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Astaxanthin as a Potential Myocardial Protection in Cardiac Surgery

Rilman Ilma Januar[1,2], Yan Efrata Sembiring[1,2*]

[1]Department of Thoracic, Cardiac and Vascular Surgery, dr Soetomo General Academic Hospital, Surabaya, East Java, Indonesia

[2]Faculty of Medicine, Airlangga University, Surabaya, East Java Indonesia

[*]**Corresponding author:**

Yan Efrata Sembiring

Email ID: yan-e-s@fk.unair.ac.id

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ABSTRACT

Background: Cardiac surgeries requiring cardiopulmonary bypass (CPB) can lead to myocardial ischemia-reperfusion injury (IRI), a condition driven by oxidative stress and inflammation that adversely affects post-operative outcomes. Traditional myocardial protection strategies, including hypothermia, ischemic conditioning, and cardioplegia, have improved patient prognosis but remain limited in completely preventing IRI-related myocardial damage.

Aim: This literature review aims to evaluate the potential of astaxanthin (AX), a potent antioxidant carotenoid, as an adjunct myocardial protection strategy during cardiac surgery involving CPB.

Methods: A comprehensive review of current literature was conducted focusing on the pathophysiology of IRI during cardiac surgery, existing myocardial protection techniques, and the pharmacological properties of astaxanthin. Preclinical and clinical studies examining AX's cardioprotective, anti-inflammatory, and antioxidant effects were analyzed.

Results: Astaxanthin exhibits superior antioxidant activity compared to traditional antioxidants, with demonstrated efficacy in reducing oxidative stress, inflammation, and apoptosis in preclinical models. Studies show AX enhances mitochondrial function and reduces myocardial fibrosis and remodeling following IRI. Despite promising findings, most evidence is limited to animal models, and human studies remain scarce.

Conclusion: Astaxanthin shows significant promise as a novel agent for myocardial protection during cardiac surgery by mitigating IRI-related damage. However, further clinical research is essential to confirm its safety, efficacy, and optimal dosing in human cardiac surgery settings.

Keywords: *Astaxanthin, myocardial ischemia-reperfusion injury, cardiac surgery, cardiopulmonary bypass, antioxidant therapy*

1. INTRODUCTION

With the advancement in technologies and medical equipment, since the 19th century, cardiac surgery had undergone several significant advancements including the development of cardiopulmonary bypass and several myocardial protection strategies to increase the post-operative prognosis. Most cardiac surgery, especially the one that need to open the heart's chamber, required the heart to stop beating and to halt the blood circulating through the heart. This allowed the surgeon to operate on a stable and bloodless field under direct vision. (Senst, Kumar & Diaz, 2024; Ismail & Semien, 2024)

However, while cardiopulmonary bypass and cardioplegic solutions have significantly improved surgical outcomes, myocardial ischemia-reperfusion (I/R) injury remains a major challenge, particularly during the periods of aortic cross-clamping and subsequent reperfusion. This injury, primarily driven by oxidative stress and inflammation, can impair myocardial recovery and contribute to postoperative complications. (Turer & Hill, 2010) As such, enhancing myocardial protection strategies is critical to further improving patient outcomes. In recent years, interest has grown in the use of pharmacological agents with antioxidant and anti-inflammatory properties to complement traditional techniques. Among these, astaxanthin, a naturally occurring carotenoid known for its strong antioxidant capacity, has emerged as a promising candidate. (Fassett & Coombes, 2011)

The aim of this literature review is to explore and evaluate the potential role of Astaxanthin (AX) as a novel myocardial protection strategy against ischemia-reperfusion injury (IRI) related to cardiac surgery using cardiopulmonary bypass.

2. CARDIOPULMONARY BYPASS

Cardiopulmonary bypass (CPB) stop the heart and divert blood circulation from the heart, which provides bloodless field of operation for the surgeon in a cardiac surgery. To imitate the physiological function of the heart and lungs, the CPB circuit consist of a pump to circulate blood bypassing the heart and an oxygenator which replicate the function of lungs in exchanging oxygen and carbon dioxide. Additionally, there are reservoir container to adjust chemical and electrolyte composition of the blood, and also a heat exchanger to adjust and regulate the blood temperature. All these components in the CPB circuit are equally important to ensure an adequate support of the patient's cardiovascular system during the cardiac surgery. (Ismail et al, 2024; Sarkar & Prabhu, 2017) With the advancement in technologies, additional components have been added to modern CPB machines, which includes system to monitor pressures, temperature, oxygen saturation, haemoglobin level, blood gases, and electrolytes, bubble detectors, oxygen sensor and reservoir low-level detection alarm. (Sarkar & Prabhu, 2017)

The decision to use cardiopulmonary bypass generally depends on the surgical procedure, patient's condition and in some situation the surgeon preferences like in the case of coronary artery bypass surgery. (Ismail et al, 2024; Razavi et al, 2025) Despite its benefit in reducing the risk of complications in complex cardiac surgery, there are several complications associated with the usage of CPB which will affect the patient's outcome including systemic inflammatory response syndrome, vasoplegic syndrome, coagulopathy, neurological complications, acute kidney injury and myocardial ischemia-reperfusion injury. (Ismail et al, 2024; Becker et al, 2021; Turer & Hill, 2010) Because of that, despite there are no absolute contraindications for CPB, it is important to consider delaying surgery when possible to optimize patient's condition before cardiac surgery. (Ismail et al, 2024)

Table 1. Indications and contraindications for cardiopulmonary bypass (CPB)

Indications	Contra indications
Coronary artery bypass graft (commonly used)	Acute kidney impairment
Valve surgery (replacement and repair)	Acute cerebral stroke
Congenital heart disease corrective surgery (including septal defects, complex structural abnormalities like Tetralogy of Fallot, transposition of great arteries, etc)	Chest infection
Surgical repair of aortic aneurysm	Severe asthma exacerbations
Cardica tumor removal surgery	
Heart transplantation	

3. ISCHEMIA-REPERFUSION INJURY IN CARDIOPULMONARY BYPASS

Ischemia-reperfusion injury (IRI) is an injury to the tissue caused by the process of ischemia followed by restoration of blood supply to the ischemic tissues. This reperfusion process triggers inflammatory response which further increase oxidative stress and results in microvascular dysfunction in the ischemic tissues and organ, including the lung, kidney, gut, skeletal muscle, brain and also the heart. (Maeda & Ruel, 2015; Cowled & Fitridge, 2011) Dysregulation of metabolic pathways tends to happen in ischemic tissue because of the deficiencies in oxygen, glucose and other components required for metabolism. Due to this dysregulation, the lack of ATP caused disruption in the ATP-dependent ionic pumps which result in the lost of transmembrane ionic gradients. Increases in the cytosolic sodium content will cause water to enter the cell which results in cells swelling and tissue edema. Additionally, ATP degradation during the ischemia will produce hypoxanthine. After reperfusion, the hypoxanthine will be degraded by xanthine oxidase which were catalysed by oxygen molecule, producing highly reactive superoxide anion (O2), a part of major reactive oxygen species (ROS). In the IRI, reactive oxygen species play a role in the destruction of reperfused tissue. (Cowled & Fitridge, 2011)

During cardiac surgery with cardiopulmonary bypass, the heart will undergo a period of ischemia caused by the diversion of blood flow from the heart. This will induce ischemia to the myocardium. The tissue injury will be worsened by the reperfusion process after the cardiac surgery resulting in myocardial ischemia-reperfusion injury. (De Hert & Moerman, 2015) IRI after cardiac surgery can manifest as arrhythmia, myocardial stunning, low cardiac output syndrome, and perioperative myocardial infarction. Different with the IRI caused by spontaneous myocardial infarct, IRI after cardiac surgery is closely related to the

cardiac surgery procedure, cardiopulmonary bypass and aortic cross clamping process which all were controlled and myocardial protection strategies can be implemented throughout this ischemic period to reduce the destructive process. (Turer & Hill, 2010)

4. MYOCARDIAL PROTECTION

Several myocardial protection strategies and techniques have been developed to reduce the extent of ischemia-reperfusion injury related to cardiac surgery and cardiopulmonary bypass. (De Hert & Moerman, 2015)

- Hypothermia

One of the most common employed myocardial protection strategy is hypothermia. A mild hypothermia condition around 32-35^{o}C will be able to reduce ischaemic time, which will reduce infarct size. Additionally, hypothermia also has the effect of improving post-ischaemic contractile function, preventing no-reflow condition or microvascular obstruction and also reduce the risk of left ventricle remodelling. (Tissier et al, 2012) Some studies have shown that hypothermia significantly affects the degree of myocardial salvage during ischaemia and reperfusion injury. IRI will caused inflammation and fibrosis, which will increase myocardial apoptosis resulting in reduced post-ischaemic cardiac function. Hypothermia, as one of myocardial protection strategy, will inhibit the inflammation and fibrosis effect in IRI. (Kanemoto et al, 2009; Zhang et al, 2022; Lim et al, 2018) Because of the difference in mechanism of myocardial protection provided by hypothermia, additional myocardial protection using pre- and post-conditioning can be added which will give better result. (Tissier et al, 2012)

- Myocardial ischemic conditioning

Myocardial ischemic conditioning can be divided into ischemic preconditioning and ischemic postconditioning. In which both are potent myocardial protection strategies by applying brief and acute period of ischemia and reperfusion to organs far from the heart. Experimental studies in human and animal have shown myocardial protective effect of ischemic conditioning. This effect includes protection against longer period of ischaemia, reduced size of infarct area, reduced severity degree of arrhythmia caused by IRI, prevention of endothelial cell dysfunction and also reduced risk of necrosis and apoptosis by increasing the myocardial tolerance to ischaemic period. (Bousselmi, Lebbi & Ferjani, 2014; Iliodromitis, Lazou & Kremastinos, 2007)

- Cardioplegia

Cardioplegia provides protection to myocardial by inducing the state of reversible cardiac arrest, which will decrease myocardial energy consumption and prevent injury caused by ischaemia state. The concept of cardioplegia solution is to shift the resting membrane potential from -90mV to -50mV, which prevent the initiation of phase 0 of cardiac action potential. In addition to the cardioprotective effect, a motionless heart in reversible cardiac arrest caused by the cardioplegia will benefit the cardiac surgeon. (Ismail & Semien, 2024; Carvajal, Goyal & Tadi, 2023)

Based on how it will be administered, cardioplegia can be divided into anterograde, retrograde or both with the former to be the common one to be done, as long as there is no anatomical variants or problem to the aortic valve or coronary arterial ostium. Although, using retrograde could be necessary in those conditions, the surgeon need to be aware of the risk on inadequate myocardial protection especially to the right ventricle and the risk of coronary sinus perforation caused by retrograde cannulation. Additionally, if there is a persistent left superior vena cava (PLSVC), it is important for the surgeon not to do retrograde cardioplegia, because in this anatomy variant, the cardioplegia will be given sistematically instead to the coronary cessels only. (Carvajal, Goyal & Tadi, 2023; Kamassai & Lowery, 2023) Cardioplegia could also be divided into single-dose cardioplegia and multi dose cardioplegia. Singe-doses cardioplegia consist of Bretschneider solution and del Nido extracellular cardioplegia solution, meanwhile multi-dose cardioplegia consist of crystalloid cardioplegia and blood cardioplegia (Buckerberg's). Single dose cardioplegia is recommended for low risk cardiac surgery, while multi dose cardioplegia is safer thus recommended for high risk cardiac surgery. (Carvajal, Goyal & Tadi, 2023) The decision to choose which cardioplegia and the technique to administer it, at the end of the day, will depend on the surgeon preferences and individual needs of the patients to provide optimal myocardial protection during cardiac surgery. Individual needs of the patient is also an important factor in deciding which cardioplegia to be used, especially regarding the patient's age. (Bradic et al, 2023)

Adequate myocardial protection is very important to ensure that the ischaemia is still on tolerated level. Despite the importance, myocardial protection strategies haven't changed for decades. (Mukharyamov et al, 2023)

5. ASTAXANTHIN

Astaxanthin (AX) is part of the xanthophyll carotenoids family, with its red-orange lipid-soluble pigment. This algae-derived substance has been gathering interest due to its physical properties, biochemical attributes, and physiological effects. The chemical structure of Astaxanthin can be seen in figure 1. The research on Astaxanthin in medical field, especially as a powerful antioxidant started around the 2000s. The antioxidant activity of Astaxanthin is believed to be achieved through direct quenching and scavenging of reactive chemical species, including reactive oxygen species (ROS). Astaxanthin will

inhibit nuclear translocation of NFkB and activation of Nrf2, additionally astaxanthin also will improve mitochondrial function, which will reduce production of ROS in vivo. (Nishida et al, 2023)

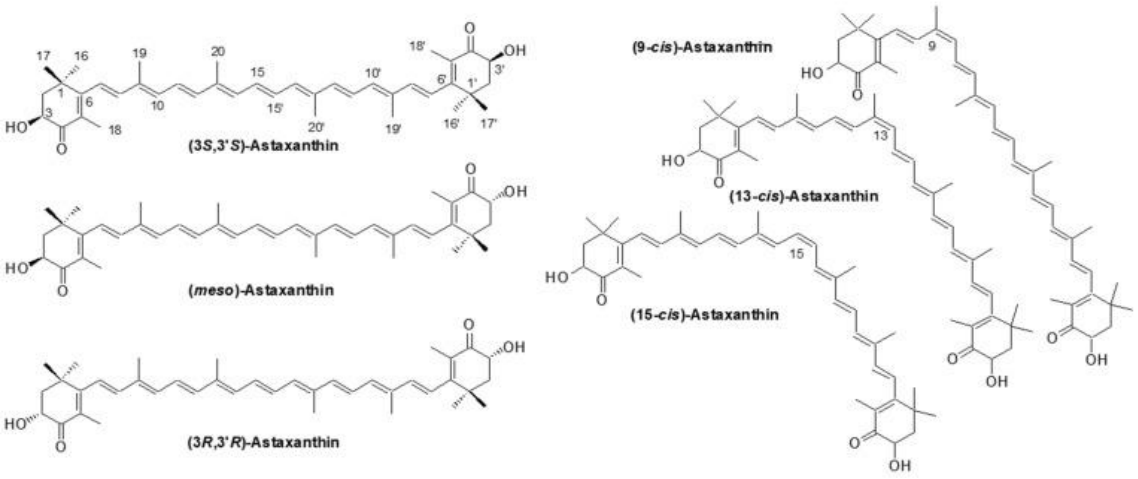

Figure 1. Chemical structure of Astaxanthin (Nishida et al, 2023)

6. ASTAXANTHIN AS A POTENTIAL MYOCARDIAL PROTECTION IN CARDIAC SURGERY

In contrast to other antioxidant therapies, such as vitamin E, vitamin C and beta-carotene, which have proved to be unsuccessful at reducing morbidity and mortality related to cardiovascular disease, Astaxanthin, as newer antioxidant has been deemed to be more potent in its antioxidant activity. (Fassett & Coombes, 2012)

In regard to cardiovascular health, several investigations on Astaxanthin in this medical field has shown that Astaxanthin could partially improve cardiac function in cardiovascular disease patients, including patients with dyslipidaemia, type 2 diabetes melitus, and also patient with glucose/lipid metabolic disorder. (Nishida et al, 2023; Ciaraldi et al, 2023; Saeidi et al, 2023; Mashhadi et al, 2018; Canas et al, 2017) ROS produced by the IRI will react with proteins, lipids and DNA causing protein and lipid oxidation and also DNA damage. In this regard, Astaxanthin as a potent antioxidant will inhibit the activity of this oxidative molecules by quenching singlet oxygen and scavenging radical molecules to stop the destructive reactions. Compare to the other carotenoid, Astaxanthin has higher antioxidant activity with enhanced activity of superoxide dismutase and thioredoxin reductase giving better result as an antioxidant agent. It also has the ability to stay both inside and outside of the cell membrane, preserving the membrane structure by inhibiting lipid peroxidation. Astaxanthin also has the ability to stop inflammation, decreasing the destruction in IRI. (Figure 2) (Ambati et al, 2014; Chang & Xiong, 2020)

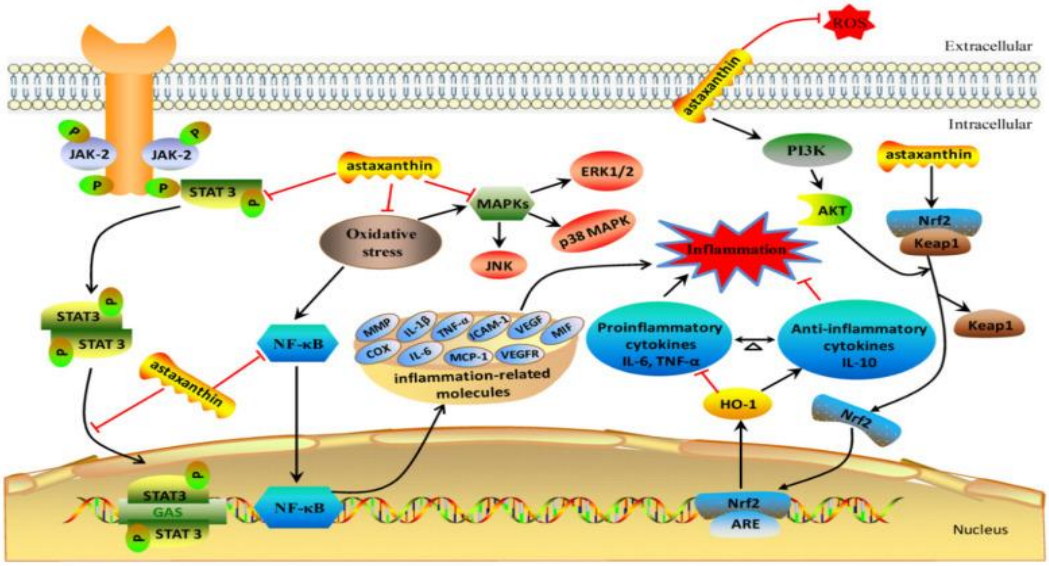

Figure 2. Anti-inflammation mechanism of Astaxanthin (Chang & Xiong, 2020)

Some studies reported that Astaxanthin has the effect of inhibiting genes related to the signaling pathways of inflammation and apoptosis, which is related to the ischemia reperfusion injury. (Zhang et al, 2023; Gai et al, 2020) Other study reported the effect of Astaxanthin in attenuating post ischemic cardiac remodelling by inhibiting inflammation and reducing

myocardial fibrosis. (Pan et al, 2020) Astaxanthin supplementation also showed to be able to increase heart mitochondrial membrane potential and contractility index showing its potential as a myocardial protectant agent. (Nakao et al, 2010)

Until the current experimental studies, no toxic side effect of Astaxanthin consumption has been reported, although excessive consumption will lead to yellow and reddish skin pigmentation of the skin in animal study. Despite abundant experimental studies of Astaxanthin as a potential new myocardial protection strategy, most of the study were done in animal model. The lack of studies in human regarding the benefit and risk of Astaxanthin as a myocardial protection strategy is the limitation in this review to conclude Astaxanthin as a new myocardial protection strategy despite all the cardioprotective benefit reported in previous studies. The current recommended dose of Astaxanthin is 2-4mg/day for healthy adult. (Ambati et al, 2014)

7. CONCLUSION

Astaxanthin is a powerful antioxidant with anti-inflammatory and mitochondrial-protective properties, showing promise as a novel agent to reduce myocardial injury during cardiac surgery. It may offer superior protection against ischemia-reperfusion injury compared to traditional methods, but more human studies are needed to confirm its safety and effectiveness.

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