A REVIEW ON THE ROLE OF QUINONES IN CARDIOVASCULAR DISEASE VIA INHIBITING NLRP3 INFLAMMASOME

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Abstract: Cardiovascular disease has caused huge health and economic burden all over the world. NLRP3 inflammasome-induced inflammatory cascade leading to pyroptosis is one of the hot spots in the pathogenesis of cardiovascular disease. Therefore, it is very important to inhibit the activity of NLRP3 inflammasome and search for natural active compounds for the prevention and treatment of cardiovascular disease. Quinones have good myocardial protection, and their function is closely related to anti-inflammatory and anti-oxidation. 9 natural quinones for the treatment of cardiovascular disease based on the inhibition of NLRP3 inflammasome were summarized and screened. Docking results showed cryptotanshinone had a better binding activity with NLRP3, which can provide theoretical support for finding novel NLRP3 inflammasome inhibitors or lead compounds in the future.

Keywords: quinones, cardiovascular diseases, molecular docking, NLRP3 inflammasome

Cardiovascular disease has caused huge health and economic burden all over the world. Among them, acute myocardial infarction (AMI) is a common phenomenon of coronary heart disease, which is considered to be the most serious public health problem in the world (1). Oxidative stress plays a key role in the pathogenesis of cardiovascular disease, characterized by excessive oxidative stress and inflammatory reaction (2).

The excessive production of free reactive oxygen species (ROS) will lead to the increase of the concentration of inflammatory cytokines. Studies have found that excessive ROS production leads to thioredoxin-interacting protein (TXNIP) dependent activation of NOD-like receptor (NLR) family, pyrin-domain containing 3 (NLRP3), and further causes inflammation (3, 4). NLRP3 inflammasome is a multi-component complex composed of NLRP3, apoptosis-associated speck-like protein (ASC), and inactive pro-caspase-1. After the formation of the NLRP3 inflammasome, pro-caspase-1 is transformed into its active form, cle-caspase-1, which stimulates the pro-inflammatory cytokine IL-1β And IL-18 (5, 6). The formation of NLRP3 inflammasome enhances the inflammatory response mediated injury, which is pyroptosis. Pyroptosis can cause cell swelling and extensive release of pro-inflammatory substances (7).

Quinones are widely distributed in bacteria, fungi, higher plants, and animals. Quinones are toxic intermediates, which can produce many hazardous effects in vivo, including acute cytotoxicity, immunotoxicity, and carcinogenesis. However, it was found that an appropriate amount of quinone compounds could play a role in preventing diseases, mainly by inducing detoxification enzymes, anti-proliferative, anti-inflammatory, anti-microbial, and antioxidant activities (8, 9). Therefore, a number of quinone compounds find use as drugs. There are many quinones with good myocardial protection, as this review of aloe-emodin, aloin, chrysophanol, emodin, and so on, has the effect of prevention and treatment.

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of cardiovascular disease, its mechanism of action is mainly related to anti-inflammatory and antioxidant effects.

In this review, we summarize the available evidence about the inhibitory potential of quinones on NLRP3 inflammasome activity in cardiovascular diseases. Molecular docking technology was used to screen quinones with cardiovascular protective effect and potential inhibition of NLRP3 inflammasome, which may aid in the development of novel strategies for the discovery of myocardial protective agents.

**Quinones**

**Aloe-emodin**

Aloe-emodin (molecular formula: C_{15}H_{10}O_{5}), a natural anthraquinone derivative, mainly exists in Chinese herbal medicines such as rhubarb, aloe vera, and *Polygonum multiflorum* has a variety of pharmacological effects, including antiviral, anti-inflammatory, antibacterial, neuroprotective, and cardioprotective activities (10, 11). Aloe-emodin can significantly reduce the area of myocardial infarction in mice with acute myocardial infarction, improve the damage of myocardial function, and reduce the inflammatory exudation of myocardial interstitial cells (12). Aloe-emodin can reduce the expression of myocardial pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and inhibit the upregulation of TLR4, IκB, p-p65 protein in vivo and in vitro, suggesting that the anti-inflammatory effect is related to the inhibition rate of TLR4/NF-κB signaling pathway (13). Aloe-emodin can inhibit the formation and activation of Ang II-induced NLRP3 inflammasome and significantly regulate NLRP3 inflammasome, which has potential therapeutic value in cardiovascular diseases (14).

**Aloin**

Aloin (molecular formula: C_{21}H_{22}O_{9}), a major anthraquinone glycoside compound extracted from Aloe species, with anti-proliferation, anti-cancer, anti-inflammatory, anti-oxidation, and other pharmacological activities (15, 16). Aloin can inhibit myocardial injury induced by DOX, improve ECG ST segment-height, and QT interval extension, which protected the heart against the lipid peroxidation, restore the level of antioxidant defense, reduce the levels of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6, and decrease CK-MB level, to achieve the anti-inflammatory effect (17, 18). Aloin can significantly inhibit LPS-induced inflammatory response, reduce the expression levels of NF-κB and NLRP3 inflammasome, and thus inhibit the activation of NLRP3 inflammasome and NF-κB signaling pathway (19).

**Chrysophanol**

Chrysophanol (molecular formula: C_{19}H_{20}O_{3}) is a natural anthraquinone compound, belongs to the anthraquinone family, is the main component of Rhubarb, is widely used in food and medicine field, has anti-platelet, anti-coagulation, anti-inflammation effects (20, 21). Chrysophanol can improve the abnormal structure and function of myocardial tissue in rats induced by ISO, improve cardiac function, and alleviate the pathological changes of the heart (22). Chrysophanol can also alleviate DOX-induced cardiac apoptosis, mitochondrial damage, and cardiac dysfunction (23). Chrysophanol may directly damage the formation of NLRP3 by inhibiting ASC or Caspase-1, which inhibit the NLRP3/Caspase-1 pathway (24).

**Cryptotanshinone**

Cryptotanshinone (molecular formula: C_{26}H_{24}O_{5}), a major component derived from Salvia miltiorrhiza Bunge, has been exerted anti-inflammatory, neuroprotective, cardioprotective activities (25, 26). Cryptotanshinone may significantly improve the cardiac function of model rats, reduce the production of collagen and inhibit the production of ROS in heart tissue, suggesting that cryptotanshinone can inhibit the cardiotoxicity caused by doxorubicin (27). Cryptotanshinone can significantly inhibit the inflammatory damage of Ang II-induced cardiomyocytes, and reduce the expression levels of TNF-α, IL-6, and other inflammatory factors, the mechanism may be related to the inhibition of NF-κB translocation to the nucleus (28). Cryptotanshinone can significantly reduce NLRP3 inflammasome mediated caspase-1 activation and IL-1β secretion, thereby reducing the NLRP3/Caspase-1 signaling pathway (29).

**Emodin**

Emodin (molecular formula: C_{15}H_{10}O_{6}) is an anthraquinone derivative extracted from *Rheum palmatum, Polygonum cuspidatum*, and *Polygonum multiflorum*, and exists in various herbal preparations. Emodin has a wide range of pharmacological effects, including anti-cancer, anti-inflammatory, antioxidant, and antibacterial activities, and can be used in the treatment of cardiovascular disease, cancer, diabetes, etc (30, 31). Emodin can significantly reduce serum LDH, thereby improving cardiac function and protecting the myocardium from I/R injury (32). Emodin may be related to the inhibition of miR-223 to alleviate LPS-induced inflammatory damage and inactivate the JNK signaling pathway (33). Emodin significantly inhibited the expression of TLR4, MyD88, Phospho-IκB, Phospho-NF-κB, and NLRP3 inflammasome in H/R cardiomyocytes.
by inhibiting the TLR4/MyD88/NF-κB/NLRP3 inflammasome pathway (34).

**Plumbagin**

Plumbagin (molecular formula: C$_{11}$H$_{8}$O$_{3}$) is a major bioactive compound found in *Plumbago indica* and *P. zeylanica*, which has many therapeutic effects and has great biological activity, such as anti-inflammatory, neuroprotective, cardioprotective, anticancer, and antimalarial properties (35, 36). Plumbagin has an obvious protective effect on DOX-induced heart tissue injury in rats, and also reduces the overexpression of inflammatory and apoptotic proteins in heart tissue, which can achieve anti-inflammatory and anti-apoptotic effects (37). Plumbagin can regulate the expression of NOX4 and down-regulate the NF-κB signaling pathway, thereby reducing the production of ROS and inhibiting the activation of NLRP3 inflammasomes (38).

**Rhein**

Rhein (molecular formula: C$_{15}$H$_{8}$O$_{6}$), the active component of rhubarb, has been shown to have multiple functions, such as antibacterial, antioxidant, anticancer, antiangiogenic, and anti-inflammatory effects (39, 40). Rhein protects H9c2 cardiomyocytes from hypoxia/reoxygenation-induced damage (41). Emodin can significantly inhibit LPS-stimulated inflammatory response, mainly by regulating the TLR4/NF-κB pathway and NLRP3 inflammasome to inhibit the expression of LPS-induced IL-1β and IL-6 (42). Rhein significantly decreased the expression of NLRP3 and IL-1β in LPS-induced RAW264.7 macrophages, suggesting that Rhein may exert anti-inflammatory effects by inhibiting the NLRP3 inflammasome pathway (43).

**Shikonin**

Shikonin (molecular formula: C$_{16}$H$_{16}$O$_{5}$), a natural naphthoquinone pigment purified from the root of lithospermum erythrorhizon (purple gromwell), has been identified as a multifunctional bioactive natural product with antioxidant and anti-inflammatory activities (44, 45). Shikonin significantly ameliorated heart function, decreased myocardial fibrosis, suppressed inflammation, and inhibited the TLR4/NF-κB pathway in mice induced by isoproterenol (46). Shionin could significantly increase cell viability, decrease LDH release, and inhibit H/ R-induced myocardial apoptosis (47). Shikonin could significantly up-regulate the expression of LPS-induced SIRT1 in heart tissue, and decrease the NLRP3, cleaved caspase-1, and caspase-1 activities, which means ameliorates LPS-induced cardiac dysfunction by inhibiting SIRT1-dependent activation of NLRP3 inflammasomes (48).

**Tanshinone IIA**

Tanshinone IIA (molecular formula: C$_{19}$H$_{18}$O$_{3}$) is the main pharmacologically active ingredient of Salvia miltiorrhiza, which has certain health care effects on patients with coronary heart disease (49, 50). Tanshinone IIA has a wide range of drug effects, such as the alleviation of myocardial lipid metabolism disorders and anti-inflammatory effects (51). Tanshinone IIA can increase coronary artery blood flow and improve myocardial metabolic disorders caused by hypoxia, thus improving myocardial hypoxia tolerance, reducing myocardial infarction area, and improving myocardial contractility (52, 53). Tanshinone IIA can improve myocardial inflammation and lipid accumulation by inhibiting cardiac ROS overproduction and TXNIP overexpression and blocking the activation of NLRP3 inflammasome in the heart (54) (Figure 1).

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Figure 1. The chemical structures of quinones.
Molecular docking

CB-DOCK was used to predict protein cavities, calculate the center and size of the cavities, and finally conduct molecular docking between ligand and receptor. PDB formats of NLRP3 (PDB Code: 6NPY) (55) and quinones in SDF format were input to CB-Dock for molecular docking (56). The style of ligand was set as “spacefill”, and the receptor was set as “cartoon”. The lower the binding energy (VINA score), that means the stronger the binding ability between ligand and target. Molecular docking showed that the top 20% of flavonoids in VINA scores are Cryptotanshinone and Tanshinone IIA. The results suggested that Cryptotanshinone is the most potent NLRP3 inhibitor (Table 1 and Figure 2).

CONCLUSIONS

In this review, quinones with myocardial protection and NLRP3 inhibitory activity were summarized and screened. The results of molecular docking showed that cryptotanshinone had a better binding activity with NLRP3. This is related to the previously reported cryptotanshinone has good myocardial protection and can significantly inhibit the activity of NLRP3 inflammasome. Therefore, cryptotanshinone is likely to be an effective NLRP3 inhibitor, which indicates cryptotanshinone can be used as an effective component of Salvia miltiorrhiza to prevent and treat cardiovascular disease for further study. The highlight of this review is that we got effective NLRP3 inhibitors through virtual screening, which can provide theoretical support for finding novel natural active ingredients. The disadvantage of this paper is only theoretical screening, but lack of experimental verification. In the future, we will carry out in vivo and in vitro experimental research on the basis of this review to clarify its myocardial protection by reducing NLRP3 activity and inhibiting pyroptosis.

Table 1. Docking of quinones with NLRP3.

| Chemicals       | Vina score | Cavity score | Center (x, y, z) | Size (x, y, z) |
|-----------------|------------|--------------|------------------|----------------|
| Cryptotanshinone| -11.5      | 12730        | 88, 94, 81       | 35, 34, 35     |
| Tanshinone IIA  | -10.1      | 12730        | 88, 94, 81       | 35, 34, 35     |
| Aloin           | -9.5       | 12730        | 88, 94, 81       | 35, 34, 35     |
| Chrysophanol    | -9.1       | 12730        | 88, 94, 81       | 35, 34, 35     |
| Rhein           | -9.1       | 12730        | 88, 94, 81       | 35, 34, 35     |
| Emodin          | -9.0       | 12730        | 88, 94, 81       | 35, 34, 35     |
| Aloe emodin     | -8.8       | 12730        | 88, 94, 81       | 35, 34, 35     |
| Shikonin        | -8.6       | 12730        | 88, 94, 81       | 35, 34, 35     |
| Plumbagin       | -7.3       | 12730        | 88, 94, 81       | 35, 34, 35     |

Figure 2. The 3D pictures of quinones and active site of NLRP3 (A) Cryptotanshinone-NLRP3, (B) Tanshinone IIA-NLRP3.
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Conflicts of interest

The author declares that he has no conflict of interest.

REFERENCES

1. Silvis M.J.M., Demkes E.J., Fiolet A.T.L., Dekker M., Bosch L., et al.: J. Cardiovasc. Transl. Res. 14, 23 (2021).
2. Sasaki K., Shoji T., Kabata D., Shintani A., Okute Y., et al.: J. Atheroscler. Thromb. 28, 249 (2021).
3. Shen S., He F., Cheng C., Xu B., Sheng J.: Biomed. Pharmacother. 206, 105789 (2021).
4. Liang H., Li F., Li H., Wang R., Du M.: Immunol. Invest. 17, 1 (2020).
5. Yang R., Yu H., Chen J., Zhu J., Song C., et al.: J. Agric. Food Chem. 69, 982 (2021).
6. Bolton J.L., Dunlap T.: Chem. Res. Toxicol. 30, 13 (2017).
7. Sunassee S.N., Davies-Coleman M.T.: Nat. Prod. Rep. 29, 513 (2021).
8. Wen J., Sawmiller D., Wheeldon B., Tan J.: CNS Neurol. Disord. Drug Targets 18, 769 (2019).
9. Devi G., Harikrishnan R., Paray B.A., Al-Sadoon M.K., Hoseinifar S.H., et al.: Fish Shellfish Immunol. 87, 669 (2019).
10. Yu Y., Liu H., Yang D., He F., Yuan Y., et al.: Pharmacol. Res. 146, 104315 (2019).
11. Chen Y., Feng B., Yuan Y., Hu J., Zhao W., et al.: Mediators Inflamm. 2020, 13 pages (2020).
12. Zhang Y., Song Z., Huang S., Zhu L., Liu T., et al.: J. Leukoc. Biol. 108, 1735 (2020).
13. Lee I.C., Bae J.S.: J. Asian Nat. Prod. Res. 23, 89 (2021).
14. Lee W., Yang S., Lee C., Park E.K., Kim K.M., et al.: Food Chem. Toxicol. 126, 67 (2019).
15. Birari L., Wagh S., Patil K.R., Mahajan U.B., Unger B., et al.: Cancer Chemother. Pharmacol. 86, 419 (2020).
16. Birari L.A., Mahajan U.B., Patil K.R., Patil D.D., Bagul N.A., et al.: Naunyn Schmiedebergs Arch. Pharmacol. 393, 1365 (2020).
17. Lei J., Shen Y., Xu G., Di Z., Li Y., et al.: Immunopharmacol. Immunotoxicol. 42, 306 (2020).
18. Lian Y., Xia X., Zhao H., Zhu Y.: Biomed. Pharmacother. 93, 1175 (2017).
19. Wen Q., Mei L., Ye S., Liu X., Xu Q., et al.: Int. Immunopharmacol. 56, 90 (2018).
20. Yuan J., Hong H., Zhang Y., Lu J., Yu Y., et al.: Cell Biol. Int. 43, 695 (2019).
21. Li, J., Li J., Hu Y., Guo Z., Sun D., et al.: Acta Pharm. Sin. B. 9, 782 (2019).
22. Li Y., Liu Y., Yan X., Liu Q., Zhao Y.H., et al.: Am. J. Chin. Med. 46, 1727 (2018).
23. Zhang W., Suo M., Yu G., Zhang M.: Chem. Biol. Interact. 305, 127 (2019).
24. Lian Y., Xia X., Liu Z., Xu Q., Tang H., et al.: Chin. Med. 15, 20 (2020).
25. Li L., Wang L., Gao J., Pang X., Chen A., Wang Y.: Front Pharmacol. 11, 17 pages (2020).
26. de Oliveira M.R., de Souza I.C.C., Brasil F.B.: Neurochem. Res. 46, 482 (2021).
27. Du Y., Ko K.M.: Mol. Cell. Biochem. 288, 135 (2006).
28. Yang Y., Jiang Z., Zhu D.: Int. Heart J. 60, 436 (2019).
42. Zhuang S., Zhong J., Zhou Q., Zhong Y., Liu P., et al.: Int. Immunopharmacol. 71, 321 (2019).
43. Ge H., Tang H., Liang Y., Wu J., Yang Q., et al.: Drug Des. Devel. Ther. 11, 1663 (2017).
44. Lü S.L., Dang G.H., Deng J.C., Liu H.Y., Liu B., et al.: Acta Pharmacol. Sin. 41, 47 (2020).
45. Lee J.H., Han S.H., Kim Y.M., Kim S.H., Yoo E.S., et al.: Biosci. Rep. 41, 10 pages (2021).
46. Yang J., Wang Z., Chen D.L.: Biomed. Pharmacother. 93, 1343 (2017).
47. Wang S., Zhu Y., Qiu R.: Biomed. Pharmacother. 104, 712 (2018).
48. Guo T., Jiang Z.B., Tong Z.Y., Zhou Y., Chai X.P., et al.: Front Physiol. 11, 11 pages (2020).
49. Zhou Z.Y., Zhao W.R., Zhang J., Chen X.L., Tang J.Y.: Biomed. Pharmacother. 118, 109362 (2019).
50. Xu H., Li H., Zhu P., Liu Y., Zhou M., et al. Drug Des. Devel. Ther. 14, 2853 (2020).
51. Wu W.Y., Wang W.Y., Ma Y.L., Yan H., Wang X.B., et al.: Br. J. Pharmacol. 169, 1058 (2013).
52. Chen F.Y., Guo R., Zhang B.K.: Zhongguo Zhong Yao Za Zhi. 40, 1649 (2015).
53. Li Q., Shen L., Wang Z., Jiang H.P., Liu L.X.: Biomed. Pharmacother. 84, 106 (2016).
54. Hu Q., Wei B., Wei L., Hua K., Yu X., et al.: Int. J. Cardiol. 196, 183 (2015).
55. Sharif H., Wang L., Wang W.L., Magupalli V.G., Andreeva L., et al.: Nature 570, 338 (2019).
56. Liu Y., Grimm M., Dai W.T., Hou M.C., Xiao Z.X., et al.: Acta Pharmacol. Sin. 41, 138 (2020).

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