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Review Article

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Myocardial infarction protective effect of xyloglucan on *Drosophila melanogaster*: A review

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ABSTRACT

Myocardial infarction, more often known as cardiac arrest, occurs when the supply of blood to the heart's coronary artery decreases or ceases, causing damage to the heart muscle. Xyloglucan is a plant polysaccharide. Xyloglucan has been proven in several studies utilizing model organisms to reduce the risk of coronary heart disease by avoiding post-occlusion phases inhibiting apoptosis and enhancing energy metabolism. Many studies utilize *Drosophila melanogaster* because its SRY-related HMG-box 5 (SOX5) gene encodes a SOX family transcription factor; the human SOX5 ortholog, Sox102F, is well conserved in *Drosophila melanogaster*. Suppressing Sox102F in flies resulted in significant heart dysfunction, structural defects, and a disturbance in notch signal transduction. This demonstrates that SOX5 serves an important functional part in the heart and that variations in SOX5 concentrations may contribute to the possibility of myocardial infarction. Xyloglucan activity is significant in myocardial infarction and may be lowered in the myocardium after H/R damage by stimulating Notch signaling, which may benefit myocardial survival, angiogenesis, and cardiac function. This review discusses the roles of the human SOX5 and Drosophila SOX102F genes, the notch signaling system, and how xyloglucan in tamarind seeds may defend against heart damage by preventing apoptosis along with improving energy metabolism.

KEYWORDS: Myocardial infarction, Xyloglucan, *Drosophila melanogaster*, Notch signaling pathway.

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INTRODUCTION

An acute myocardial infarction (AMI), sometimes known as a cardiac arrest, is caused largely by a decrease or stoppage in blood flow to a segment of the heart, leading to necrosis of heart muscle (Reed *et al.*, 2017). A clot of blood frequently develops within the epicardial artery, supplying blood to the heart muscle in that location. The most prevalent cause of myocardial infarction is thrombotic blockage of a coronary channel caused by a weak plaque rupture (Li *et al.*, 2017). 70% of mortality in individuals with acute myocardial infarction is caused by atherosclerotic plaque blockage. Because atherosclerosis is the most prevalent cause of acute myocardial infarction, risk factors for atherosclerotic disease are frequently reduced in disease prevention. Modifiable risk factors induce 90% of men's and 94% of women's myocardial infarctions. Risk factors that can be changed include cholesterol, triglycerides, low-density lipoproteins, obesity, hypertension, exercise, and cigarette smoking. Gender, family history and age are non-modifiable risk factors for atherosclerosis on the other hand (Berg *et al.*, 2018; Deng *et al.*, 2018) (Figure 1).

The SRY-related HMG-box 5 (SOX5) gene on chromosome 12p12 (OMNI 604975) encodes a transcription factor that binds to DNA. SOX5 is found in many different organs, including the human liver, heart, kidney, lung, spleen, testis

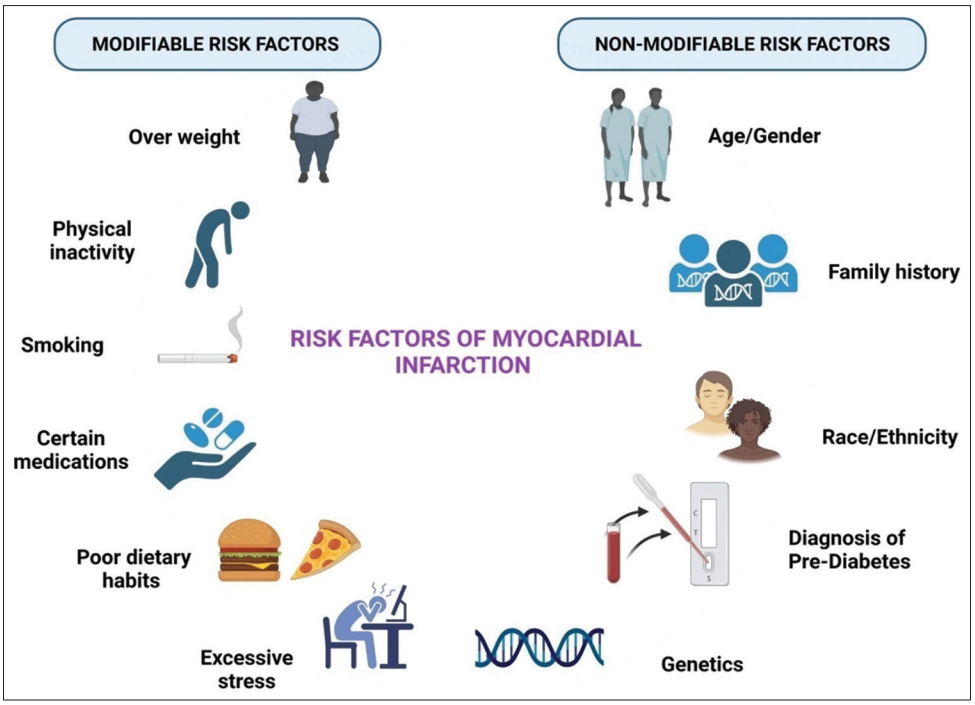

Figure 1: Risk factors of Myocardial infarction

and fetal brain. SOX5 has been shown in studies to influence cell proliferation, cell destiny, and the formation of neurons and cartilage. In genome-wide association studies, SOX5 has recently been discovered as a potential gene for vulnerability to four cardiac endophenotypes: higher resting heart rate (HR), atrial fibrillation, the electrocardiographic PR interval, and left ventricular mass. The adult fly cardiac function is provided by Sox102F, a highly conserved Drosophila homologue of human SOX5. Silencing Sox102F in adult flies resulted in a considerable reduction in HR, cardiac wall velocities and heart chamber size, as well as an increase in ventricular wall thickness and disruption of myofibril structure. Furthermore, silencing Sox102F in the wing resulted in increased expression of wingless, a key element of the notch signaling pathway, as well as raised and disorganized L2, L3, and wing marginal veins. Ultimately, Sox102F silencing triggered structural flaws, severe cardiac dysfunction, and a disruption in notch signaling transduction in flies (Li *et al.*, 2013, 2017). Changes in SOX5 levels may lead to the development of a variety of heart diseases or features (Li *et al.*, 2013; Dong *et al.*, 2021).

According to a recent study, tamarind seeds contain xyloglucan, a naturally occurring, water-soluble, non-toxic, and edible polymer (Lim & Lee, 2017; Nguyen *et al.*, 2019). Although *Copaifera langsdorffii* and *Hymenaea courbaril*are two other types of seeds that contain xyloglucan, tamarind seed is the most prevalent source of xyloglucan (*Tamarindus indica*). Xyloglucan, a branched heteropolysaccharide, contains a backbone chain consisting of D-glucan. This backbone chain undergoes partial substitution at the O-6 position. Substitutions occur with D-glucopyranosyl residues, which can be replaced by 2-O-D-galactopyranosyl, 2-O-D-xylopyranose, or D-xylopyranose. The tamarind xyloglucan has three distinct repeating unit structures: monosaccharide (Glc_4 Xyl_3 Gal_2), heptasaccharide (Glc4 Xyl3) and octasaccharide (Glc_4 Xyl_3 Gal) (Nguyen *et al.*, 2019). It was determined that tamarind xyloglucan is a high-molecular-weight polysaccharide with an average weight of 1,331 kDa. Using gel permeation chromatography (Lim & Lee, 2017), Xyloglucan isolated from various sources of material may have various architectures (Lim & Lee, 2017; Arshad *et al.*, 2019). In native xyloglucan, xylose, glucose, and galactose were present in the molar ratios of 2.8:3.7:1. The antioxidant composition of the tamarind xyloglucan gives it both antioxidant and radical-scavenging properties. In the presence of polyphenols, alcohol, and sugar, xyloglucan often forms a gel. Xyloglucan has been utilized for a range of applications in both edible and nonedible products, including emulsification, stability, gelling, textural improvement, thickening, crystallization inhibition, and bulking (Frangogiannis, 2015). In addition to the typical industrial applications of xyloglucan, original and customized xyloglucans are being researched for use as tissue engineering biomaterials, antiviral agents, and delivery vehicles for drugs. The antibacterial drug ciprofloxacin, which is helpful in treating eye infections, can be delivered to the eyes via xyloglucan, a possible film-forming polymer (Frangogiannis, 2015; Lim & Lee, 2017; Arshad *et al.*, 2019). Moreover, it was used in polymeric composites with other polymers to modulate drug release from different microspheres and beads over time. Furthermore, Xyloglucan may aid in the healing of corneal wounds, regeneration of the skin, and general injuries. Many studies have demonstrated protection against myocardial infarction by utilizing model organisms that prevent apoptosis and increase energy metabolism (Lim & Lee, 2017), showing that xyloglucan consumption reduces coronary heart disease risk by inhibiting post-occlusion processes (Lim & Lee, 2017; Arshad *et al.*, 2019).

ROLE OF HUMAN SOX5 AND *DROSOPHILA MELANOGASTER* SOX102F IN MYOCARDIAL INFARCTION

The SRY-related HMG-box 5 (SOX5) gene encodes a transcription factor from the SOX family. SOX5 may have an important role in the control of cardiac function. In recent genome-wide association studies, SOX5 has been determined to be a potential causal gene for vulnerability to four cardiac endophenotypes, including higher resting heart rate, atrial fibrillation, the electrocardiographic PR interval and left ventricular mass (Li *et al.*, 2013, 2017). Sox102F, a Drosophila homologue of human SOX5, is a highly conserved protein, that has been shown in numerous studies, and transgenic drosophila models have been used to quantitatively quantify heart function in mature flies. In adult flies, silencing of Sox102F caused a large drop-in heart rate, cardiac wall velocities, and heart chamber size, as well as a considerable raise in the thickness cardiac wall along with a disruption of myofibril structure (Li *et al.*, 2017). Silencing Sox102F in the wing caused bigger wing marginal veins and L2, L3, as well as enhanced and disordered expression of wingless, a key component of the notch signaling system (Li *et al.*, 2010). Overall, the silencing of Sox102F caused structural abnormalities, significant cardiac dysfunction, and a breakdown in notch signal transduction in flies (Li *et al.*, 2017). This demonstrates that SOX5 plays an important functional role in the heart and that variations in SOX5 levels might have an essential part in the development of a variety of cardiac illnesses or characteristics (Table 1) (Li *et al.*, 2017; Kachanova *et al.*, 2022).

THE NOTCH SIGNALLING PATHWAYS ROLE IN MYOCARDIAL INFARCTION

In flies, Sox102F silencing caused severe cardiac dysfunction, structural flaws, and a disruption in notch signal transduction (Berg *et al.*, 2018; Kachanova *et al.*, 2022). At several stages of myocardial infarction, including ischemia-induced cardio myocyte damage, scarring, and the reactive stage, the Notch signaling system exerts cardio protective benefits (Arshad *et al.*, 2019). Notch decreases oxidative stress in the earlier stages of myocardial infarction by limiting the number of mitochondria and activating the MFN protein. Moreover, Akt is stimulated by Notch, and Akt is responsible for the mitochondria's production of antioxidant enzymes (Frangogiannis, 2015). Notch supports the activation of an AMP-activated protein kinase pathway, which enhances reserves of energy in cells. By promoting the synthesis of anti-apoptotic proteins and survival factors (PI3K/AKT), apoptosis can be avoided. As a result, Notch promotes the CMC's survival and lessens the harm caused by MI (Frangogiannis, 2015). Since Notch blocks the exchange of TGF-1/Smad$_3$ signals, myofibroblasts produce less ECM, which reduces cardiac fibrosis (Figure 2). Nonetheless, it is critical to assess Notch's capacity to induce the transformation of epicardial cells to a group of multipotent stem cells with a myofibroblast characteristic. Notch inhibits cardiac remodeling by increasing the expression of hypertrophy markers (Li *et al.*, 2010; Kachanova *et al.*, 2022). The development of new vessels from old one's results in the restoration of blood flow in the latter stages of MI. It is regulated by the interaction between VEGF and Notch. Moreover, Notch aids in endothelium's homeostatic control. Although the entire Notch signaling pathway has many traditional characteristics, several parts of its activity

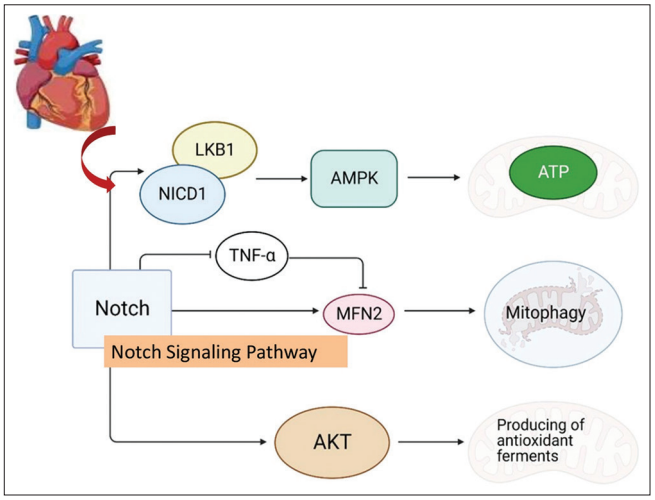

Figure 2: The role of the Notch signaling pathway in reducing oxidative stress (Kachanova *et al.*, 2022)

Table 1: Investigating the roles of human SOX5 and *Drosophila melanogaster's* SOX102F in myocardial infarction

Gene (Homologue)	Function in Heart	Genome-Wide Association Studies (Cardiac Endophenotypes)	Drosophila Homologue (So×102F)	Effects on Heart Function (Adult Flies)	Effects on Wing (Silencing in Wing)
SOX5	Control of cardiac function	Potential causal gene for: -Atrial fibrillation -Left ventricular mass	N/A	-Higher resting heart rate -Electrocardiographic PR interval	N/A
SOX102F	Highly conserved protein	Transgenic Drosophila models used for heart function	Silencing causes	-Drop in heart rate	-Bigger wing marginal veins and L2, L3
Drosophila (homologue)			-Decreased cardiac wall -Velocities -Reduced heart chamber size -Increased cardiac wall thickness	-Decreased cardiac wall velocities -Reduced heart chamber size -Increased cardiac wall thickness -Disruption of myofibril structure -Breakdown of notch signal transduction	-Enhanced and disordered expression of wingless (Notch) -Signaling component

are different in mammals and in *Drosophila melanogaster*. Its function alters during the ontogenesis process because of epigenetic alterations. Notch's influence is greatly dependent on cellular and tissue a condition which further complicates the investigation of this problem (de Celis & García-Bellido, 1994; Kachanova *et al.*, 2022). This is explained in part by the close contact among the Notch signaling pathway and other regulatory mechanisms involved in the systemic response to MI. Hypoxic conditions cause HIF-1a to be activated, which then activates Notch and its target genes (Wu *et al.*, 2017; Zhou *et al.*, 2018). Different effects arise from interactions between TNF and Notch in distinct circumstances. Yet, based on broad observations, one could summarize that Notch is involved in the pathophysiology of MI that is primarily cardioprotective. This needs the development of strategies for altering during both the early phases of MI and the later stages of cardiac muscle regeneration, the Notch signaling pathway was activated (Nistri *et al.*, 2017; MacGrogan *et al.*, 2018; Zhang *et al.*, 2022).

ROLE OF XYLOGLUCAN IN PREVENTION OF MYOCARDIAL INJURY

Xyloglucan (XyG) is generated from higher plant cell walls and is abundant in dicotyledonous plants (Mishra & Malhotra, 2009). *Tamarindus indica L.* (tamarind) represents a dicotyledonous plant with high xyloglucan content. Xyloglucan is a common polysaccharide with a beneficial impact on myocardial infarction. Enzymes encoded in the human genome cannot directly degrade xyloglucan. Enzymes encoded in the human genome cannot directly degrade xyloglucan because it is a non-starch polysaccharide. Myocardial infarction refers to a pathological disease defined by the loss of many cardiomyocytes (CMC) as a result of ischemia. The progression of coronary heart disease can be split into two stages: pre-occlusion and post-occlusion (Mishra & Malhotra, 2009; van de Vegte *et al.*, 2019). Previous research found that tamarind seed polysaccharides with a high xyloglucan content protected against cardiac damage by inhibiting post-occlusion processes. In this case, xyloglucan, a polysaccharide rich in xylose, glucose, and galactose, may also provide myocardial protection (Lim *et al.*, 2016). An *in-vivo* investigation revealed that activated monosaccharides such as xylose and arabinose decrease apoptosis, sparing the heart from harm. The active component xylose in xyloglucan contributes to its potency. TXG increases the expression of myoglobin & fatty acid-binding proteins, both of which are implicated in apoptosis and ATP production (Figure 3). TXG inhibits apoptosis via decreasing p38 and JNK phosphorylation (Mishra & Malhotra, 2009; Dong *et al.*, 2021). Increased Bcl-2/Bax ratio, suppression of procaspase-3 conversion to cleaved caspase-3, and decreased DNA nick formation (Mishra & Malhotra, 2009; Singh *et al.*, 2023). These findings imply that xyloglucan found in tamarind seeds can protect the heart by preventing apoptosis and improving energy metabolism (Mishra & Malhotra, 2009; Pfeufer *et al.*, 2010). As a consequence, tamarind seed xyloglucan adds to the known advantages of tamarind in decreasing the risk of coronary heart disease by delaying post-occlusion stages via apoptosis (Yamatoya *et al.*, 2000; Lim & Lee, 2017; Chen *et al.*, 2020).

The intake of Xyloglucan enhances the production of microbial products during ischemia/reperfusion (I/R), fatty acid binding protein (FABP) and Myoglobin (Mb) levels rise as a result. These increased FABP and Mb levels contribute to increased Adenosine triphosphate (ATP) production within the mitochondria and decreased reactive oxygen species (ROS). As a result, JNK and P38 phosphorylation is effectively inhibited. In addition, the Bcl-2 to Bax ratio has gotten better. This crucial process extends cardiomyocyte longevity by limiting the conversion of procaspase-3 to caspase-3 by restricting the release of cytochrome c from the mitochondria. Notably, XyG microbial fermentation yields both xylose and short-chain fatty acids. Furthermore, FA-FABP is generated when fatty acid (FA) and FABP are united, whereas FACoA is formed when fatty acylCoA and FABP are combined. Furthermore, oxygen is coupled to the metal (Mb + O2) (Lim & Lee, 2017).

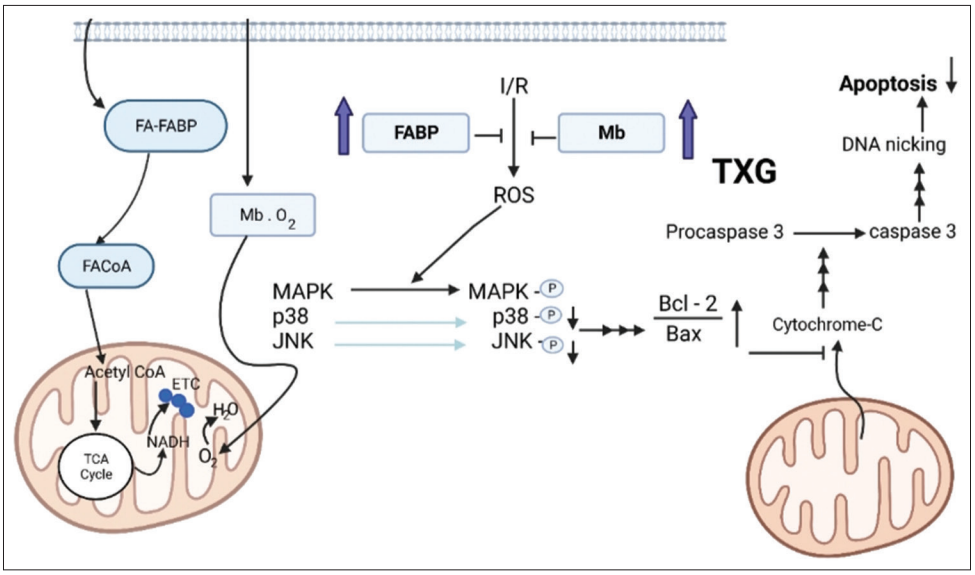

Figure 3: The role of Xyloglucan in prevention of myocardial injury

CONCLUSION

In recent years, there has been a surge in interest in active ingredients present in traditional herbs, driven by the expanding field of botanical medicine. In cardiovascular problem research, polysaccharides have drawn a lot of attention among these ingredients because they make up a sizable amount of plant extracts. However, current research focuses mostly on the the extraction process, separation, and physical and chemical characteristics of plant polysaccharides, whereas pharmacological analysis of these compounds is still in its infancy. To get a thorough understanding of plant polysaccharides' cardiovascular preventive benefits, future research should focus on identifying their targets inside the body and deciphering the underlying molecular pathways. It is vital to highlight that the structural complexity of polysaccharide monomers in plants, as well as individual variances, may result in undesirable outcomes. Despite the widely held belief that plant polysaccharides have low toxicity and little side effects, it is critical to determine their molecular structure and analyse any potential adverse reactions.

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