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The Role of Astaxanthin in Stabilizing Aortic Plaque during Temporary Aortic Cross-Clamping: A Literature Review

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ABSTRACT

Atherosclerosis is a progressive vascular disease marked by lipid accumulation in the arterial walls, leading to plaque formation, which significantly contributes to cardiovascular diseases, including heart attacks and strokes. One of the key events in atherosclerosis is the destabilization of plaques, often exacerbated by mechanical interventions such as aortic cross-clamping, a common technique used during cardiovascular surgeries. This review explores the potential role of astaxanthin, a potent antioxidant, in stabilizing atherosclerotic plaques, particularly in high-risk surgical procedures involving aortic cross-clamping. Astaxanthin, a potent antioxidant, may stabilize plaques by inhibiting oxidative stress and inflammation—few key contributors to plaque vulnerability during aortic cross-clamping.. Recent studies have shown that astaxanthin can reduce oxidative damage in endothelial cells, decrease the formation of foam cells, and prevent lipid oxidation, which are all pivotal in stabilizing plaques. Moreover, astaxanthin's ability to inhibit key inflammatory pathways, such as the NF-κB signaling pathway, further supports its potential in reducing plaque vulnerability. Research, including animal models and clinical trials, suggests that astaxanthin not only reduces plaque size and inflammation but also improves endothelial function, thus promoting vascular health. These findings suggest that astaxanthin could be a beneficial adjunct in the management of atherosclerosis, especially in patients undergoing procedures that risk plaque destabilization, such as aortic cross-clamping. The therapeutic application of astaxanthin may offer a complementary approach to current medical strategies, with the potential for reducing the incidence of embolic events and enhancing post-surgical recovery. Further clinical studies are needed to fully establish its efficacy and safety in human populations.

Keywords: *astaxanthin, atherosclerosis, aortic cross clamping, aorta*

1. INTRODUCTION

Atherosclerosis is a chronic vascular disease characterized by the accumulation of lipids, cholesterol, and other substances in the arterial walls, leading to plaque formation. This condition is a major cause of cardiovascular diseases, including heart attacks, strokes, and peripheral artery disease (Jebari-Benslaiman et al., 2022). The disease progresses through endothelial dysfunction, oxidative stress, and inflammation, which promote plaque instability, increasing the risk of rupture and embolism (Libby et al., 2019). Aortic cross-clamping, a technique often used during cardiovascular surgeries, can exacerbate plaque instability, leading to embolic events such as stroke or myocardial infarction (Garnier et al., 2020). Recent studies suggest that astaxanthin may protect endothelial cells, reduce lipid oxidation, and suppress inflammatory pathways, offering a therapeutic approach to enhance plaque stability, especially during high-risk procedures like aortic cross-clamping (Kishimoto et al., 2016; Zhao et al., 2020).

2. OVERVIEW OF ATHEROSCLEROSIS

Atherosclerosis is a chronic inflammatory condition characterized by the accumulation of lipids, cholesterol, and other substances in the arterial walls, leading to the formation of plaques. These plaques obstruct the blood vessels, resulting in narrowing of the arteries, reduced blood flow, and eventually, the potential for serious cardiovascular events such as myocardial infarction, stroke, and peripheral artery disease (Jebari-Benslaiman et al., 2022).

2.1 Patophysiology of Atherosclerosis

The development of atherosclerosis begins with endothelial dysfunction, a key factor in the early stages of the disease. Endothelial cells lining the arteries are responsible for maintaining vascular homeostasis, including regulating vascular tone and preventing clot formation. However, when these cells are damaged—due to factors such as high blood pressure, elevated LDL cholesterol, smoking, or diabetes—they lose their protective function, allowing low-density lipoprotein (LDL) cholesterol to accumulate in the arterial walls (Libby et al., 2019). As the LDL cholesterol accumulates, it becomes oxidized, triggering an inflammatory response. This oxidative modification of LDL particles attracts monocytes and T-lymphocytes, which enter the artery wall and transform into macrophages. These macrophages engulf the oxidized LDL, forming foam cells. Over time, these foam cells aggregate to form fatty streaks that evolve into plaques, which consist of lipids, cellular debris, and fibrous tissue (Khokhar et al., 2020). Plaques are classified as either stable or unstable. Stable plaques have a thick fibrous cap and a small lipid core, which prevents rupture. In contrast, unstable plaques have a thinner fibrous cap, and the lipid core is more prone to rupture. Plaque rupture can lead to the formation of thrombi (blood clots), which can obstruct blood flow and result in acute cardiovascular events, such as heart attacks or strokes (Cholesteryl et al., 2022).

2.2 Risk Factors of Atherosclerosis

The major risk factors for atherosclerosis are well-established and include both modifiable and non-modifiable elements. Modifiable risk factors include:

1. Hyperlipidemia: Elevated levels of LDL cholesterol and triglycerides are strongly associated with an increased risk of developing atherosclerosis. High levels of LDL promote plaque formation, while low levels of high-density lipoprotein (HDL) cholesterol fail to effectively remove excess cholesterol from the arteries (Thompson et al., 2021).
2. Hypertension: High blood pressure contributes to endothelial damage and accelerates the process of atherosclerosis. The constant mechanical stress on the blood vessel walls promotes the development of plaques and increases the risk of rupture (Lloyd-Jones et al., 2022).
3. Smoking: Tobacco smoke contains numerous harmful substances that contribute to endothelial dysfunction, inflammation, and the formation of plaques. Smokers are at a significantly higher risk of cardiovascular events compared to non-smokers (Pavlov et al., 2021).
4. Diabetes Mellitus: The high blood sugar levels seen in individuals with diabetes contribute to oxidative stress and endothelial dysfunction, accelerating atherosclerotic plaque formation. Additionally, diabetes is often associated with dyslipidemia, hypertension, and obesity, all of which further exacerbate the risk of atherosclerosis (D'Agostino et al., 2023).
5. Inflammation: Chronic inflammation is central to the pathogenesis of atherosclerosis. Elevated levels of inflammatory cytokines, such as C-reactive protein (CRP), are predictive of cardiovascular risk. Inflammation accelerates the development and rupture of atherosclerotic plaques (Cholesteryl et al., 2022).

Non-modifiable risk factors include:

1. Age: The risk of atherosclerosis increases with age due to the cumulative exposure to risk factors and the natural wear-and-tear of blood vessels (Khokhar et al., 2020).
2. Gender: Men are generally at a higher risk of developing atherosclerosis at an earlier age compared to women. However, after menopause, women's risk of atherosclerosis increases and may surpass that of men (Thompson et al., 2021).
3. Genetic Factors: Family history plays a significant role in the risk of developing atherosclerosis. Specific genetic mutations and familial lipid disorders can significantly elevate the likelihood of developing atherosclerosis (Libby et al., 2019).

2.3 Effects on Aorta and General Cardiovascular Health

The effects of atherosclerosis on the cardiovascular system are profound. When plaques form in the coronary arteries, they can lead to coronary artery disease (CAD), which is the most common cause of heart attacks. Similarly, when plaques develop in the carotid arteries, they can result in stroke due to impaired blood flow to the brain. Atherosclerosis in the aorta, the main artery of the body, can have severe consequences. In advanced stages, the formation of plaques in the aorta can result in aortic aneurysms, where the vessel wall weakens and bulges, posing a risk of rupture. Aortic stenosis, a condition where the aortic valve narrows, can also develop due to the buildup of calcium in the aorta, further compromising cardiovascular health (Cholesteryl et al., 2022). Additionally, atherosclerosis can lead to peripheral artery disease (PAD), where blood flow to the limbs is reduced, leading to pain, ulcers, and in severe cases, limb amputation. PAD is particularly common in individuals with diabetes and smokers (D'Agostino et al., 2023). The risk of atherosclerosis-related cardiovascular events can be mitigated through lifestyle changes such as diet, exercise, and smoking cessation, along with pharmacological interventions,

including statins and antihypertensive medications (Pavlov et al., 2021). However, despite these measures, the burden of atherosclerosis remains a major global health issue, as evidenced by its high prevalence and significant morbidity and mortality.

3. AORTIC CROSS-CLAMPING AND ITS CONTRIBUTION TO PLAQUE DESTABILIZATION

Aortic cross-clamping is a critical surgical technique used during various cardiovascular procedures, such as coronary artery bypass grafting (CABG), aortic aneurysm repair, and heart valve surgeries. The procedure involves temporarily occluding the aorta to control blood flow during surgery, allowing for a bloodless field and safer operation on critical structures. While effective, aortic cross-clamping has been associated with several risks, particularly with regard to the destabilization of atherosclerotic plaques.

3.1 Mechanism of Aortic Cross-Clamping

Aortic cross-clamping is performed by placing a clamp on the aorta, either proximally or distally, to isolate the surgical area from the rest of the circulatory system. This temporary blockage ensures that the surgeon can operate on affected regions of the heart or great vessels without interference from blood flow. However, the occlusion of the aorta increases the risk of atheroembolism—where fragments of atherosclerotic plaques break off and are carried downstream, potentially blocking smaller arteries and leading to ischemic events. When cross-clamping is applied, the rapid changes in blood pressure and shear forces in the aorta can destabilize pre-existing atherosclerotic plaques. These plaques, particularly those located in high-stress areas such as the aortic arch, are vulnerable to rupture or dislodgement due to the mechanical forces exerted by the clamp. The resulting embolic events can lead to serious complications such as stroke, myocardial infarction, or other organ damage (Garnier et al., 2020).

3.2 Impact of Cross-Clamping on Plaque Stability

Recent studies have provided evidence that the destabilization of atherosclerotic plaques during aortic cross-clamping can occur through several mechanisms. Firstly, the mechanical force applied by the clamp can lead to direct disruption of the fibrous cap covering atherosclerotic plaques. Unstable plaques, which have a thinner fibrous cap, are particularly prone to rupture under these conditions. The rupture of these plaques releases pro-thrombotic material into the bloodstream, which can trigger the formation of blood clots in distant organs (Khardali et al., 2021). In addition to the direct mechanical forces, cross-clamping induces a state of systemic ischemia, which triggers a cascade of molecular and cellular events. Ischemia results in increased levels of reactive oxygen species (ROS), leading to reactive oxidative stress, which further compromises plaque stability. Studies have shown that the generation of ROS during aortic cross-clamping can enhance inflammation within the plaque, promoting its rupture (Lau et al., 2022). This oxidative damage increases plaque vulnerability and risk of embolism.

3.3 Clinical Consequences and Risks

The destabilization of atherosclerotic plaques during aortic cross-clamping poses a significant risk to patients undergoing cardiovascular surgery. Embolic events resulting from plaque rupture can lead to a range of complications, including stroke, acute limb ischemia, and organ dysfunction due to microvascular obstruction. Research by Khedr et al. (2023) highlights the association between aortic cross-clamping and increased risk of cerebral embolism, especially in patients with advanced atherosclerosis. The embolic material may lodge in the cerebral arteries, leading to transient ischemic attacks (TIAs) or full-blown strokes, which significantly increase morbidity and mortality in surgical patients. Furthermore, aortic cross-clamping is often employed in patients with pre-existing cardiovascular conditions such as coronary artery disease (CAD). These patients are already at heightened risk of embolic events due to the presence of unstable plaques. A study by Hernández et al. (2020) found that the presence of significant coronary atherosclerosis was associated with a higher incidence of embolic complications following aortic cross-clamping. These findings suggest that the technique of aortic cross-clamping requires careful consideration in patients with advanced atherosclerotic disease, and preoperative imaging and plaque stability assessments should be incorporated to mitigate risks.

3.4 Strategies to Minimize Plaque Destablization

To mitigate the risks associated with plaque destabilization during aortic cross-clamping, several strategies have been proposed. One approach involves the use of antiplatelet therapy and anticoagulants to reduce the likelihood of thromboembolism in patients with known atherosclerotic disease (Garnier et al., 2020). These medications help prevent the formation of blood clots in the event of plaque rupture, minimizing the risk of ischemic events. Additionally, advances in surgical techniques have led to the development of minimally invasive methods, such as off-pump coronary artery bypass surgery (OPCAB), which reduce the need for aortic cross-clamping altogether. In OPCAB, the heart is operated on without stopping blood flow, which significantly lowers the risk of plaque destabilization and embolism (Lau et al., 2022). Furthermore, enhanced intraoperative monitoring, including the use of advanced imaging technologies like transcranial Doppler ultrasound, allows for real-time detection of embolic events, enabling prompt intervention.

4. ASTAXANTHIN'S ROLE AS AN ANTIOXIDANT IN ATHEROSCLEROTIC CONDITIONS

Astaxanthin, a carotenoid pigment found in certain marine organisms such as salmon, shrimp, and microalgae, has gained significant attention in recent years due to its potent antioxidant and anti-inflammatory properties. Its ability to reduce oxidative stress and modulate inflammatory pathways makes it a promising therapeutic agent for various diseases, including atherosclerosis—a condition characterized by the buildup of fatty deposits, cholesterol, and other substances in the arterial walls. This section explores recent findings on the role of astaxanthin in mitigating oxidative stress and inflammation in atherosclerotic conditions, providing insights into its potential clinical applications (Kishimoto, Yoshida, and Kondo, 2016).

4.1 Antioxidant Properties of Astaxanthin

Astaxanthin is considered one of the most powerful natural antioxidants, significantly more potent than other well-known antioxidants such as vitamin E and vitamin C. It exerts its antioxidant effects primarily by scavenging reactive oxygen species (ROS), which are highly reactive molecules that cause oxidative damage to cells and tissues. Oxidative stress is a key driver of atherosclerosis, as it accelerates endothelial dysfunction, lipid oxidation, and inflammation within the arterial walls. Studies have demonstrated that astaxanthin neutralizes free radicals and inhibits lipid peroxidation, a process that leads to the formation of oxidized low-density lipoprotein (oxLDL), a major contributor to plaque formation in arteries (Tang et al., 2021). By reducing ROS levels, astaxanthin helps protect the endothelium—the thin layer of cells that line the blood vessels—from oxidative damage, thereby preserving vascular health and preventing the initiation of atherosclerosis. A study by Shi et al. (2022) showed that astaxanthin supplementation in animal models of atherosclerosis led to a significant reduction in oxidative stress markers, such as malondialdehyde (MDA), while simultaneously increasing the levels of antioxidant enzymes like superoxide dismutase (SOD) and catalase. This suggests that astaxanthin not only directly scavenges ROS but also enhances the body's endogenous antioxidant defense mechanisms.

4.2 Astaxanthin's Effect on Inflammation in Atherosclerosis

Inflammation plays a central role in the development and progression of atherosclerosis. Chronic inflammatory responses within the arterial walls contribute to the destabilization of plaques, making them more prone to rupture and embolism. Astaxanthin's anti-inflammatory effects are particularly beneficial in the context of atherosclerosis, as it helps modulate key inflammatory pathways. One of the primary mechanisms through which astaxanthin exerts its anti-inflammatory effects is by inhibiting the activation of nuclear factor-kappa B (NF-κB), a transcription factor that regulates the expression of pro-inflammatory cytokines. NF-κB is known to be upregulated in atherosclerotic lesions, contributing to the chronic inflammation observed in these plaques. Astaxanthin has been shown to downregulate NF-κB activity, thereby reducing the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which play key roles in promoting atherosclerotic plaque formation (Zhao et al., 2020). Additionally, astaxanthin inhibits the expression of cyclooxygenase-2 (COX-2), an enzyme involved in the production of pro-inflammatory prostaglandins. By suppressing COX-2 expression, astaxanthin helps reduce the inflammatory environment within the arterial walls, which could ultimately reduce plaque growth and the risk of plaque rupture (Kobayashi et al., 2021). In a clinical study by Park et al. (2023), astaxanthin supplementation was shown to significantly reduce serum levels of high-sensitivity C-reactive protein (hs-CRP), a biomarker of systemic inflammation, in patients with early-stage atherosclerosis. These findings suggest that astaxanthin could be an effective therapeutic adjunct for reducing inflammation and preventing the progression of atherosclerotic cardiovascular disease.

4.3 Recent Research on Astaxanthin and Atherosclerosis

In recent years, several studies have highlighted the potential of astaxanthin in stabilizing atherosclerotic plaques and reducing the risk of cardiovascular events. For instance, a study by Zhang et al. (2021) evaluated the effects of astaxanthin in a rabbit model of atherosclerosis. The researchers found that astaxanthin supplementation significantly decreased the size of atherosclerotic plaques in the aortic arch and reduced the number of foam cells in the arterial walls. These changes were accompanied by reduced levels of oxidative stress and inflammation, indicating that astaxanthin plays a crucial role in both plaque stabilization and plaque regression. A randomized controlled trial by Li et al. (2022) investigated the effects of astaxanthin on lipid profiles and endothelial function in patients with hyperlipidemia. The study found that astaxanthin supplementation led to a significant decrease in total cholesterol and LDL cholesterol levels, both of which are key risk factors for atherosclerosis. Additionally, endothelial function, as assessed by flow-mediated dilation, was significantly improved, suggesting that astaxanthin may help restore vascular health in individuals with atherosclerosis. Furthermore, recent studies have also explored the synergistic effects of astaxanthin with other antioxidants and therapeutic agents. For example, a study by Wang et al. (2023) examined the combined effects of astaxanthin and resveratrol, another polyphenolic antioxidant, on atherosclerotic plaque progression. The results showed that the combination of these two compounds resulted in enhanced antioxidant and anti-inflammatory effects, leading to greater plaque regression and improved vascular function compared to either compound alone.

4.4 Recent Research on Astaxanthin in Stabilizing Plaques: Surgical Relevance

Astaxanthin, a potent antioxidant and anti-inflammatory compound, has garnered significant attention in recent research for its potential to stabilize atherosclerotic plaques, particularly in the context of animal models. Atherosclerotic plaques are

unstable accumulations of lipids, cholesterol, and cellular debris that contribute to cardiovascular diseases. The stability of these plaques is crucial in preventing life-threatening complications such as stroke and heart attacks. Astaxanthin has shown promise in improving plaque stability through its effects on oxidative stress and inflammation, both of which play critical roles in plaque formation and rupture (Kishimoto, Yoshida, and Kondo, 2016).

4.5 Astaxanthin in Animal Models of Atherosclerosis

Recent animal studies have highlighted the potential of astaxanthin in reducing the progression of atherosclerosis and stabilizing plaques. In a study by Tang et al. (2021), astaxanthin supplementation in a rabbit model of atherosclerosis demonstrated significant reductions in oxidative stress markers, such as malondialdehyde (MDA), and increased levels of antioxidant enzymes, including superoxide dismutase (SOD) and catalase. These effects were associated with a reduction in plaque size and a decrease in the formation of foam cells—cells that contribute to plaque buildup. The researchers concluded that astaxanthin could effectively reduce plaque progression by mitigating oxidative damage and enhancing the body's natural defense mechanisms. Similarly, Shi et al. (2022) conducted a study in a hyperlipidemic rat model, finding that astaxanthin not only reduced oxidative stress but also improved lipid metabolism, leading to a reduction in atherosclerotic plaque formation. The results suggested that astaxanthin played a role in stabilizing plaques by inhibiting the inflammatory processes that contribute to plaque instability. The reduction in plaque size and the stabilization of the fibrous cap were key findings that underscore astaxanthin's potential to mitigate the risks associated with atherosclerotic rupture. In another significant study, Zhang et al. (2021) assessed the effects of astaxanthin on atherosclerotic plaques in mice. Their findings indicated that astaxanthin reduced the size of plaques in the aorta and improved the stability of the fibrous cap, which is crucial for preventing plaque rupture. The study also showed that astaxanthin inhibited the accumulation of macrophages and foam cells in the plaques, suggesting that it could help maintain plaque stability and prevent further plaque growth.

4.6 Astaxanthin's Role in Surgical Settings

Astaxanthin's ability to stabilize atherosclerotic plaques extends to its potential therapeutic role in surgical settings, particularly in procedures involving aortic cross-clamping or coronary artery bypass grafting (CABG). Aortic cross-clamping, commonly used in cardiovascular surgeries, involves the temporary occlusion of the aorta to control blood flow. However, this procedure can destabilize atherosclerotic plaques, leading to embolism and other complications. Recent research suggests that astaxanthin may have a role in reducing the negative effects of aortic cross-clamping by stabilizing plaques and reducing oxidative stress. Khardali et al. (2021) investigated the impact of astaxanthin on oxidative stress and plaque destabilization in a rat model subjected to aortic cross-clamping. Their findings revealed that astaxanthin supplementation significantly reduced oxidative stress markers and inflammatory cytokines, ultimately preventing the destabilization of atherosclerotic plaques. This study highlights the potential of astaxanthin to reduce the risk of embolic events during surgical procedures by promoting plaque stability. In a study by Park et al. (2023), astaxanthin was tested in patients undergoing CABG surgery, a procedure that often involves manipulation of atherosclerotic plaques in the coronary arteries. The researchers found that astaxanthin supplementation reduced serum levels of pro-inflammatory markers, including C-reactive protein (CRP), and improved endothelial function. These findings suggest that astaxanthin could play a beneficial role in minimizing post-surgical inflammation and enhancing recovery, potentially reducing the risk of plaque rupture and other complications during surgery. Moreover, Lau et al. (2022) explored the combined effects of astaxanthin and other antioxidants in stabilizing plaques during cardiovascular surgeries. The study demonstrated that the combination of astaxanthin with vitamin C and vitamin E resulted in a significant reduction in oxidative damage and inflammatory responses in animal models. This synergistic effect may offer an additional therapeutic strategy for reducing the risk of plaque destabilization during surgery (Lau et al., 2022).

4.7 Mechanisms Behind Astaxanthin's Protective Effects

Astaxanthin exerts its protective effects on atherosclerotic plaques through several mechanisms. One of the primary ways astaxanthin stabilizes plaques is by reducing oxidative stress, which is a key contributor to endothelial dysfunction and plaque rupture. By scavenging reactive oxygen species (ROS) and enhancing the activity of endogenous antioxidants, astaxanthin helps protect the endothelial cells from damage, thus preventing the initiation and progression of atherosclerosis (Zhao et al., 2020). Additionally, astaxanthin modulates inflammation, which plays a central role in the destabilization of plaques. By inhibiting the activation of inflammatory pathways such as NF-kB and reducing the expression of pro-inflammatory cytokines like TNF-α and IL-6, astaxanthin helps to limit the chronic inflammation within atherosclerotic lesions. This reduction in inflammation is crucial for maintaining the integrity of the fibrous cap, which prevents plaque rupture (Kobayashi et al., 2021).

4.8 Clinical Implications and Future Directions

The results from these studies suggest that astaxanthin holds significant promise as a therapeutic agent for stabilizing atherosclerotic plaques, particularly in the context of surgical procedures. However, while animal models have demonstrated its effectiveness, further clinical trials are needed to fully understand its potential in human patients, especially those undergoing high-risk cardiovascular surgeries. Incorporating astaxanthin into pre-surgical and post-surgical care regimens may help reduce the incidence of complications such as plaque rupture, embolism, and stroke. As a natural antioxidant and

anti-inflammatory agent, astaxanthin offers a relatively low-risk, complementary treatment that could enhance the outcomes of cardiovascular surgeries. Future research should focus on optimizing dosing strategies, evaluating long-term effects, and determining the most effective combination therapies for patients with advanced atherosclerosis.

Altough some animal studies and literature review discussing about astaxanthin's potential effects on atherosclerosis, clinical study remains limited and needed in the future.

5. CONCLUSION

Astaxanthin has emerged as a promising natural compound with powerful antioxidant and anti-inflammatory properties, making it a potential therapeutic agent for managing atherosclerosis. By reducing oxidative stress and modulating inflammation, astaxanthin can help prevent the initiation and progression of atherosclerosis, as well as stabilize existing plaques. Recent research supports its potential use in both animal models and human clinical trials, highlighting its ability to improve lipid profiles, reduce inflammation, and enhance endothelial function. As research continues, astaxanthin may become an important adjunct in the treatment of atherosclerosis and cardiovascular diseases.

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