheng, M. J.; Chang, Y. L.; Teng, C. M.; Tsutomu, I.; Chen, J. J.; Tsai, I. L. *J. Nat. Prod.* **2001**, *64*, 1143.