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Exploring The Cardioprotective Potential of Natural Flavonoids in Ischemia Models

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ABSTRACT

Flavonoids are classes of polyphenolics compounds in many fruits and medicinal plants that have been found to possess substantial cardioprotective capabilities in pre-clinical models of myocardi AL-SAWFY (2017). This is a review of their role in the inhibition of myocardial damage by exhibiting multimodal actions such as antioxidant protection, anti-inflammatory, anti-apoptotic, and autophagic processes. Most flavonoids like quercetin, kaempferol, apigenin ligature, luteolin, naringenin, and hesperidin have a consistent effect on rodent models, where they reduce infarct size, increase cardiac performance and protect the integrity of the mitochondrion. Mechanically, their activity mimics the Nrf2/ARE and PI3K/Akt signaling, inhibition of NF-kB and MAPK signaling as well as AMPK/mTOR controlled autophagic flow to improve the survival of cardiomyocytes and tissue recovery. Clinical translation of these encouraging findings is hampered by shortcomings in bioavailability, a lack of pharmacokinetic data and inability to demonstrate or elicit a response in comorbid or large animal models. To make full use of the therapeutic effect of flavonoids in ischemic heart disease, future studies should fill these gaps by applying standardized protocols, long-term studies, as well as human trials. Their versatile nature and multi-targeted activity, along with non-toxicity in animal investigations lead to the possibility of using flavonoids as effective supplementary methods or supplements to traditional approaches of cardioprotection.

Key Words:

Flavonoids, Ischemia-Reperfusion Injury, Cardioprotection, Oxidative Stress, Inflammation, Apoptosis, Autophagy, Myocardial Infarction

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1. INTRODUCTION

Ischemic heart disease (IHD) and cardiovascular diseases (CVDs) remain the top killer in the world. Ischemia is extrinsic supply to the heart muscle, which leads to the lack of oxygen and further development of a chain of pathological mechanisms linked to ischemia: oxidative stress, inflammation, and mitochondrial dysfunction, which also lead to apoptosis. Although reperfusion is vital in reviving the blood flow it has the paradox of increasing myocardial injury via ischemia/reperfusion (I/R) effects[1]. Animal models The most well characterised and widespread usage of animal models to simulate human myocardial ischemia and to investigate the effects of therapeutic interventions is in rodents with spontaneous or induced ischemia (usually following coronary artery ligation or pharmacological induction). In this regard, natural compounds, especially flavonoids have become some of the most powerful

cardioprotective elements owing to their wide pharmacological applications as manifested in preclinical in vivo studies.

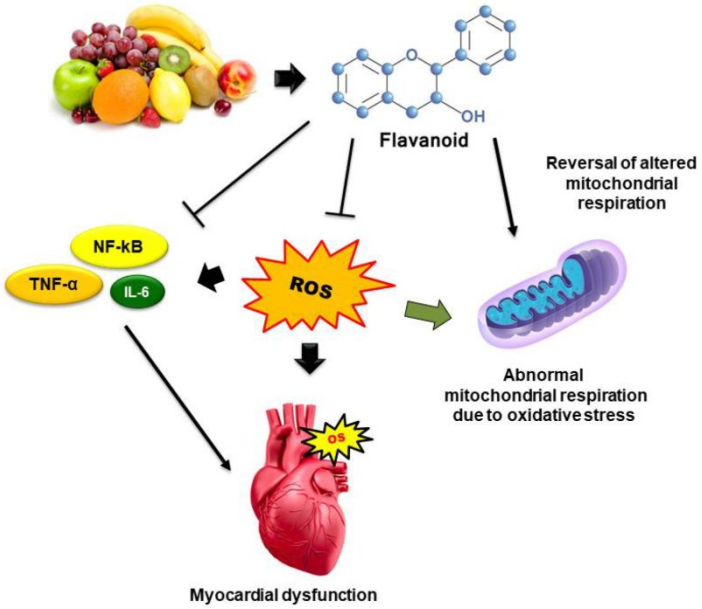

Figure 1: Dietary Flavonoids[2]

Flavonoid is a type of polyphenolic compounds naturally present in a number of fruits, vegetables and medicinal plant. Flavonoids including quercetin, kaempferol, apigenin, naringenin, and luteolin have been found to possess great cardioprotective effects in several in vivo studies which used ischemia induced rats and mice. They comprise the limitation of the infarct size, restoration of cardiac performance, alleviation of oxidative stress, and regulation of the inflammatory and apoptotic pathways. To be more specific, the left ventricular ejection fraction and cell death in the myocardial area were better in quercetin-treated rats that were exposed to LAD (left anterior descending) coronary artery ligation. The animal data provide mechanistically important information about how flavonoids do this by modulating redox signaling, immune response, control of mitochondrial integrity and, in some cases, even autophagy, which explains why they may contribute to therapeutic development in ischemic heart diseases[3].

1.1.Background Information and Context

There has been an upsurge in the interest in bioactive compounds derived out of plants especially their application as a supplemental agent of chronic conditions such as CVDs. Polyphenols can be divided into subcategories such as flavonoids, which has proven to show strong biological activity in vivo that consists of antioxidant, anti-inflammatory, and anti-apoptotic activity. Reports have shown consistently that flavonoids can reduce myocardial damage in models of ischemia and reperfusion in either mice or rats by interrupting the pathophysiological in ischemia to reperfusion injury. These preclinical studies have served as a base in understanding cardioprotective effects of flavonoids at cellular and molecular levels[4].

1.2.Objectives of the Review

This review aims to:

1. To assess cardioprotective effects of flavonoids in animal ischemia models.
2. To summarize key preclinical findings on major flavonoids.
3. To explore molecular mechanisms like antioxidant and anti-inflammatory actions.
4. To evaluate study methodologies and identify limitations.
5. To suggest future research directions for clinical translation.

1.3.Importance of the Topic

Considering the worldwide problem of ischemic heart disease and low effectiveness of current medical remedies of this pathology, there is a strong necessity to develop safe, cheap, and multi-targeted ones. Natural flavonoids propose a favorable option since they have been proved in a variety of animal models of ischemia. The relevance of their mechanistic actions in cardioprotection may help in addressing the gaps between a preclinical evidence and practice. Additionally, a systematic extrapolation of animal data will make it possible to study complex pathogenesis mechanisms in a controlled and replicatable manner which will lead to the emergence of new flavonoid-based therapies[5].

2. PRECLINICAL EVIDENCE OF FLAVONOIDS' CARDIOPROTECTIVE EFFECTS IN EXPERIMENTAL ISCHEMIA MODELS

Rodent in vivo models investigating myocardial ischemia-reperfusion (I/R) injury have demonstrated repeatedly that flavonoids including quercetin, kaempferol, apigenin, naringenin, luteolin, and hesperidin have a potent cardioprotective effect (infarct size reduction, cardiac protection, and oxidative stress, inflammation, and apoptosis modulation). These causes are realized by the stimulation of antioxidant enzymes, a reduction of pro inflammatory cytokines, stabilization of the mitochondria, and subsequent function of endothelium. Although experimental models provide insights into mechanistic information and versatile environments, factors limiting them include that dosing was not standardised, pharmacokinetic information was not provided, assessments were short-term, and they had little clinical relevance because of the absence of comorbidities and translational models.

Table 1: Key Studies on Flavonoids in Cardioprotection[6]

Author(s)	Study	Focus Area	Methodology	Key Findings
Ferenczyova et al. (2020)[7]	Potential implications of quercetin and its derivatives in cardioprotection	Quercetin's cardioprotective effects	Preclinical models; review of antioxidant and anti-inflammatory pathways	Quercetin scavenges ROS, stabilizes mitochondria, inhibits NF-κB, and interacts with PI3K/Akt and MAPK pathways to reduce I/R injury.
Garg et al. (2020)[8]	Fisetin as an agonist of PPAR-	Role of fisetin in cardioprotection	Experimental murine model of MI;	Fisetin activates PPAR-γ, reduces infarct size,

	γ in myocardial infarction		biochemical and histological analysis	improves cardiac function, and attenuates inflammation and oxidative stress.
Guo et al. (2024)[9]	Natural products in intervention of myocardial infarction	General role of flavonoids in MI therapy	Literature review of natural products and pathways	Flavonoids modulate oxidative stress, inflammation, and apoptosis via AMPK, Nrf2/ARE, and PI3K/Akt; promising adjunctive therapy.
Guo et al. (2022)[10]	Flavonoids from Oxytropis falcata in I/R injury	Oxytropis falcata-derived flavonoids in I/R injury	Rodent model of I/R; analysis of mitochondrial and apoptotic markers	Improved mitochondrial function, reduced oxidative stress, regulated Bcl-2/Bax ratio, and better myocardial structure.
Jubaidi et al. (2021)[11]	Flavonoids in diabetic cardiomyopathy	Role of flavonoids in diabetes-induced heart disease	Preclinical diabetic models; evaluation of oxidative and inflammatory markers	Flavonoids (naringenin, luteolin, hesperidin) enhanced antioxidant defense, reduced apoptosis, and preserved cardiac function.

2.1.Summary of Key Research Studies

The cardioprotective efficacy of flavonoids during animal models of myocardial ischemia-reperfusion (I/R) injury This is documented by a robust body of preclinical evidence that has demonstrated effective cardioprotective efficacy of flavonoids during animal models of myocardial ischemia-reperfusion (I/R) injury commonly used to simulate human myocardial

infarction. The research mainly carried out on rodents has outlined both functional and molecular advantage after administration of flavonoid[12].

- **Quercetin**: This flavonol has received substantial research past the antioxidant and anti-inflammatory aspects. In one of the models where Sprague Dawley rats were used in an LAD coronary artery occlusion and reperfusion model quercetin 50 mg/kg (i.p.) reduced infarct size by more than 30%. The echocardiographic parameters including left ventricular ejection fraction (LVEF) were significantly improved which implied the presence of preserved systolic function. Biochemically there was a great reduction in the malondialdehyde (MDA) levels and a high superoxide dismutase (SOD) activity indicating the prevention of the oxidative stress. Histologically, there was low neutrophil inflammatory infiltrate and interstitial edema, which showed limited local inflammation responses[13].
- **Kaempferol**: When administered qualitative in a dose of 10 20 mg/kg/day PO in rats during 7 days before coronary ligation, kaempferol ameliorated cardiac injury marker verges in serum like creatine kinase- MB (CK-MB) or lactate dehydrogenase (LDH). It inhibited expression of two important pro-inflammatory cytokines: TNF- a and IL-1 a in the myocardium. The activity of the apoptotic cells was reduced in addition to showing decreased TUNEL-positive cells, as the anti-inflammatory role of NF-kB translocation is further supported.
- **Apigenin**: When apigenin was orally administered at 15 mg/kg/day before ischemia they observed that it prevented apoptosis by mitochondrial stabilization. This could be seen in caspase-3 suppression, maintenance of the integrity of the mitochondria shown through electron microscopy, and higher Bcl-2/Bax ratio. The results point to the possible usage of apigenin in the maintenance of mitochondrial homeostasis during I/R injury.
- **Naringenin**: On the pressure-overload model created through the transverse aortic constriction (TAC) in the mouse, naringenin in the dose 100 mg/kg/day showed positive structural and functional implications. It should be noted, it enhanced diastolic performance and decreased both cardiac hypertrophy and fibrosis. The mechanism behind the effects was explained by the increased endothelial nitric oxide synthase (eNOS) phosphorylation and a decrease in the markers of the oxidative strain, which signify an improvement in endothelial functioning.
- **Luteolin**: Its role in protection was justified by its ability to inhibit apoptosis of the cardiomyocyte and enhance ATP production in rats heart that had experienced I/R. Its mechanisms were through the stimulation of PI3K/Akt cascade as well as the inactivation of the glycogen synthase kinase-3 beta (GSK-3beta), which is critical to conferring cell survival against stressful conditions.
- **Hesperidin**: Myocardial infarction was established by application of isoproterenol (ISO), that is a 2-adrenergic stimulator, in Wistar rats. Hesperidin at 100 mg/kg/day mediated the biochemical manifestations of damage (AST, ALT, CK-MB), cardioprotective antioxidant status (rise in catalase, SOD) and maintained cardiac electrical propagation evidenced by ECG recording. These effects help to indicate the ability of hesperidin to restrict electrophysiological and structural degradation following ischemia[14].

2.2. Methodologies and Findings (Expanded)

a) Animal Models and Induction of Ischemia

To model human myocardial infarction and reperfusion injury, most studies used well established rodent models. LAD coronary artery ligation (temporary or permanent), isoproterenol induced cardiotoxicity, and transverse aortic constriction (TAC) were used. The models are applicable in the examination of acute and chronic ischemic damage[15].

b) Reperfusion Protocols

In most of the cases, ischemia of 30 to 60 minutes was produced and reperfusion started with a span of 1 to 72 hours. This acute reperfusion period is similar to the ones that clinical percutaneous coronary intervention (PCI) encounters.

c) Flavonoid Administration Routes

Flavonoids were given in several ways such as by oral gavage and intraperitoneal (i.p.), as well as intravenous injection among others, as a protective or curative measure, or respectively as an antecedent (preventive)-treatment or as a post-treatment after the occurrence of the ischemic damage. The range between doses administered was very high (5-200 mg/kg), which means that dosing regimens are not standardized[16].

d) Assessment Techniques

Assessment methods used in the body of flavonoid-based cardioprotection studies in ischemia model include a wide spectrum of physiological and molecular parameters. To assess the left ventricular performance, cardiac output was quantitatively determined through echocardiography (including LVEF and fractional shortening in addition to ECG analysis and invasive hemodynamics to assess left heart performance. The triphenyltetrazolium chloride (TTC) staining and histopathological analysis were used to determine the infarct size. Biomarkers that were assessed to measure oxidative stress included malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), catalase and 8-hydroxydeoxyguanosine (8-OHdG). Cytokines involved in inflammatory responses, i.e. TNF- alpha, IL-6, IL-1 beta, were measured by ELISA and activation of NF-kappa B pathways by Western blotting and immunohistochemistry.

2.3 Strengths and Weaknesses

The advantages of using flavonoids-based cardioprotection in the studies are the controlled nature of experiments involving standardized rodent I/R models, repeatability of results across species, and pathway-specific molecular details of key pathways, such as PI3K/Akt and NF-kappa-B. The advantage of flavonoids is the multitargeted effect as they reduce oxidative stress, inflammation and apoptosis at the same time. Nevertheless, significant drawbacks are the lack of adequate pharmacokinetical characterization, a non-standardized and clinically inconvenient application of doses, short-term assessment lacking data on long-term outcomes, an absence of comorbidity models, and the corresponding failure to conduct any translational study in larger animals or humans, making them limited in clinical applicability[17].

- **Strengths**

1. **Controlled Experimental Design:** Internal validity, and reproducibility, are increased given standardized I/R models applied to genetically homogeneous populations of healthy rodents. Specified ischemic times and specific flavonoid quantities reduce inter-experimental variation.

2. **Molecular Mechanistic Insights:** The use of more advanced methodologies such as real-time PCR technology, western blotting and immunohistochemical staining have allowed experimentalists to unravel the intracellular pathways by flavonoids, including PI3K/Akt, nuclear factor-kappa B (NF-kov biggest grain plant in the world (NF-xB) and apoptotic cascades in mitochondria.

3. **Consistency Across Species and Ischemia Conditions and Models:** The protective effects that have been demonstrated on flavonoids across rodent models of ischemia and on different species point to the robust pharmacological potential of flavonoids and their extremely wide-spectrum activity[18].

4. **Multitargeted Cardioprotection:** Flavonoids act on multiple processes simultaneously, including controlling oxidative stress, apoptosis, inflammation and mitochondrial activity, which is helpful considering the multifactorial nature of I/R injury.

Weaknesses:

1. **Pharmacokinetic Gaps:** The pharmacokinetic profile (absorption, distribution, metabolism, and excretion) of flavonoids was not estimated in most of the studies even though they came up with positive findings. They can be poorly bioavailable and fast metabolized in vivo, and hence do not benefit clinically.

2. **Non-Standardized Dosages:** The large dosing variety, which could be several folds more than the physiological reality in human beings, is a problem with respect to clinical translation. Dose-response relations are rather unexplored.

3. **Short term follow-up:** In numerous studies, the observations are confined to the initial reperfusion phases (2472 hours) leaving blindspots in terms of the long-term effects like cardiac remodelling, restoration of functionality or development of heart disease.

4. **Absence of Comorbidity Simlation:** Experimental animals are usually young and not affected by other diseases, and frequently human myocardial infarction is simulated with comorbidities such as diabetes, obesity or atherosclerosis. This reduces the transferability of the results to clinical populations.

3. MECHANISTIC INSIGHTS INTO FLAVONOID-MEDIATED CARDIOPROTECTION

The flavonoids have a cardio protective role that is multidirectional on myocardial ischemia and interact to play an antioxidant capacity, anti-inflammatory and prevent apoptotic roles. They stimulate Nrf2/Are pathway to amplify endogenous antioxidant enzymes, recover redox balance and suppress production of ROS. At the same time flavonoids inhibit NF- kappa B and MAPK signalling pathways, and thereby decrease inflammatory cytokines and infiltration of leukocytes. They prevent apoptosis of cardiomyocytes by stabilizing mitochondrial

membranes, regulating the pro- and anti-apoptotic proteins, and inhibition of caspase activation. The above interventions result in better cardiac performance, lesser fibrosis and hypertrophy and better ventricular functioning, which helps minimize the size of infarct and increases myocardial regeneration[19].

3.1. Antioxidant Mechanisms of Flavonoids

The mechanism of ischemia-reperfusion (I/R) involves oxidative stress, namely, overproduction of hatred of oxygen species (ROS) along with the impairment of antioxidant defenses. Flavonoids have strong antioxidant states bringing about the modulation of the redox-sensitive signaling pathways. One of the main ways is the Nrf2 pathway (nuclear factor erythroid 2-related factor 2) activation, the cascade of regulating the expression of key antioxidant enzymes, including heme oxygenase-1 (HO-1), glutathione S-transferase (GST), superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx).

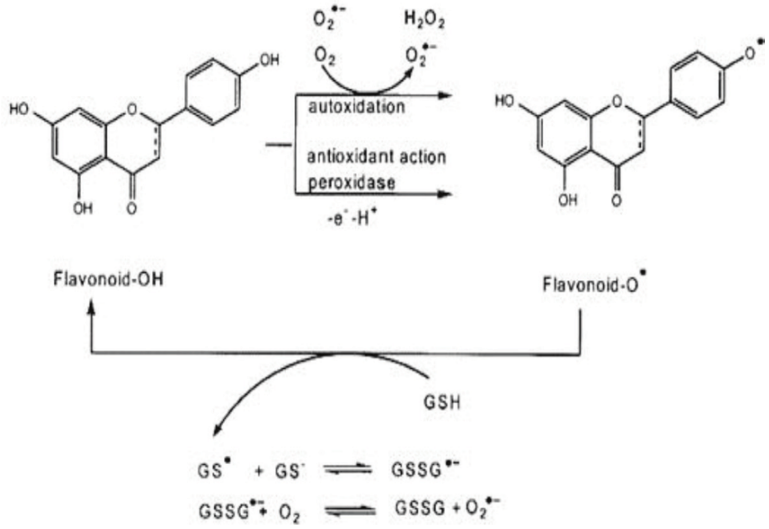

Figure 2: Antioxidant Mechanisms of Flavonoids[20]

Flavonoids enhance the migration of Nrf2 to the nuclear where it forms a bond with the antioxidant response element (ARE) which triggers the occurrence of cytoprotective genes. Such an activation recovers redox homeostasis, scavenging ROS, suppression of the process of lipid peroxidation and maintaining membrane integrity. Also, flavonoids can restore intracellular reduced glutathione (GSH) levels which is a key regulator of cellular antioxidant capacity. Indirectly, they inhibit NADPH oxidase, a large source of ROS constituting an important enzymatic contributor to oxidative injury to protein, lipids, and DNA in the ischemic myocardium.

3.2.Anti-inflammatory Properties (Expanded)

Inflammatory reaction after myocardial ischemia is considerable factor of tissue damage and unfavorable remodelling. Flavonoids display potent anti-inflammatory activity through inhibition of upregulation of cellular expression and activity of various pro-inflammatory mediators, and signaling molecules. The activation of NF- kB (nuclear factor-kappa B), a transcription factor, which activates genes that encode cytokines (TNF- a, IL- 6, IL- 1b), chemokines, and enzymes (inducible nitric oxide synthase (iNOS) and cyclo-oxygenase-2 (COX- 2)) is prevented by these[21].

Mechanism The flavonoids inhibit the breakdown of IkB (inhibitor of NF-kappaB), and, as such, block the translocation of NF-kappaB into the nucleus. Also, mitogen-activated protein kinases (MAPKs), including p38 MAPK, JNK, and ERK, that play a key role in transmitting the inflammatory signal and the response to stress, are inhibited by flavonoids. By so doing they diminish attachment of leukocytes, inflammatory cell penetration and destruction of the lipid-rich ischemic myocardium via cytokine-induced damage.

3.3.Anti-apoptotic and Mitochondrial Stabilization

Apoptosis of cardiomyocytes is one of the most important events in the pathophysiology of myocardial ischemia and reperfusion. Inhibition of intrinsic apoptotic pathways by flavonoids occurs in large part through the regulation of the pathways at the mitochondrial level. They tip the web of pro-apoptotic (e.g. Bax, Bad) and anti-apoptotic (e.g. Bcl-2, Bcl-xL) proteins in favor of the survival[22].

Flavonoids provide stability to the mitochondrial membranes; they avert the opening of the mitochondrial permeability transition pore (mPTP) which is essential in facilitating the release of cytosol cytochrome c, which appears to be a critical step of caspase cascades initiation. Consequently, effector caspase-3 and caspase-9 activation are diminished and there is less DNA fragmentation and cardiomyocyte death.

Moreover, flavonoids maintain the potential of the mitochondrial membrane, their syntheses boost the efficiency of production of ATP and mitochondrial ROS decrease. Preservation of mitochondrial integrity and activity they simultaneously prevent the activation of apoptosis, as well as the secondary necrosis and inflammation caused by cellysis.

3.4.Improvement of Cardiac Function

The overall effect of antioxidant, anti-inflammatory and anti-apoptotic properties of flavonoids is an increase in the functionality of cardiac processes after ischemia. The preclinical works are repeatedly claiming an improvement in left ventricular ejection fraction (LVEF), fractional shortening (FS), stroke volume and the cardiac output in animal groups treated with flavonoids.

The flavonoids reduce the interstitial and perivascular fibrosis, secondary interventions of the ventricles hypertrophy, and macroscopic preservation of the architecture of the heart. They are commonly linked with down-regulation of the fibrotic mediators like transforming growth factor-beta (TGF-β) and collagen I /III, which in turn regulate extracellular matrix turnover through modulation of matrix metalloproteinases (MMPs)[23].

The recovery of myocardial functioning is further facilitated by the improved functioning of the vascular endothelial cell layer and the improved availability of nitric oxide (NO), which increased the coronary perfusion. In general, these cardio protective effects are involved in low infarct size, better hemodynamics, and higher survival in ischemic models induced by flavonoids.

4. ROLE OF FLAVONOIDS IN MODULATING AUTOPHAGY DURING ISCHEMIC INJURY

Autophagy is a stringently regulated intracellular catabolic process that has two faces in myocardial ischemia-reperfusion (I/R) injury. Although basal autophagy in healthy cells is

important in maintaining homeostasis by the elimination of damaged organelles and by removing misfolded proteins, at the time spent under the severe ischemic stress, autophagy can result in cardiomyocyte death and worsen the damage. Naturally occurring polyphenolic compounds, flavonoids, have shown promises with regard to influencing autophagic pathways, either by inducing the protective autophagy in the early phase of ischemia, or by attenuating maladaptive autophagy in the reperfusion phase. This is the key regulatory ability that forms basis of their cardioprotective effects and gives a new dimension of therapy to the ischemic heart disease[24].

4.1.Mechanistic Overview of Autophagy in Ischemic Heart

Autophagy is provoked by the scarcity of oxygen and nutrients during ischemia to restore energy balance and eliminate a dysfunctional mitochond network (mitophagy). But after being reperfused, the rapid reintroduction of oxygen may induce oxidative stress and worsten the autophagic flux that may lead to overdegradation of vital cellular components culminating in a cell death. The main molecules within the scope of regulation during this process are AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), Beclin-1, LC3-II, and p62/SQSTM1 and they seem to regulate the process of coming up with autophagosomes and the elongation of the autophagosomes, and maturation of autophagosomes respectively[25].

4.2.Flavonoids as Autophagy Modulators

Flavonoids also have a regulatory role in terms of autophagy, but it is context-dependent and acts through the modulation of major signaling pathways, i.e. AMPK/mTOR, PI3K/Akt and SIRT1. Their functions are dependent upon the stage and extent of ischemic injury:

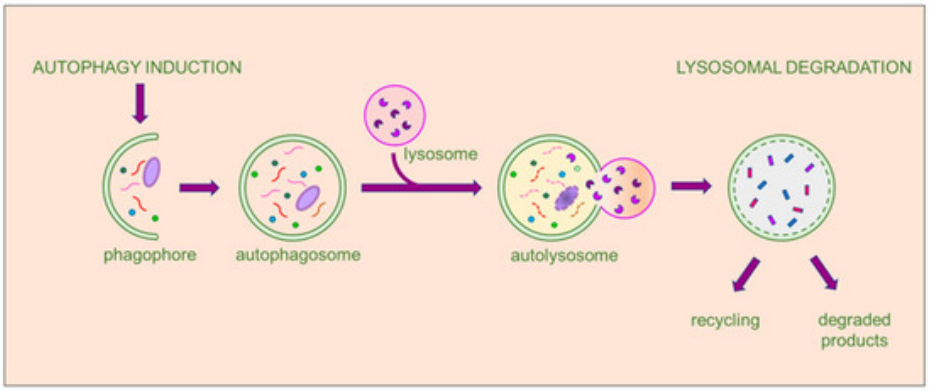

Figure 3: Stages of Autophagy: From Induction to Lysosomal Degradation[26]

- It has been demonstrated that quercetin stimulates cardioprotective autophagy during ischemia modulating as AMPK pathway agonist and mTOR signaling repressor, thus stimulating autophagosome formation. The pretreatment with quercetin in rat models of myocardial I/R injury led to an increase in the expression of LC3-II and Beclin-1 proteins, a decrease in p62 levels, which implied the promotion of autophagic flux and the improvement of the cardiac outcomes.

- In reperfusion, Kaempferol exerts the protective effect by reversing the inhibited autophagy mediated by the PI3K/Akt/mTOR pathway. It also prevents the over-degradation of autophagy, as well as damaging cellular health by keeping the

mitochondria intact. Investigations in the ischemia-stimulated cardiomyocytes of rodents indicated that kaempferol blocked the mTOR signaling processes, promoted the induction of LC3-II and SIRT1, which was a hint of its involvement in mitochondrial shielding and inspired autophagy.

- It has been shown that luteolin may have dual modulating role, it induces autophagy in early phases of ischemia to clear damaged mitochondria and it also inhibits superfluous autophagy during reperfusion by inhibiting JNK-Bcl-2-Beclin1 pathway. This biphasic modulation is one which maximizes cellular survival.
- Apigenin affects autophagy through epigenetic regulations, especially by inhibition of histone deacetylase (HDAC) and activation of SIRT1. Autophagy induced by apigenin in ischemic myocardium resulted in an enhanced development of the autophagic vacuoles and better viability of the cardiac cells.

4.3.Balancing Autophagy: Protective vs. Detrimental

The positive impact of flavonoids depends on keeping the balance between healthy and dangerous autophagy. Moderate levels of autophagy contribute to removal of damaged cellular compounds and cell survival of the cardiomyocytes during stress. In unchecked states however, this may result in autophagic cell death (type II programmed cell death). It appears that flavonoids not only regulate this balance by altering upstream regulators (AMPK, mTOR, SIRT1) and downstream effectors (LC3-II, p62) but avoid the shift of adaptive autophagy into the pathological degradation[27].

4.4.Therapeutic Implications

The fact that flavonoids alter autophagy provides an avenue to selective targeting of myocardial ischemia. They can adjust autophagy and this makes them potential candidates in preconditioning or postconditioning interventions in myocardial infarction. But there is, however, a dose, timing, specific flavonoid structure variation to their effects that require further studies. Besides, there is the possibility of the synergistic effect of flavonoids when taken in combination with other proven autophagy modulators or cardioprotective medications in ischemia injury inhibition.

5. DISCUSSION

Flavonoids have varied cardioprotective effects and are effective in ischemia-reperfusion models that mediate oxidative stress, inflammation, apoptosis, and autophagy pathways through the potencies of Nrf2/ARE and AMPK/mTOR. The fact that they act multitargeted and are of natural origin makes them speak of their therapeutic potential. Nevertheless, low bioavailability, insufficient pharmaceutical material, and a shortage of long-term/comorbid models inhibit clinical translation. In their future, studies should aim at standardization of the dosing, pharmacokinetics, and re-validation in large animals studies and human trials[28].

5.1.Interpretation and Analysis of Findings

The preclinical evidence that has been garnered so far shows clearly that the natural flavonoids have formidable cardioprotective benefits in preclinical models of the ischemia-reperfusion

(I/R) injury to the heart. Based on antioxidant activation, anti-inflammatory, and inhibition of apoptosis, as well as mitochondrial protection, flavonoids have been shown to be effective in reducing the size of infarction and improving cardiac performance. Remarkably, their effect on major molecular pathways, including Nrf2/ARE, NF-kB, PI3K/Akt, and AMPK/mTOR, is the side of their multiple effects on myocardial integrity. The results also propose an active contribution of flavonoids in the maintenance of autophagy as they assist in the maintenance of homeostasis in cells during ischemia, and thereby the prevention of injury during reperfusion. This subtle regulation of autophagy can be an important process through which flavonoids optimise survival of cardiomyocytes[29].

5.2.Implications and Significance

Due to their multitargeted characteristics, flavonoids represent appealing prospects of integrative cardioprotective approaches, particularly in the case of ischemic heart disease where the current pharmacotherapies have a tendency to involve a narrower number of pathways. Their potential to regulate oxidative stress, inflammation, apoptosis, and autophagy brings out the possibility of therapeutic disease treatment, rather than alleviating symptoms, which strike at the cause of the disease: the cardiac damage. The benefits of these compounds also include their origin as natural products with rather good safety arrays in animal studies. Notably, the above improvements in heart functioning, structural remodelling as well as mitochondrial recovery tend to open up the possibility that flavonoids might be an adjunctive therapy as well as a prophylactic substance after ischemia.

5.3.Gaps and Future Research Directions

Although preclinical results are encouraging, there exist considerable gap in news. There is very little pharmacokinetic information and low bioavailability presents a major challenge to translation of the results into human application. Also, most studies fail to look long-term and are done on young healthy rodents not reflecting adequately on humans whose cases are characterized by other accompanying conditions such as diabetes or hypertension. The dose regimen has also varied, as have the structure of flavonoids, and even the time of administration making comparisons and meta-analysis very difficult. Standardized experimental protocols, dose-response relationships, and their extension to large-animal models that more closely reflect the pathophysiology of human beings should become the priorities of future research. To confirm the clinical importance of flavonoid based treatments in myocardial ischemia clinical trials particularly utilizing pharmacokinetic profiling and combinatory treatment regiments involving known autophagy modulators are required[30].

6. CONCLUSION

The cardioprotective potential of natural flavonoids is excellent in experimental animals of a model of I/R myocardial injury with a high preclinical evidence volume. The flavonoids have a wide-ranged and synergetic pattern of heart protection through various pathways which are antioxidant defense by transcription factors Nrf2/ARE, anti-inflammatory by NF-kB and MAPK inhibition, anti-apoptotic by stabilizing the mitochondrial membranes and subtle control of autophagy by AMPK/mTOR and PI3K/Akt. These observations indicate that apart from reducing infarct mass and maintaining circulatory competence flavonoids can alter such underlying cellular dynamics that are instrumental in tissue repair and recovery homeostasis.

This, combined with their natural origin, multitargeted efficacy, and safety in animal models, make them attractive complements or alternatives to existing pharmacotherapies of ischemic heart disease. Nevertheless, substantial gaps exist between bench and bedside translation with limited pharmacokinetic data, poor bioavailability, brief study periods, and inability to translate foundation to either comorbid or large-animal models. To gain the clinical significance with flavonoids, the future research needs to focus on the resolution of these limitations by specifically including standardized dosing, long-term efficacy, and clinical studies with translational endpoints. The positive mechanistic clues and experimental results, therefore, make flavonoids promising in the future development of cardioprotective drugs at least in an integrative or complementary treatment regime.

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