Protective effects of flavonoids against intracerebral and subarachnoid hemorrhage (Review)

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Received February 12, 2024; Accepted June 12, 2024

DOI: 10.3892/etm.2024.12639

Abstract. Intracerebral hemorrhage (ICH), known as non-traumatic cerebrovascular rupture and hemorrhage, often occurs in the deep basal brain segment. It is known for its high morbidity and mortality rates. Subarachnoid hemorrhage (SAH) is a clinical syndrome caused by the rupture of blood vessels at the base or surface of the brain that allows blood to flow directly into the subarachnoid space. It progresses quickly and typically manifests at younger ages compared with ICH. ICH and SAH are both devastating events in the category of hemorrhagic strokes and are attracting increasing attention from researchers. Flavonoids, being important natural molecules, have remarkable anti-inflammatory and antioxidant effects. Flavonoids have extensive biological activities in inflammation and oxidative stress (OS), and have protective effects in vascular function associated with cerebrovascular diseases. They have an impact on the onset of ICH and SAH by targeting various pathways, including the suppression of inflammation and OS. Recently, the role of flavonoid compounds in ICH and SAH has also received increasing interest. Thus, to serve as a resource for the prevention and treatment of ICH and SAH, the present review provided an overview of the research on flavonoid compounds in the prevention of brain damage after these two conditions have occurred.

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Key words: flavonoids, intracerebral hemorrhage, subarachnoid hemorrhage, early brain injury, cerebral vasospasm

1. Introduction

Intracerebral hemorrhage and subarachnoid hemorrhage. Intracerebral hemorrhage (ICH) is a deleterious form of stroke that results from cerebral vascular rupture and hemorrhage. It commonly occurs in the deep basal ganglia region of the brain and is associated with a high incidence and mortality rate (1). This subtype of hemorrhagic stroke comprises 10-20% of all documented stroke cases worldwide, based on statistical data from 1970 to 2008 (2). A systematic review and meta-analysis published in 2010 showed that the overall incidence of ICH was 24.6 per 100,000 person-years; among them, incidence of ICH per 100,000 person-years was 51.8 in East and Southeast Asian individuals, which was much higher compared with that in white individuals in Oceania, Europe and northern Manhattan (24.2), black individuals in Africa, Caribbean and northern Manhattan (22.9) and Hispanic individuals in Brazil, northern Manhattan, Caribbean and northern Chile (19.6); moreover, the incidence rate of ICH was higher in the elderly, with an incidence per 100,000 person-years of ICH in individuals >55 years old (36.5-196.0), which was much higher compared with that in individuals aged ≤54 (1.9-19.1) (3).

ICH is a devastating condition with a reported mortality of ~40% within the first month (3). Despite the temporary lack of comprehensive epidemiological data on ICH of the last five years, it is undeniable that, having being recognized as one of the most challenging conditions for the prognosis of patients with stroke (4), ICH is likely to remain a serious public health problem that cannot be ignored in the near future, even after the progress in medicine in the past few years. There are two types of damage caused by ICH: Primary injury and secondary injury (5). In ICH, the primary injury occurs during the initial stage. It is characterized by physical damage to the brain cell structure caused by the hematoma (6). The increased intracranial pressure from the hematoma mass leads to compression of the brain region, causing mechanical damage (7). Following this, a series of reactions occur, including neuroinflammation and oxidative stress (OS), leading to further damage such as blood-brain barrier (BBB) dysfunction and cerebral edema. This is referred to as a secondary injury (4). They both seriously harm the health of patients with ICH.

Subarachnoid hemorrhage (SAH) has also attracted considerable interest in the study of hemorrhagic stroke in recent years. It is a type of neurological emergency that arises from the rupture of diseased blood vessels found either at the brain's surface or at the base of the brain. The blood flows directly into the subarachnoid space (8), resulting in the third most prevalent subtype of stroke (9) mainly attributed to aneurysm rupture (10). It may have severe consequences for patients, such as cognitive decline and secondary cerebral ischemia (11). It occurs at a relatively young age, despite comprising only 5% of all strokes (12). Unlike ICH, SAH starts very quickly, and symptoms can peak in a few minutes, with a thunderclap headache which can peak within just 1 minute after SAH (13). The complex pathophysiological cascade that occurs after SAH is primarily triggered by increased intracranial pressure (ICP) and blood components (14). These factors can lead to unpredictable diffuse brain damage, which is challenging to detect until it reaches an irreversible stage (15).

Two areas in the pathophysiology of SAH have attracted significant attention in scientific research: Early brain injury (EBI) and cerebral vasospasm (CVS) (16). Among them, EBI after SAH refers to secondary brain injury within 72 h after SAH, including microcirculation dysfunction, neuroinflammation damage, BBB disruption, cerebral edema, neuronal death and oxidative cascade (17). The EBI after SAH is associated with several pathogenic mechanisms, including inflammation, OS, and ferroptosis (18,19). Moreover, CVS is a significant contributor to the high mortality and morbidity associated with SAH (20). CVS usually occurs on day 3 after SAH, peaks on days 6 and 8, lasts 2 to 3 weeks (17) and has lasting and serious consequences after SAH. After a review of the relevant literature, it was observed that the EBI and CVS after SAH have similar mediating pathways, including OS and inflammation. This suggests that flavonoid compounds have the potential to protect against a number of significant injury modes in SAH.

Flavonoids. Flavonoids, which have 2-phenylchromone as their fundamental structural unit, are among the most abundant secondary metabolites found in plants. They can be found in herbs and different dietary sources, including fruits, vegetables, teas and grains, in glycosides or a number of free forms (21). Flavonoid compounds consist of a shared C6-C3-C6 backbone where two aromatic rings are linked by 3-carbon bridges, typically forming a phenyltropane configuration (22). Several studies have shown that natural flavonoid compounds have neuroprotective effects in brain diseases (23,24), suggesting that understanding the functions and mechanisms of flavonoids in preventing neuroinflammation may hold immense significance in the advancement of nutritional guidelines and therapeutic approaches for brain diseases.

2. Protective effects of flavonoid compounds against ICH

Flavonoids protect against brain damage after ICH by inhibiting inflammation and OS. The potential of flavonoids to protect against ICH through their superior anti-inflammatory and antioxidant properties has been the main focus of recent studies.

Puerarin is a natural isoflavone extracted from the roots of pueraria species. A previous study has documented the protective effects of puerarin against various diseases such as Alzheimer's disease and cerebral ischemic disease (23). The PI3K/Akt signaling pathway is involved in regulating the NF-κB pathway. The activation of PI3K/Akt signaling has been shown to effectively decrease the levels of phosphorylated NF-κB p65 and to inhibit the production of inflammatory cytokines such as TNF-α and IL-1β. Zeng *et al* (24) showed that puerarin can activate PI3K/Akt signaling, thereby inhibiting inflammatory reactions caused by the NF-κB pathway and ultimately attenuating the EBI after ICH. Specifically, puerarin activates the PI3K/Akt pathway and reduces NF-κB activation, significantly increasing the expression level of Bcl-2 and inhibiting the expression of Bax and Caspase-3, thereby inhibiting ICH-induced activation of apoptosis signaling (24). At the same time, the inflammatory factors that are promoted by NF-κB are downregulated, reducing the inflammatory damage after ICH. In addition, puerarin also reduces the levels of 8-OHdG and 3-NT after ICH, inhibiting the production of reactive oxygen species (ROS) and thus alleviating OS damage after ICH (24).

In addition, a previous study has revealed that luteolin, which is classified as a flavonoid compound and has anti-inflammatory properties, has been found to stimulate the Nrf2 pathway and facilitate the nuclear translocation of Nrf2 after ICH (25). The study has shown that luteolin can prevent ICH by stimulating the p62/Keap1/Nrf2 pathway and substantially increasing the expression levels of its downstream antioxidant proteins heme oxygenase 1 (HO-1) and NQO1 (26). NQO1 regulates ROS production to inhibit oxidative stress (5), while increased expression of HO-1 can inhibit the activation of NF-κB, thereby inhibiting NF-κB-mediated inflammatory responses (27). Further, luteolin inhibits the activation of the TLR4/TRAF6/NF-κB signaling pathway by binding to TRAF6. This mechanism of action reduces neuroinflammation, thereby providing a protective effect against ICH by attenuating the overproduction of inflammatory cytokines, the inflammatory cascade, apoptosis and structural and functional disruption of BBB may result (28).

Baicalein is a bioactive flavonoid with anti-inflammatory and antitumor activities (29). Based on a report, ICH rats treated with baicalein showed significant reductions in lesion volume and brain water content. On the one hand, its action was manifested as decreasing the expression levels of pro-inflammatory cytokines (IL-1β, IL-4, IL-6 and TNF-α), and inhibiting apoptosis. On the other hand, it also increased the activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), while decreasing the malondialdehyde (MDA) level in the brain tissues of rats (30). MDA is an important marker in oxidative stress, and the enhanced activity of SOD and GSH-Px can strongly inhibit the production of MDA by lipid peroxidation to improve oxidative damage after ICH (31). The results of the research indicated that baicalein may have a therapeutic impact on brain injury by reducing apoptosis, OS and neuroinflammation. This suggests that baicalein could be a promising treatment option for ICH and related brain injury (30). Another study on ICH supports that baicalein may reduce brain damage by inhibiting ROS and the NLRP3 inflammasome, thus inhibiting NLRP3-mediated

inflammatory responses. This research further highlights the potential of baicalein to protect against ICH (32).

Moreover, didymin, a dietary citrus flavonoid, was shown to upregulate RAF kinase inhibitor protein (RKIP) expression in a preclinical model of ICH (33). The research has shown that RKIP can directly bind ASC, thereby disrupting the formation of the NLRP3 inflammasome after ICH (33). In this way, didymin blocks cell pyroptosis and the inflammatory response in the Caspase-1/GSDMD pathway, protecting against injury after ICH (33).

Quercetin, a special subclass of flavonoids, which is a bioactive natural compound established on the structure of flavonoids (34). Based on a recent study, the efficacy of quercetin in a non-clinical model of ICH has been demonstrated. The study reviewed that, the lesion volume and brain water content are significantly reduced in ICH rats after quercetin treatment. These outcomes provided evidence that quercetin has the potential to suppress inflammation and cell death, and is capable of aiding in the restoration of neural function by reducing levels of inflammatory mediators and inhibiting apoptosis mediated by cleaved Caspase-3 (35).

Baicalin is an active ingredient of the traditional Chinese drug baicalensis that shows biological activity, including anti-inflammatory properties (36,37). A study found that baicalin displays a dose-dependent suppression of NF-κB expression in the surrounding tissues of the hematoma caused by ICH, and thereby reduces the secretion of IL-1β and IL-6. Additionally, baicalin inhibits the expression of matrix metalloproteinases (MMP)-9, and blocks the degradation of the extracellular matrix (ECM) by MMP-9, thereby helping maintain the integrity of the BBB. It was also suggests that baicalin may have a protective effect against ICH by regulating the expression of protease-activating receptor-1 (PAR-1) to inhibit the cellular apoptosis pathway mediated by PAR-1 (38).

A number of other potential flavonoid compounds have demonstrated a protective effect against the OS and inflammation mediated by ICH; for example, a study has highlighted that isoliquiritigenin can inhibit ROS and the activation of the NF-κB-mediated NLRP3 inflammasome through the stimulation of the Nrf2 antioxidant pathway, which in turn alleviates EBI after experimental ICH (39). Breviscapine, a medicinal plant, reportedly possesses a substantial inhibitory effect on the expression of NF-κB pathway-related factors after ICH (40). Another study suggests that pinocembrin lowers the expression of TLR4, myeloid differentiation primary response 88 (MyD88) and TIR-domain-containing adapter-inducing interferon-β and downregulates NF-κB signaling, alleviating brain injury after ICH by inhibiting the inflammatory response (41). Except for pinocembrin, eupatilin has also been confirmed to reduce the inflammatory response triggered by ICH through the TLR4/MyD88 pathway (42). In addition to the aforementioned studies, fisetin, naringin, calycosin and procyanidins have also been demonstrated to protect against the neuroinflammation and/or OS resulting from ICH via various mechanisms, such as inhibiting NF-κB, inhibiting lipid peroxidation and activating the Nrf2 pathway (43-46).

Flavonoids protect ICH by facilitating TGF-β1. The aforementioned materials demonstrate that flavonoids have a wide range of potential as antioxidants and/or anti-inflammatory agents for the prevention and treatment of ICH. However, aside from neuroinflammation and OS, a number of researchers have also identified alternative pathways through which flavonoids can protect ICH. For example, hesperidin, a biologically active flavonoid that can be found in citrus fruits (47), has been highlighted to promote the expression of TGF-β1, while TGF-β1 can promote the production and reconstitution of ECM and protects the BBB by inhibiting the expression of MMP9 and MMP2, to attenuate the damage caused by adverse symptomatic ICH caused by ischemic stroke (48). At present, there are few studies on the protective effect of flavonoid compounds on ICH, which have highlighted the role of TGF-β1; however, the present study provides a reference for future research directions.

Based on the aforementioned studies it is evident that flavonoids have the potential to provide significant protection against ICH through various mechanisms, such as anti-inflammatory, anti-oxidative and anti-pyroptotic actions (Fig. 1; Table I). These findings suggest that flavonoids may be promising candidates for the development of preventive and therapeutic drugs.

3. Protective effects of flavonoid compounds against SAH

Flavonoids protect SAH by inhibiting inflammation, OS and apoptosis. Neuroinflammation and OS are significant factors in the EBI and CVS that occur after SAH (49-51). A number of studies have demonstrated that flavonoids can exert protective effects on SAH by suppressing inflammation and OS. For example, the study by Kuo *et al* (52) has highlighted the positive effects of early baicalein treatment on rats after SAH. This treatment has been shown to decrease the mortality rate and brain water content in experimental rats, as well as reduce neuronal degeneration by inhibiting CVS (52). In addition, baicalein increases astrocyte activity and retains glutamate transporter-1, thus attenuating OS induced by the glutamate surge after SAH; baicalein also provided resistance against OS by maintaining SOD and catalase activity and reducing MDA levels after SAH (52). Several studies have also emphasized the functions of flavonoid compounds in the similar aspects in SAH, such as luteolin, rutin, apigenin, baicalein, quercetin and proanthocyanidin, which have been shown to have inhibitory effects on inflammation and/or OS after SAH (53-60). Their mechanisms of action include several pathways as described above, such as modulating Nrf2 to inhibit oxidative stress and NLRP3 inflammasome-mediated inflammation, reducing NF-κB activation by inhibiting TLR4 or RAGE, and inhibiting of MDA by increasing SOD and GSH-Px to alleviate oxidative damage (53-60).

Simultaneously, the damage caused by apoptosis after SAH is equally remarkable. Apoptosis is a significant factor in the development of EBI and is also involved in the formation of CVS in patients with SAH. According to the study of Zhang *et al* (61), puerarin ameliorates the neurological impairment observed in mice, suppresses cerebral edema, decreases BBB destruction and also decreases the apoptosis of cellular neurons. In addition, Zhang *et al* (61) has shown that puerarin-treated SAH mice have a significantly higher Blc-2/Bax ratio and a reduced level of cleaved Caspase-3 compared with vehicle-treated SAH animals; that is to say, puerarin inhibits

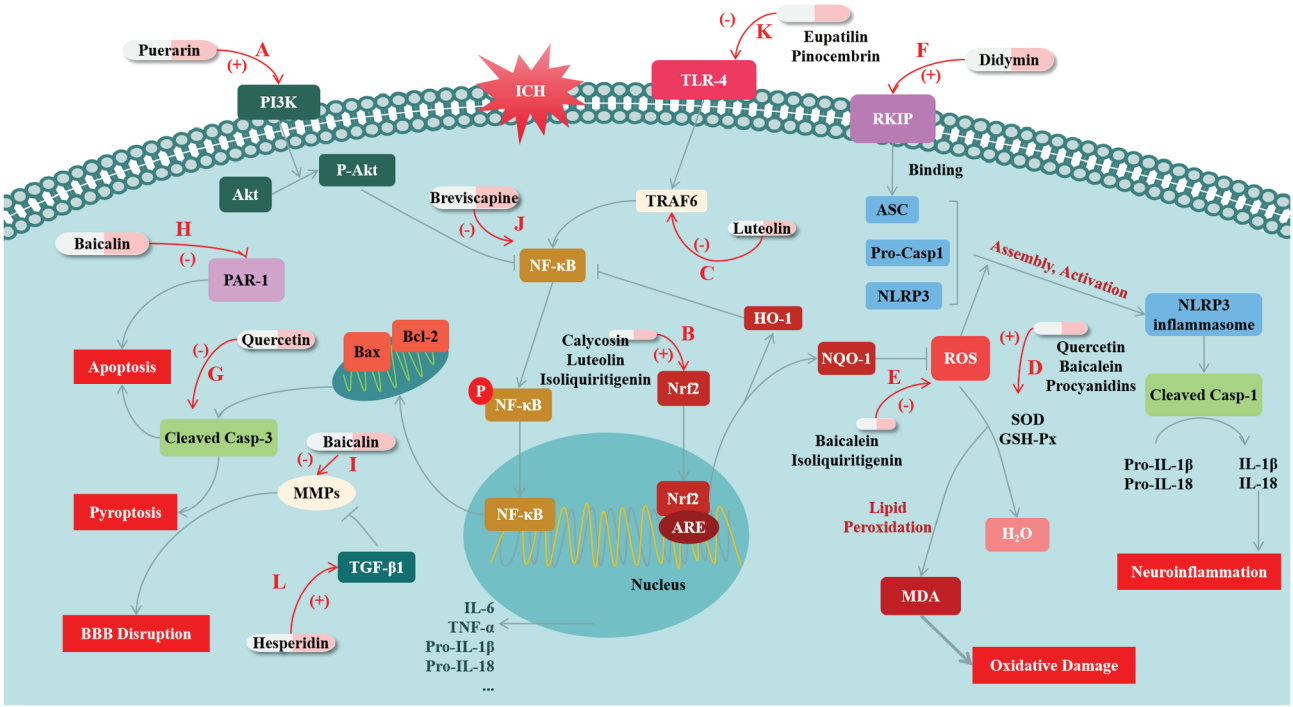

Figure 1. Mechanisms of flavonoid compounds exerting protective effects against brain injury after ICH. (A) Puerarin activates the PI3K/Akt pathway and reduces NF-κB activation, increases the expression level of Bcl-2 and inhibits the expression of Bax and Caspase-3, thereby inhibiting ICH-induced apoptosis. (B) Calycosin, luteolin and isoliquiritigenin protects ICH by modulating Nrf2. They both activate Nrf2 and promote its nuclear translocation, thereby inhibiting OS. In addition, calycosin and isoliquiritigenin further inhibit NF-κB and/or NLRP3-mediated inflammation through promoting Nrf2. (C) Luteolin inhibits the activation of the TLR4/TRAF6/NF-κB signaling pathway by binding to TRAF6, thus reducing inflammation. (D) Quercetin, baicalein and procyanidins increase the activities of SOD and GSH-Px, while decreasing the MDA level, and thus improves oxidative damage after ICH. (E) Baicalein and isoliquiritigenin inhibit NLRP3-mediated inflammation by inhibiting ROS production. (F) Didymin upregulates the expression of RKIP; RKIP combines with Asc, thus inhibiting the assembly of NLRP3 inflammasomes, to inhibit NLRP3-mediated inflammatory response. (G) Quercetin inhibits apoptosis mediated by cleaved Caspase-3. (H) Baicalin downregulates the expression of PAR-1 to inhibit cellular apoptosis. (I) Baicalin inhibits the expression of MMPs to ameliorate the disruption of BBB. (J) Breviscapine attenuates the inflammatory response by inhibiting the activation of NF-κB. (K) Eupatilin and pinocembrin lower the expression of TLR4 and downregulate NF-κB signaling to inhibit the inflammatory response. (L) Hesperidin promotes the expression of TGF-β1 to inhibit expression of MMPs, thus protecting the BBB from disruption. ICH, intracerebral hemorrhage; OS, oxidative stress; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; ROS, reactive oxygen species; RKIP, RAF kinase inhibitor protein; PAR-1, protease-activating receptor-1; MMP, matrix metalloproteinases; BBB, blood-brain barrier.

apoptosis mediated by cleaved Caspase-3 by inhibiting Bax expression and promoting Blc-2 expression. Meanwhile, puerarin also blocks SAH-induced ROS production, protects the synthesis of Sirt3 after SAH and enhances the function of SOD2 after SAH, thus attenuating oxidative damage after SAH. Overall, the study suggests that puerarin has the potential to reduce neurological dysfunction in mice with SAH by targeting specific pathways involved in apoptosis, including Bcl-2/Bax/cleaved caspase-3 and Sirt3/SOD2 (61).

Flavonoids protect against brain damage after SAH by activating SIRT1. In addition to the aforementioned pathways, a number of other flavonoids have been shown to protect against brain damage after SAH through other routes.

Pinocembrin is a natural compound distributed in propolis. In a study, Zeng *et al* (62) found that pinocembrin has a significant impact on improving behavior and reducing brain tissue damage after SAH, and that its mechanism of action might be related to Sirtuin-1 (62). Sirtuin-1, also known as SIRT-1, is a histone deacetylase that can be found in different parts of the cerebral cortex. Accumulating preclinical evidence has indicated that SIRT1 is a promising molecular candidate for treating SAH. By deacetylating a variety of intracellular targets such as Pgc-1α and ac-NF-κB, SIRT1 provides protection by reducing inflammatory injury, free radical damage and cell death (62). Specifically, inhibition of ac-NF-κB can inhibit its downstream inflammatory pathway, while activation of Pgc-1α can promote the entry of Pgc-1α into the nucleus to promote the expression of antioxidant enzymes, such as SOD, to reduce intracellular ROS levels, thereby protecting normal mitochondrial function and protecting cells from oxidative damage (63). In the study by Zeng *et al* (62), treatment with pinocembrin significantly increases the levels of SIRT1 and Pgc-1α, and suppresses the expression of ac-NF-κB; therefore, treatment with pinocembrin plays a protective role against brain injury after SAH (62). Although SIRT1 was shown in this aforementioned study to exert a protective effect on SAH by inhibiting inflammation and OS, as a potential target for the treatment of SAH, SIRT1 is less studied in the direction of the protective effects of flavonoids on SAH. Overall, the potential of flavonoids to play a role in the treatment of SAH through SIRT1 still needs to be further explored.

Flavonoids protect against brain injury after SAH by promoting the endothelial nitric oxide (NO) pathway. Concerning the pathophysiology of CVS, the endothelial NO pathway is also

Table I. Flavonoids with protective effects on ICH and their mechanisms of action.

Compound	Protective mechanism	Indexes	Pathways/targets of action
Puerarin	Inhibiting OS and inflammation	PI3K↑, Akt↑, NF-κB↓, Bcl/Bax↑, 3-NT↓, 8-OHdG↓, ROS↓	PI3K/Akt/NF-κB pathway
Luteolin	Inhibiting OS and inflammation	Nrf2↑, HO-1↑, NQO1↑, TLR-4↓, TRAF6↓, NF-κB↓	p62/Keap1/Nrf2; TLR4/TRAF6/NF-κB pathway
Baicalein	Inhibiting OS and inflammation	SOD↑, GSH-Px↑, MDA↓, ROS↓, NLRP3↓	ROS/NLRP3 pathway and lipid peroxidation pathway
Didymin	Inhibiting pyroptosis and inflammation	RKIP↑, NLRP3↓, GSDMD↓	Asc/NLRP3/Caspase-1/GSDMD pathway
Quercetin	Inhibiting cell apoptosis and inflammation	Cleaved Caspase-3↓	Caspase-3-mediated apoptosis pathway
Baicalin	Inhibiting cell apoptosis	PAR-1↓	PAR-1-mediated apoptosis pathway
Isoliquiritigenin	Inhibiting OS and inflammation	Nrf2↑, ROS↓, NF-κB↓, NLRP3↓	Nrf2/ROS, NF-κB, NLRP3 pathway
Breviscapine	Inhibiting inflammation	NF-κB↓, IL-6↓, TNF-α↓	NF-κB pathway
Pinocembrin	Inhibiting inflammation	TLR4↓, TRIF↓, MyD88↓, NF-κB↓	TLR4/NF-κB pathway
Eupatilin	Inhibiting inflammation	TLR4↓, MyD88↓	TLR4/NF-κB pathway
Fisetin	Inhibiting inflammation	NF-κB↓	NF-κB pathway
Calycosin	Inhibiting OS and inflammation	Nrf2↑, NLRP3↓, NF-κB↓	NACHT, NLRP3, NF-κB
Hesperidin	Assist in rt-PA treatment	TGF-β1↑, MMP-2↓, MMP-9↓	TGF-β1
Procyanidins	Inhibiting OS	LDH↓, SOD↑, MDA↓	Lipid peroxidation pathway

ROS, reactive oxygen species; OS, oxidative stress; HO-1, heme oxygenase 1; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; RKIP, RAF kinase inhibitor protein; PAR-1, protease-activating receptor-1; TRIF, TIR-domain-containing adapter-inducing interferon-β; MyD88, myeloid differentiation primary response 88.

regarded as one of the primary mechanisms. The production of NO by endothelial nitric oxide synthase (eNOS) in the cerebrovascular endothelium can spread to nearby smooth muscle cells, triggering the activation of soluble guanylyl cyclase. This, in turn, results in the production of cyclic guanosine monophosphate (cGMP). The stimulation of intracellular calcium channels by cGMP facilitates the transport of free Ca^{2+} to the intracellular zone compartment, resulting in the relaxation of smooth muscle cells, and eventually inhibits CVS (16). Li *et al* (64) demonstrated that scutellarin can reduce vasospasm and neurological deficits by regulating the Erk5-KLF2-eNOS pathway, confirming the protective effect of scutellarin through the endothelial NO pathway on CVS after SAH (64).

Flavonoids protects against brain injury after SAH by inhibiting ferroptosis. Ferroptosis is a type of programmed cell death characterized by iron-dependent lipid peroxidation. Ferroptosis can trigger some inflammatory mediators, such as TNF-α, IL-1β and IL-6, which can contribute to inflammation by promoting the aggregation and activation of inflammatory cells (65,66). Ferroptosis can also enhance the accumulation of ROS within cells, thereby intensifying the OS damage (67,68). Recently, ferroptosis has been reported in the pathological course of hemorrhagic stroke, including SAH (69). One study has indicated that baicalin may be effective in reducing the damage caused by SAH by preventing ferroptosis. The research highlighted that baicalin attenuates SAH-induced elevation of Fe^{2+} levels and production of OS markers MDA and ROS in rat brain tissue, and eliminates SAH-induced reduction of GSH levels. In addition to validating Baicalin's inhibition of lipid peroxidation, the study also revealed that baicalin maintains the expression level of glutathione peroxidase 4 (GPX4) protein, which can reduce phospholipid hydroperoxide and inhibit lipoxygenase-mediated lipid peroxidation, thereby exerting a protective effect against ferroptosis. In addition, baicalin also inhibits the protein level of beclin1 and the ratio of LC3-II/I in the brain tissues of SAH rats, suggesting the suppressive effect of baicalin on autophagy in SAH rats. This study demonstrates the ability of baicalin to attenuate brain damage following SAH by inhibiting autophagy-dependent ferroptosis (70).

In conclusion, flavonoids regulate and improve brain damage after SAH in various ways. These are a class of drugs with potential for the treatment of SAH (Fig. 2; Table II). However, further research is still required to elucidate their mode of action.

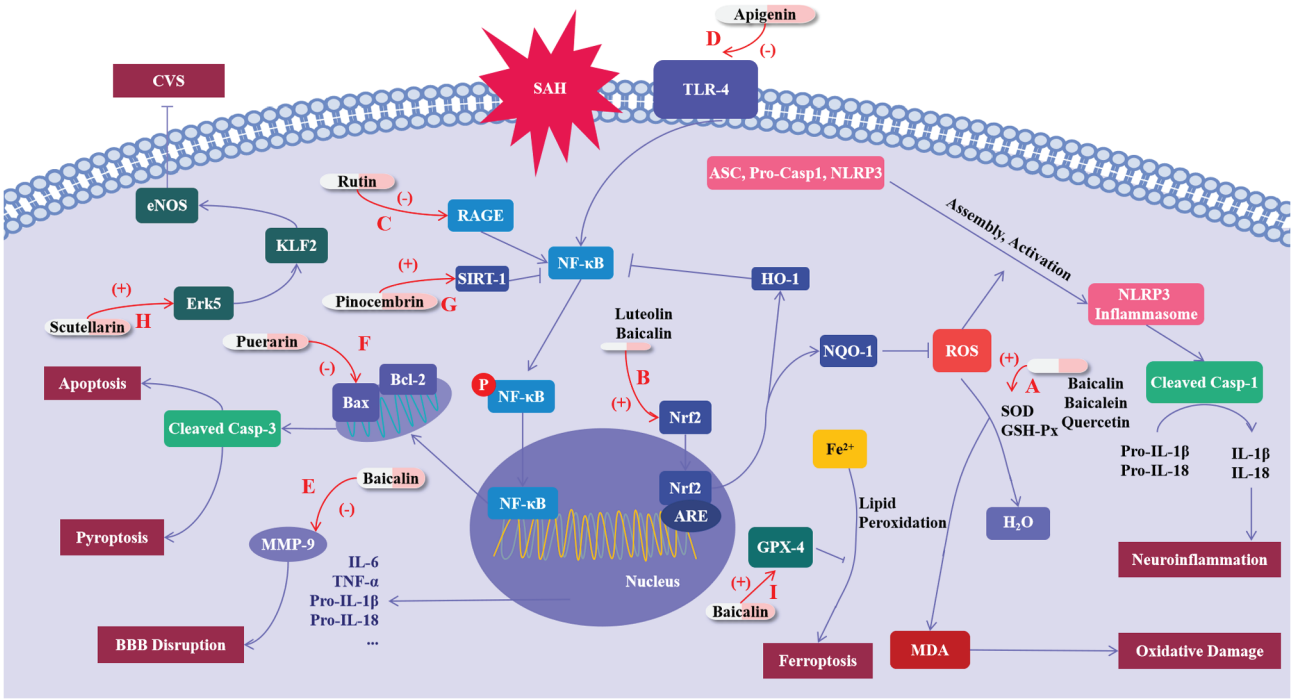

Figure 2. Mechanisms of flavonoid compounds exerting protective effects on SAH. (A) Baicalin, baicalein and quercetin increase the activities of SOD and GSH-Px, while decreasing the MDA level, thus inhibiting oxidative damage. (B) Luteolin and baicalin inhibit oxidative damage by activating Nrf2, and luteolin also inhibits the NLRP3-mediated inflammatory response through regulating Nrf2. (C) Rutin inhibits the inflammatory response by inhibiting the RAGE-NF-κB pathway. (D) Apigenin inhibits the TLR4-induced inflammatory response. (E) Baicalin prevents t blood-brain barrier disruption by inhibiting the expression of MMP-9. (F) Puerarin attenuates apoptosis by regulating the Bcl-2/Bax/cleaved Caspase-3 pathway. (G) Pinocembrin inhibits the inflammation mediated by NF-κB by promoting SIRT-1. (H) Scutellarin promotes the Erk5-KLF2-eNOS pathway, thus reducing CVS by promoting smooth muscle cell relaxation. (I) Baicalin maintains the expression levels of GPX4 protein and inhibits the ferroptosis after SAH. SAH, subarachnoid hemorrhage; OS, oxidative stress; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; ROS, reactive oxygen species; RKIP, RAF kinase inhibitor protein; CVS, cerebral vasospasm; MMP, matrix metalloproteinases; BBB, blood-brain barrier.

4. Conclusion

ICH and SAH are harmful brain diseases that cause severe damage to patients globally. Flavonoids, as potent antioxidants and anti-inflammatory agents, have consistently demonstrated their neuroprotective effects in preclinical studies involving ICH and SAH. They have been shown to regulate inflammation, pyroptosis and OS pathways, which in turn involve, for example, the NF-κB-related inflammatory pathways, Nrf2-related antioxidant pathways, lipid peroxidation pathways and caspase-3-mediated pyroptosis. Although their anti-inflammatory, antioxidant and other effects have been demonstrated, flavonoid compounds still need more research to investigate their potential, and they are still constrained by a number of obstructions on the way to the clinic, for example, the mechanism research is not in-depth enough, and the potential toxic and side effects of flavonoids need to be discovered and avoided.

More pathways, targets and more specific mechanisms remain to be discovered and exploited. Other than the researches mentioned in the previous chapters, it is important to highlight that some targets have attracted less attention in the available research. Targets such as TGF-β1, SIRT1, ERK1/2 and RAGE, and pathways such as ferroptosis may potentially be affected by a number of flavonoids. Especially, the activation of the ERK1/2 signaling pathway is implicated in the pathological process of vascular wall proliferation in CVS (71). It has been revealed that cell proliferation in the vessel wall is a crucial factor in the development of CVS in SAH (71), and TLR4, downstream of ERK1/2, can exacerbate the inflammatory response by promoting the secretion of inflammatory factors through c-Fos phosphorylation (72). This, in turn, increases the damage caused by SAH. Moreover, numerous studies have confirmed the inhibitory effects of various flavonoid compounds on ERK1/2-related pathways (73,74). These findings also provide considerable reference value for studies targeting SAH. These targets and pathways may serve as potential sites of damage for different flavonoids, and their research directions are both attractive and immensely valuable.

While studying the effects of flavonoids on new pathways and targets, the studies of pathways and targets that have been demonstrated to be affected by flavonoids should not be stopped. While numerous studies have explored the mechanisms by which flavonoids exert protective effects on ICH and SAH in the studies cited in the present paper, the ways in which flavonoids interact with the specific biomarkers they affect are rarely mentioned. Future research is still necessary to explore this point in depth; for example, to study whether flavonoids play a role as activators or inhibitors of certain enzymes, and to study the binding mode and binding sites of flavonoids to various targets, so as to lay a more reliable theoretical basis for their clinical treatment of ICH and SAH.

Table II. Flavonoids with protective effects on SAH and their mechanisms of action.

Compound	Protective mechanism	Improved damage	Indexes	Pathways/targets of action
Baicalein	Inhibiting OS	CVS	GLT-1↑, SOD↑, MDA↓	Lipid peroxidation pathway
Luteolin	Inhibiting OS and inflammation	CVS	Nrf2↑, NLRP3↓	Nrf2/NLRP3 pathway
Rutin	Inhibiting inflammation	EBI	RAGE↓, NF-κB↓	RAGE-NF-κB pathway
Apigenin	Inhibiting inflammation	EBI	TLR4↓, NF-κB↓	TLR4-NF-κB pathway
Baicalin	Inhibiting OS and ferroptosis	EBI	SOD↑, MDA↓, Nrf2↑, MMP9↓, Fe^{2+}↓, ROS↓	Nrf2 pathway, lipid peroxidation pathway, and ferroptosis pathway
Quercetin	Inhibiting OS and apoptosis	CVS	MDA↓, CuZn-SOD↑, GSH-Px↑, MDA↓, Cleaved Caspase-3↓	Lipid peroxidation pathway, Caspase-3-mediated apoptosis pathway
Puerarin	Inhibiting OS and apoptosis	EBI	Blc-2/Bax↑, cleaved Caspase-3↓, ROS↓, SIRT3↑, SOD2↑	Bcl-2/Bax/caspase-3; Sirt3/SOD2 pathway
Pinocembrin	Inhibiting OS and inflammation	EBI	SIRT1↑, Pgc-1α↑, ac-NF-κB↓, SOD↑, GSH↑, MDA↓, IL-1β↓, IL-6↓	SIRT1 pathway and lipid peroxidation pathway
Scutellarin	Promoting endothelial NO pathway	CVS	p-Erk5↑, KLF2↑, eNOS↑	Erk5/KLF2/eNOS pathway

CVS, cerebral vasospasm; EBI, early brain injury; GLT-1, glutamate transporter-1; ROS, reactive oxygen species; OS, oxidative stress; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; MDA, malondialdehyde; RAGE, multi-ligand receptor for advanced glycation endproducts; eNOS, endothelial nitric oxide synthase; p-, phosphorylated.

Flavonoids may also have negative effects. In a number of studies flavonoid compounds have played a role that can exert protective effects against a variety of diseases. Inevitably, however, there are exceptions to everything and the effects of flavonoid compounds on hemorrhagic stroke are also complex and two-sided. In a certain study, the present study noted that rotenone, a flavonoid compound, has been shown to accelerate ferroptosis after ICH (75). It appears that this type of compound may not be beneficial for treating ICH and SAH. This may be due to the special structure of rotenone, which makes it an inhibitor of mitochondrial respiratory chain complex I, which can enhance the production of mitochondrial ROS (76). The increased production of ROS aggravates lipid peroxidation, which ultimately promotes ferroptosis. This also indicates that some flavonoid compounds may not have a positive impact on hemorrhagic strokes. Upon closer investigation, the present study revealed that there are a number of flavonoid compounds with some potential toxic side effects, including but not limited to: i) Baicalin can induce acetylation of Smad3 through the interaction of Smad3 with the transcriptional coactivator p300 and reduce phosphorylation of AMPK, a metabolic master kinase, leading to increased kidney damage, including glomerular hypertrophy, collagen deposition, inflammatory cell infiltration among the renal tubules and even kidney fibrosis (77); and ii) under the conditions of high dose and long-term use, luteolin induces glutathione depletion and activates the metabolism of CYP450, mediating the formation of o-benzoquinone metabolites, thereby causing cytotoxicity including damage to multiple structures and functions in cells, and even cell apoptosis in primary rat hepatocytes (78).

The potential toxicity of flavonoid compounds has become a non-negligible obstacle to their clinical development. Not only that, but the decision on the dosage and the risks involved in the long-term use of the drug should not be ignored. A too-high dosage or long-term use of a drug may have strong toxic side effects and even a risk of death. Nowadays, there is still a lack of more specific and comprehensive clinical studies on the efficacy and toxicity of flavonoids at different doses and the risks of long-term use of flavonoid drugs. Therefore, in future studies, flavonoid compounds with specific structures, toxicity, functions, dose-dependent toxicity and/or side effects and long-term medication risks should be identified and screened and selectively used. This shows a new opportunity for further research, while also raising new challenges. At present, some studies have made attempts to investigate this; for example, Choi *et al* (79) revealed that long-term combined administration of quercetin and daidzein can inhibit quercetin-induced suppression of glutathione antioxidant defenses (79). Such studies undoubtedly provide evidence to further study the safety of flavonoids and propose treatment options those are safer and more effective.

Issues of bioavailability and biological activities of flavonoid compounds. Another challenge for flavonoids moving towards clinical practice is that the bioavailability of flavonoid compounds varies (80). However, new delivery systems may help different flavonoid compounds play a fuller role in the prevention and treatment of diseases such as ICH and SAH. As research reports, the application of quercetin in nanoemulsion has been found to significantly boost its antioxidant effect (81). This study indicated that the biological activity and pharmacological effects of flavonoids may vary depending on the dosage form of their administration. This finding offers a strong basis and motivation for further research into the potential of these compounds.

Presently, there is a continuous influx of new dosage forms being identified. Several potent flavonoids may be formulated into various dosage forms so that their protective and toxic levels in each formulation can be determined. This could be another interesting point of research. On the other hand, derivatives are also important in enhancing the efficiency of flavonoid compounds. A previous study has shown that the C- and O-glycosides of flavonoids generally show higher radical scavenging activity compared with aglycones; for example, kaempferol C3-O-glycoside (astragalin) shows higher activity compared with kaempferol (82). This study reveals that making flavonoid compounds into different derivatives may reveal unexpected effects. At the same time, in future research, researchers should also pay attention to the selection of patients. Patients with different constitutions may also show considerable differences in drug compliance, which is also a direction worthy of further study.

Considering the aforementioned research progress, flavonoid compounds have shown significant bioactivity and promising clinical potential in ICH and SAH. Nevertheless, the current studies still have some limitations. Firstly, in the studies mentioned in the present review, the experimental animal breeds, animal models, measurement methods and measurement indicators are uneven, making a systematic comparison of their specific efficacy difficult. Therefore, for each compound, it is necessary to compare the protective effects of flavonoids on ICH and SAH in different experimental animal breeds and by different ICH or SAH model construction methods. This not only helps to compare the efficacy of different flavonoids, but also supports the existing research results.

In addition, to the best of our knowledge, there is a lack of large-scale clinical trials and extensive exploration of mechanistic studies. The 'from the bench to the bedside' process still contains more unknowns waiting to be explored. Despite this, in our opinion, foods containing flavonoids may play an unexpected role in preventing diseases such as ICH, SAH and other interrelated diseases, and would be readily available as a daily dietary supplement by the concept of 'homology of medicine and food' in traditional Chinese medicine. In daily life, individuals can selectively increase their intake of foods that contain beneficial flavonoid compounds, in order to prevent diseases such as ICH and SAH. For example, a study showed that individuals with higher daily intake of flavonoids, such as anthocyanin (predominantly from blueberries and strawberries), had a lower incidence of hypertension (83). Hypertension is an important cause of ICH (84), therefore, increasing the intake of these flavonoids will also probably reduce the risk of ICH accordingly. Flavonoid compounds are widely found in a variety of fruits and vegetables, for example, celery and parsley contain apigenin (85), apples contain rutin (86) and strawberries and blueberries contain anthocyanin (83), and advocating for an appropriate increase in the intake of flavonoids containing those beneficial flavonoids may be of considerable benefit in preventing ICH and SAH and reducing their incidence.

A number of previous reviews have summarized studies on flavonoids. Jäger and Saaby (87) discussed the effects of flavonoids on the central nervous system, including oral bioavailability, BBB permeability and the interaction of flavonoids with several biomarkers. The review by Parrella *et al* (88) summarized the therapeutic effects of polyphenols, including flavonoids, shown in non-clinical and clinical studies of stroke, while the article by Chen *et al* (21) summarized the beneficial effects of natural flavonoids on neuroinflammation. However, to the best of our knowledge, there is no review that specifically summarizes the protective effects of flavonoids on ICH and SAH; therefore, the present review summarized the protective effects of flavonoids on ICH and SAH and the mechanisms by which they exert protective effects in detail, which provides a reference for the treatment of ICH and SAH by flavonoids. The current review discussed the challenges of flavonoids towards clinical practice, the limitations of current researches on the protective effects of flavonoids in ICH and SAH and the beneficial directions for future research on flavonoids in ICH and SAH. In our opinion, flavonoids are a class of compounds with potential, and it is hypothesized that their therapeutic potential for ICH and SAH can be more and more fully explored in future studies.

Acknowledgements

Not applicable.

Funding

This work was partially supported by the National Natural Science Foundation of China (grant no. 81973547).

Availability of data and materials

Not applicable.

Authors' contributions

HD designed and drafted the manuscript. HD, XG, HL and JG revised the manuscript. LZ conceived and designed the whole project. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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