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(REVIEW ARTICLE)

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Cardioprotective effects of novel antioxidants post-myocardial infarction: An integrative review of preclinical and clinical data

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Abstract

Myocardial infarction (MI), is still a major public health problem, and oxidative stress contributes to the degree of myocardial damage after MI. Oxygen-derived free radicals (ODFR) worsen myocardial injury and result in chronic heart failure in many patients. These harms have led to interest in antioxidant treatment to reduce these adverse effects; new antioxidants with the potential for cardioprotection are the subject of significant interest. This review summarizes basic and clinical research comparing the effectiveness of newly synthesized antioxidants in attenuating oxidative stress and enhancing recovery after myocardial infarction.

The review synthesizes evidence of a reduction in infarct size, enhancement of cardiac function, and repression of apoptosis in myocardial cells by the use of antioxidants from animal models. Melatonin, N-acetylcysteine, edaravone, and coenzyme Q10 demonstrated a wide range of preclinical positive effects by acting as ROS free radicals scavengers, modulating mitochondria dysfunction, and reducing inflammation. These findings are extrapolated from humans, although advances in antioxidant therapy are beginning to be viewed in initial clinical trials.

From human data, although clinical trials are scarce, the evidence of new antioxidants can improve point and long-term outcomes in patients undergoing MI, help to increase the contractility of the injured myocardium, and decrease the mortality level. However, some issues are still there, such as high inter- and intra-individual variability in patient response and dosing schedule, as well as adverse effects such as pro-oxidant activity at high Oral administered doses of melatonin. The limitations of the current research discussed in this review include the general lack of large-scale, well-controlled clinical trials and the need for long-term follow-up studies. This review also proposed future research directions for improving antioxidant applications in post-MI management.

Keywords: Myocardial Infarction; Antioxidants; Cardioprotection; Oxidative Stress; Preclinical Studies; Clinical Trials; ROS.

1. Introduction

Myocardial infarction (MI), otherwise known as heart attack, is still a major cause of death, with escalating morbidity and disability rates across the world. MI is when a part of the heart is under-supplied with blood, so the muscle receives inadequate oxygen. The incidence of MI and its consequent global morbidity is still high. Millions of people are affected by this disease annually, and it continues to be a major source of health and economic burden (Murray and Lopez, 2017).

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Cardiovascular diseases, including MI, contribute heavily to mortality worldwide, and these factors include inadequate diet, smoking, and physical inactivity, which contribute to increasing this burden (World Health Organization, 2011).

The mechanisms of oxidative stress by which MI occurs have been well described. In the same process of MI, there are a lot of generations of ROS, which results in oxidant stress of cardiac tissue. This oxidative stress potentiates myocardial damage and the progression of chronic heart failure in the long term (Madamanchi & Runge 2007). ROS leads to inflammation, apoptosis, and necrosis of cardiomyocytes, apart from initiating adverse cardiac remodeling post-infarction, has been demonstrated by Chen et al. (2013). Reducing oxidative stress through pharmacological treatments is now a central tenant of cardiovascular pharmacology.

Oxidative agents have long been thought to have the ability to decrease the levels of oxidative stress and prevent further damage to the heart. Originally, psychotropic medications like vitamins C and E were evaluated for their capabilities to scavenge ROS and lessen oxidative damage. However, the findings of these studies could be more conclusive, and more recently, researchers have turned their focus to newly identified and more selective, efficient antioxidants (Rodrigo et al., 2013). Due to their better cardioprotective characteristic, this new generation of antioxidants consists of melatonin, N-acetylcysteine, and edaravone. For instance, they effectively regulate the redox status of cells, decrease mitochondria dysfunction, and decrease apoptosis in myocardial tissues (Dhalla et al., 2000).

However, concerning the discussed advantages, the practical use of antioxidants for MI patients has yet to be discovered. While basic research for these agents looks rather favorable, clinical trial studies on a large scale still need to be included to finally endorse these agents in clinics (Gutteridge & Halliwell, 2015). With cardiovascular diseases still threatening the lives of millions of people globally, there is research potential for understanding other eccentric antioxidants after MI.

1.1. Overview

MI sets off a chain of biochemical reactions; increased generation of ROS and oxidative stress are two of them, and they contribute to myocardial damage. If ROS exceeds antioxidant capacity, oxidative stress rises, resulting in lipid peroxidation, protein oxidation, and DNA damage, impeding cell survival and tissue integrity in the heart (Rodrigo et al., 2013). This oxidative injury not only imparts the initial damage to the myocardial tissues but also has other effects, including adverse remodeling of cardiac structure, chronic inflammation, and heart failure.

Furthermore, during surgeries involving ischemia-reperfusion – which is the process of returning blood flow in the heart after the infarction – oxidative stress rises, which leads to continued myocardial injury. Restoring blood flow and oxygen availability can further injure tissues through ROS-dependent processes in a reperfusion injury reaction (Ferrari et al., 2006). Reducing oxidative stress, therefore, becomes very important in managing MI and preventing further deterioration.

Oxidative stress managed by antioxidants that neutralize ROS has received much attention in preventing and reducing myocardial damage following MI. Consequently, conventional and novel antioxidants have been regarded for their prospect of conferring selective cardioprotection. These compounds act therapeutically in different ways, such as altering mitochondrial function, suppressing inflammatory mediators, and preventing apoptosis (Rodrigo et al., 2013). For instance, melatonin has proved to possess potent antioxidant properties by preventing oxidative stress in the heart and maintaining mitochondrial function (Reiter et al., 2014). Another antioxidant compound, called edaravone, has been reported to avoid lipid peroxidation and lessen infarct size in animal models of MI (Yamashita et al., 2003).

Another new antioxidant identified as N-acetylcysteine (NAC) has been approved to enhance the private performance of the heart after MI by regenerating glutathione. This endogenous antioxidant neutralizes ROS (Das & Maulik, 2001). These new SC antioxidants manage oxidative stress and enhance myocardial repair and function by protecting cellular structures and avoiding cell death.

Although conventional antioxidants given in clinical trials have shown varied efficacy, these novel molecules offer more precise and energetic ways of gaining cardioprotection. However, additional human research remains to be undertaken to accurately evaluate their potential in clinical settings because most studies are based on animal experiments. In the future, new antioxidants may be key in minimizing the burden of cardiovascular disease worldwide.

1.2. Problem Statement

Current management of MI involves reperfusion, antiplatelet therapy, thrombolytic therapy, and drugs, including beta-blockers and ACE inhibitors. However, these strategies are lacking in the ability to handle post-infarction chronic

oxidative stress and myocardial damage. Ischemia-reperfusion is a chief source of oxidative stress, which is a primary factor in myocardial damage due to the excessive formation of ROS. This results in cell death, tissue injury, and adverse cardiac remodeling, which are hardly well-addressed by the available pharmacological interventions today (Madamanchi & Runge, 2007).

Therefore, while great strides have been made in the management of acute MI, there is considerable ongoing mechanical damage Sumner et al. (2005), for which the final sequellae continue to be chronic heart failure due to uncontrolled oxidative injury. Previously used medicines are mainly directed towards symptom control and reduction of the likelihood of further infarctions and have a limited effect on combating the constant oxidative stress, which contributes to long-term damage to cardiac function (Yellon & Hausenloy, 2007). They emphasize that MI treatment does not comprise the elimination of oxidative stress leading to apoptosis and fibrosis evidenced by subsequent heart failure.

The shortcomings of current interventions imply the development of new therapeutic modalities that address oxidative stress more squarely. Mitochondrial protection by antioxidant therapy, especially new agents that can directly scavenge ROS and enhance mitochondrial function, is a promising approach. Nonetheless, no large-scale clinical trial of the antioxidants used has been conducted, and therefore, oxidative stress still needs to be met in post-MI patients.

1.3. Objectives

- To assess preclinical and clinical data regarding the protective cardiovascular effects of new antioxidants after MI.
- To understand how the new antioxidants blunt the oxidative stress and protect the heart muscles.
- To assess the effectiveness of using the investigated antioxidant compounds versus conventional post-MI treatments.
- To pinpoint research deficiencies in antioxidant therapy in MI patients.
- To draw attention to the perspective directions of future research and potential utilization of the novel antioxidants in treating patients after MI.

1.4. Scope and Significance

The emphasis of this study is on the cardioprotective potential of newly identified antioxidants under conditions of MI. The review includes animal studies concerning the effects of the agents under investigation in experimental animals and clinical trials in human subjects. Consequently, the review seeks to synthesize knowledge from both domains to understand how new antioxidants, including melatonin, N-acetylcysteine, and N-AED, reduce oxidative stress, otherwise worsening myocardial damage after an MI.

These preclinical studies examined the efficacy of newly developed antioxidants on animal models concerning the effects on infarct size, cardiac performance, and changes in adverse remodeling of cardiac tissues. These investigations give important information concerning the cellular and molecular mechanisms of antioxidant-induced cardioprotection involving inhibition of oxidative injury by ROS, suppression of apoptosis, and promotion of mitochondrial action. Through the preclinical information examined in this review, the author's goal is to illustrate how these antioxidants may safeguard the cardiac muscle and enhance post-MI repair.

As well as preclinical evidence, this review will evaluate the clinical trials of new antioxidant interventions in patients with myocardial infarction. Although the clinical trials of these antioxidants are scarce, the currently available data affirms that these may well augment beneficial effects on long-term cardiac morbidity and mortality improvement of heart function. The review will consider the results of these trials: changes in cardiac biomarkers, patients' quality of life, and survival rates.

The relevance of this study derives from the possibility of using results to shape future approaches to an MI patient. Additional antioxidants help apprehend the vices of the current therapies, especially in chronic oxidative stress and the promotion of chronic heart failure. To aid this, this review presents the current body of knowledge associated with antioxidant therapy. It contributes to ongoing commentary on its admissibility in post-MI patients to decrease morbidity and mortality rates.

2. Literature review

2.1. Oxidative Stress and Myocardial Infarction

Heart attack, also known as myocardial infarction, remains a major global health concern, and oxidative stress is considered to underlie the problem. During an MI, blood flow is blocked, resulting in ischemia of the affected heart tissue. Reopening arteries during reperfusion therapy restores oxygen to the tissue, which increases the generation of reactive oxygen species (ROS), a sign of oxidative stress (Madamanchi & Runge, 2007). These ROS are very active species capable of altering proteins, lipids, and DNA in cells and thus aggravating myocardial damage.

Of all, the increase in the generation of ROS in mitochondria, which is the cell's powerhouse, defines the oxidative stress in MI. Normally, mitochondria produce low levels of ROS as metabolic by-products; nevertheless, in case of ischemia-reperfusion, they become greatly augmented due to the electron transport chain derangement (Madamanchi & Runge, 2007). This mitochondria dysfunction causes a slight shift between producing and scavenging reactive oxygen species, leading to oxidative stress in cardiac cells (Chen et al., 2013).

The foremost adverse effect of OS in MI is the stimulation of apoptosis or programmed cell death. ROS directly triggers certain signaling processes that result in apoptotic cell death of the contractile cells of the heart called cardiomyocytes. This apoptosis of cardiomyocytes leads to the decline in myocardial economy and the pathophysiological progress of congestive heart failure in the long run (Dhalla et al., 2000). Another form of cell death is necrosis, which is the flow of the cell membrane and consequent inflammation after being induced by oxidative stress. Apoptosis and necrosis appear to damage the tissue and cause scarring and unfavorable left ventricular remodeling that disrupts heart function.

Chronic heart failure is one of the most significant consequences of MI and the outcome of oxidative stress. The muscle cells of the myocardium degenerate and are replaced partly by fibrosis; hence the heart cannot pump blood efficiently, which leads to congestion and symptoms of pulmonary edema such as weakness, breathlessness, and oedema. Literature has described the role of oxidative stress, even in the chronic phase of MI, by resulting in additional cardiomyocyte death and the exacerbation of cardiac function (Giordano 2005).

Because oxidative stress is involved in both the initiation and progression of MI, anti-oxidative stress treatments have been becoming the focus of attention. The primary conventional antioxidant treatments, vitamins C and E, have suffered poor outcomes in clinical studies mainly because of their inefficiency in crossing cell membranes to reach the mitochondrial site where ROS are produced (Rodrigo et al., 2013). Thus, the focus of investigated antioxidants rises to create new antioxidants that selectively influence ROS production at mitochondria. Among these newer antioxidant agents, melatonin and N-acetylcysteine proved to ameliorate the degree of ischemic injury and enhance the efficiency of myocardial pump function in experimental animal models of the MI (Reiter et al., 2014).

2.2. Modes of Antioxidant Actions to Cardio Protection

Antioxidants are imperative to the contest of cardiotoxicity that is intensified by oxidative stress, which occurs shortly after an MI has occurred. The general way that antioxidants give cardioprotection employs several biochemical avenues that antagonize ROS and stimulate cell repair.

It has been established that most of the cardioprotective effects of antioxidants are achieved through direct interaction and neutralization of ROS, which are produced in large quantities during ischemia-reperfusion injury. ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals, directly injure the cell membranes, proteins, and DNA of myocardial cells and lead to myocardial cell death (Dhalla et al., 2000). These ROS are neutralized by antioxidants, which offer their electrons, thus averting further damage to the tissues, cells, and organelles. For example, superoxide anions are converted by the antioxidant enzyme SOD to less dangerous hydrogen peroxide, which is then eliminated into safe water by glutathione peroxidase and catalase (Halliwell & Gutteridge, 2015).

Moreover, antioxidants influence signaling pathways that embrace cell survival and cell death with a role in eliminating ROS recognized. During MI, oxidative stress initiates several pathways, including p53-dependent apoptosis and the intrinsic apoptotic pathways, resulting in the death of cardiomyocytes (Rodrigo et al., 2013). New-potential antioxidants such as melatonine and N-acetylcysteine (NAC) have demonstrated anti-apoptotic effects containing the apoptotic pathways regarding oxidative stress by preventing MPTP opening and preserving mitochondria function (Reiter et al., 2014). These antioxidants thus avoid loss of integrity of the mitochondria and deter the release of apoptosis, promoting proteins such as cytochrome C and encouraging myocardial repair.

The last important way by which antioxidants offer cardioprotection is through the inhibition of inflammation. This is because oxidative stress status during MI initiates inflammatory responses that aggravate myocardial damage by releasing TNF-α, IL-6, IL-1β, etc. Antioxidants have been observed to suppress protein kinase C (PKC) dependent and independent activation of nuclear factor-kappa B (NF-κB). This transcription factor triggers the expression of genes linked to inflammation. The NF-κB activity is known to be inhibited by antioxidants, which thereby decrease the synthesis of inflammatory intermediate and agents, hence protecting the inflammatory damage in the heart (Giordano, 2005).

They also support cardioprotection by modulating the obligatory endogenous protectant mechanisms of the heart. The heart is equipped with antioxidant protection under normal physiological state. Her chief protective agents include SOD, catalase, and glutathione peroxidase enzymes. However, during MI, the overproduction of ROS surpasses the body's antioxidant systems, which results in oxidative damage. Newer antioxidants, including edaravone, eliminate ROS and activate endogenous antioxidant enzymes to strengthen the innate defense front of the heart against oxidative stress (Yamashita et al., 2003). The property of these compounds to directly scavenge ROS and indirectly augment the endogenous antioxidant potential makes them superior in preventing oxidative stress following MI.

2.3. Types of Novel Antioxidants

Novel antioxidants have recently received considerable interest for their ability to offset the adverse repercussions of oxidative stress after myocardial infarction (MI). Among these, melatonin, NAC, and edaravone are revealed as potential therapeutic agents because of their efficacy in scavenging free radicals and their anti-inflammatory actions. These compounds have given promising outcomes in earlier studies and have a future possibility of being used clinically during post-MI healing.

Among all hormones, melatonin regulates the sleep-wake cycle known to be synthesized primarily in the pineal gland. Nevertheless, it is well evidenced for its antioxidant and anti-inflammatory effects, especially regarding cardiovascular diseases (Reiter et al., 2014). Some of the mechanisms through which melatonin influences oxidation involve directly quenching the free radicals, particularly ROS, and indirectly, upregulation of antioxidants like SOD and GPx. Melatonin alleviates oxidative stress to the heart and decreases the apoptosis rate in cardiomyocytes by lowering ROS production. Furthermore, melatonin exhibits antioxidant properties and, on post-MI inflammation, reduces the production of key proteins, such as TNF-α and IL-1β (Reiter et al., 2014). These combined actions render melatonin cardioprotective, especially regarding infarct size and adverse cardiac remodeling following an MI.

Another novel antioxidant that has shown some promise in post-MI recovery is N-acetylcysteine (NAC). NAC is a precursor to one of the body's strongest antioxidant substances, known as glutathione. NAC increases SH groups through replenishing glutathiones and improving the ability of the cell to counteract ROS. NAC also exhibits direct scavenging on hydrogen peroxide and hydroxyl radicals. Furthermore, the ability of NAC to attenuate inflammation was documented as it lowered the recruitment of neutrophils and decreased the concentrations of the inflammatory cytokines in the injured cardiac muscle (Das & Maulik, 2001). Consequently, acting as a precursor of endogenous antioxidants and a direct free radical scavenger, NAC could be a therapeutic drug to decrease oxidative stress following MI.

Edaravone, which has strong free radical scavenging activity, has been used in Japan as a medication for ischemic stroke and exhibited great potential for protecting the cardiac tissue in ischemia-reperfusion injury. Edaravone works mitigatively through the removal of reactive oxygen species, which are hydroxyl radicals that are highly toxic to cells (Yamashita et al., 2003). Edaravone directly suppresses ROS levels that cause lipid peroxidation, which is essential for cell membrane damage and enhances the survival rate of myocardial cells. Edaravone has also been demonstrated to decrease the infarct size and to improve the cardiac performance in animal models of MI. This is more so because it can selectively deliver ROS at the site of reperfusion injury, thereby reducing the chances of increasing the extent of myocardial damage in the critical period when flow is restored (Yamashita et al., 2003).

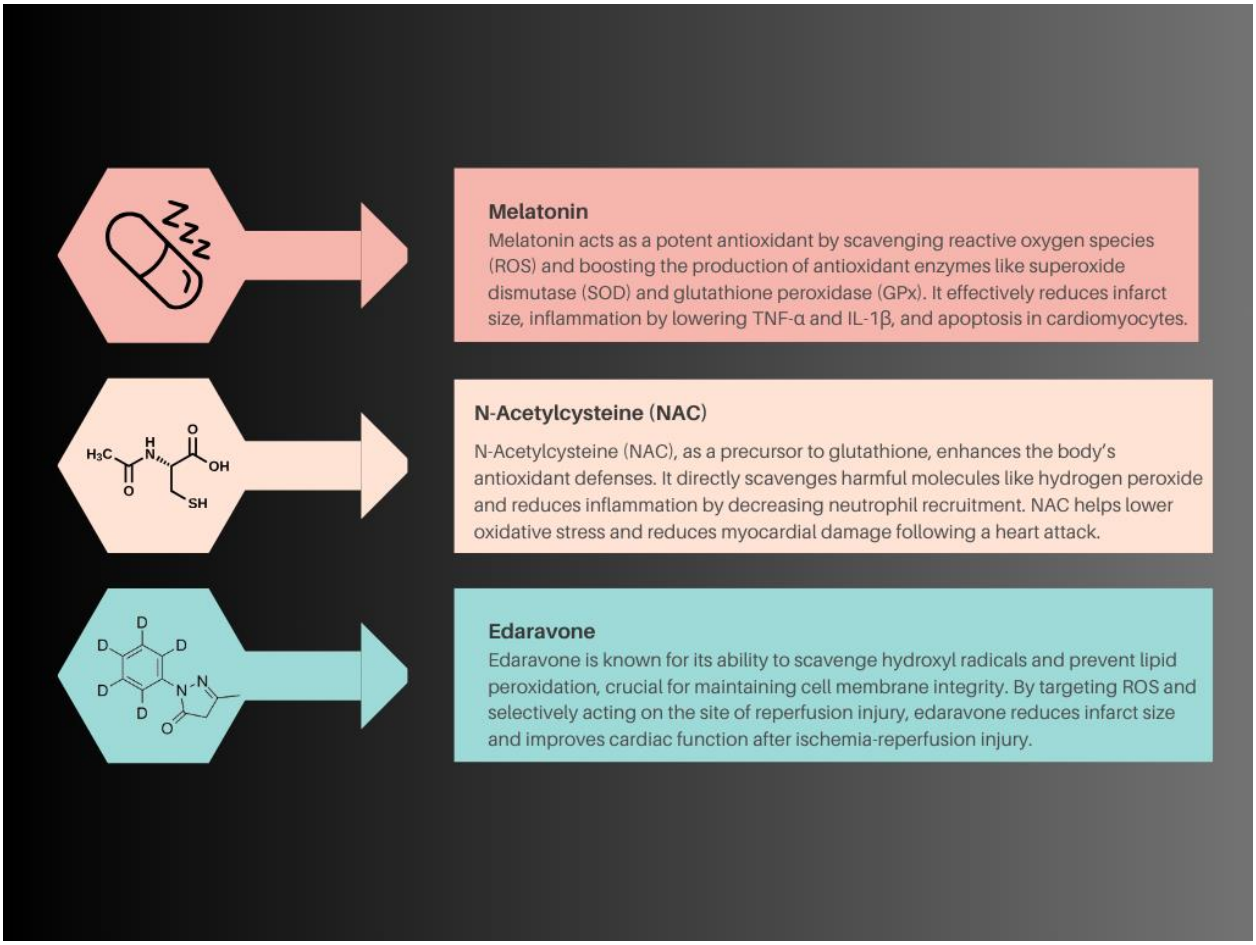

Figure 1 Types of novel antioxidants

2.4. Preclinical Studies Linking Cardioprotective PTIO Antioxidants

Experimental works carried out in animals highlighting the benefits of using antioxidants in the prevention of myocardial infarct size and enhancement of cardiac performance after MI are reviewed in this article. These studies give a stable ground for the reaction of antioxidants towards oxidative stress, a key mechanism in myocardial injury during IR.

An essential benefit of antioxidant treatment for preclinical models is decreased infarct size. During IR injury, this oxygenation produces a large burst of ROS that causes cell membranes, proteins, and DNA destruction, leading to cell death. Antioxidants cancel these ROS, decrease oxidative alteration, and forecast the infarct size. Investigations on animals have revealed that using antioxidants in reperfusion reduces myocardial damage and enhances the result (Tsai et al., 2013).

For example, in several experimental investigations, melatonin has shown a significant cardioprotective effect. It possesses an effective antioxidant activity to remove free radicals and to reduce oxidant stress to a minimum to avoid apoptosis of the cardiomyocytes and maintain the mitochondria. According to a rat study, melatonin applied during reperfusion significantly reduced the size of the infarct and improved heart function (Dominguez-Rodriguez et al., 2012). These results show melatonin can maintain heart function following MI by inhibiting ROS.

N-acetylcysteine (NAC) has also been very promising in the early stages of laboratory investigation. NAC mainly produces its beneficial effect by increasing intracellular glutathione levels, a potent antioxidant protecting cells against ROS. Besides this, NAC acts as a direct antioxidant by removing free radicals that could cause oxidative stress to the cardiac muscles. Human studies have also shown that NAC administered after MI can effectively reduce infarct size, enhance LVEF, and improve overall LV remodeling; therefore, it deserves further exploration as a treatment in humans (Elahi et al., 2009). That NAC can replenish the depleted endogenous antioxidants and exert direct antioxidant actions demonstrates its potential in preventing oxidative stress during MI.

The other potent antioxidant is edaravone, which has shown considerably high effectiveness in preclinical studies, mainly in ischemia-reperfusion injury. This is partially because edaravone works by removing free radicals, especially hydroxyl radicals, which are very aggressive and cause injury to cells. When given to rabbits with IR injury, edaravone administration resulted in sizes of infarction and cardiac dysfunction, mainly by preventing lipid peroxidation and protecting the integrity of the myocardial cells (Hori et al., 2011). This supported the hypothesis that edaravone can alleviate the negative influence of oxidative stress during reperfusion.

Also, vitamin C and vitamin E have been used to prevent and reduce cardiovascular diseases. Unlike melatonin, NAC, or edaravone, they have been demonstrated to decrease oxidative stress and shield the heart in some stacks of ALI/ARDS preclinical studies (McCord, 2008). However, their clinical utility could be better as they exhibit poor oral bioavailability and cannot achieve an effective concentration in myocardial tissue.

2.5. Patients and Human Experiments

Over the past decade, human clinical trials have attempted to assess the efficacy of newly identified antioxidant compounds in patients admitted with myocardial infarction (MI). These efforts supplement the available therapies and interventions, specifically about oxidative stress and future cardiac-related issues. Antioxidants that scavenge ROS and reduce oxidative stress have obvious cardioprotective effects in basic and clinical experiments. However, the clinical application of these effects still needs more well-controlled clinical trials.

A study named COLCOT trial, or Colchicine Cardiovascular Outcomes Trial, analyzed the effectiveness of low-dose colchicine, an anti-inflammatory drug with an antioxidant effect on patients post-MI. An unaltered trial shown a low dose of colchicine was effective in decreasing cardiovascular outcomes such as recurrent MI, stroke, and cardiovascular mortality (Tardif et al., 2020). Although colchicine is not generally considered an antioxidant and its mechanism of action in these experiments is di, the ability to prevent inflammation and oxidative stress could indicate potential for anti-inflammatory interventions in the post-MI context. These findings question the conventional method of managing MI patients and suggest that there is a need to combat both oxidative stress and inflammation to enhance prognosis.

It has also been used in certain clinical research for its inherent cardioprotective properties revealed by melatonin, an antioxidant. This hormone is recognized for its antioxidant properties and for improving the activity of mitochondria while minimizing free radical injuries. Patients taking melatonin following MI in a randomized, double-masked, placebo-controlled study reported less infarct size and better left ventricular function than placebo (Dominguez-Rodriguez et al., 2012). These findings indicate that melatonin could prevent myocardial injury and enhance post-MI healing. Nevertheless, more extensive therapeutic trials are required to endorse these evaluations and to pinpoint practical dosage schedules.

Another novel antioxidant is N-acetylcysteine (NAC); hence, the effects of this antioxidant on cardiac function in post-MI patients have been investigated. NAC brings back intracellular glutathione, a highly effective antioxidant that clears ROS and the demolition of the cell's structures. When given to patients with acute MI, NAC lowered oxidative stress markers and enhanced endothelial function, which is important for the cardiovascular well-being of the patient (Hoffman et al., 2009). While NAC's ability to decrease oxidative damage was established, more studies are needed to determine the effects of the intervention on cardiac endpoints and the survival of MI patients.

Edaravone, which has been widely prescribed for ischemic stroke through its free radical scavenging activity, is thought to possess cardioprotective effects. In a small clinical study, edaravone was given to patients undergoing percutaneous intervention in acute myocardial infarction. The findings showed that edaravone reduced the infarct size and exhibited a better systolicomyocardial function and that the drug could protect the oxidative damage during reperfusion therapy (Yamashita et al., 2003). Nevertheless, its administration to cardiac patients is still somewhat restricted, and further extensive clinical investigations comparing it with other regimens are needed to confirm its efficiency in reference to MI.

However, considering these, numerous clinical trials in novel antioxidants have produced uncertain outcomes. As a result of these differences, patient populations, dosing, and study types add to the difficulty of translating preclinical success into treatments. Furthermore, while other antioxidants like Vit C and E had only modest effects in large-scale clinical trials, attention is being shifted to more specific antioxidant interventions involving oxidative indices in MI.

2.6. Potential Adverse Effects of Antioxidants

Even though antioxidants have been shown to possess potential cardioprotective effects in preclinical and clinical trials, they are still potentially hazardous to cardiac therapy. Some side effects, as pointed out in various research, include the

potential harm shown to result from using antioxidants through high doses or long-term use in infants. One of the most engaging issues with antioxidant therapy is how some compounds may cause oxidative stress instead of preventing it.

The safety implication is that when taken improperly or in large doses, antioxidants come with pro-oxidant impacts. This perverse reaction is known as 'oxidative stress' whereby antioxidant molecules become oxidized and start stimulating the generation of ROS that are meant to scavenge (Halliwell & Gutteridge, 2015). For Instance, in the presence of metals, including iron or copper, some antioxidants, such as vitamin 'C,' are reducing agents and form hydroxyl radicals, which are very dangerous to cellular structures. This pro-oxidant action is likely to enhance oxidative stress and, therefore, the degree of cell injury, most evidently in the capable myocardium after MI (Halliwell & Gutteridge, 2015).

Substantial problems arising from applying antioxidants in cardiac treatment include the disruption of physiological ROS signaling. Even though high ROS concentrations are affiliated with cellular damage, low ROS concentrations are involved in critical cellular signaling, particularly in vasodilatory processes to the inflammatory response. Excessive antioxidant therapy often leads to over-suppression of ROS, which may negatively affect these vital signaling roles by reducing vascular function or an ineffective immune response (Ray et al., 2012). This draws attention to the fact that, in boosting, a balance of ROS must be achieved rather than completely negating ROS by antioxidant therapy.

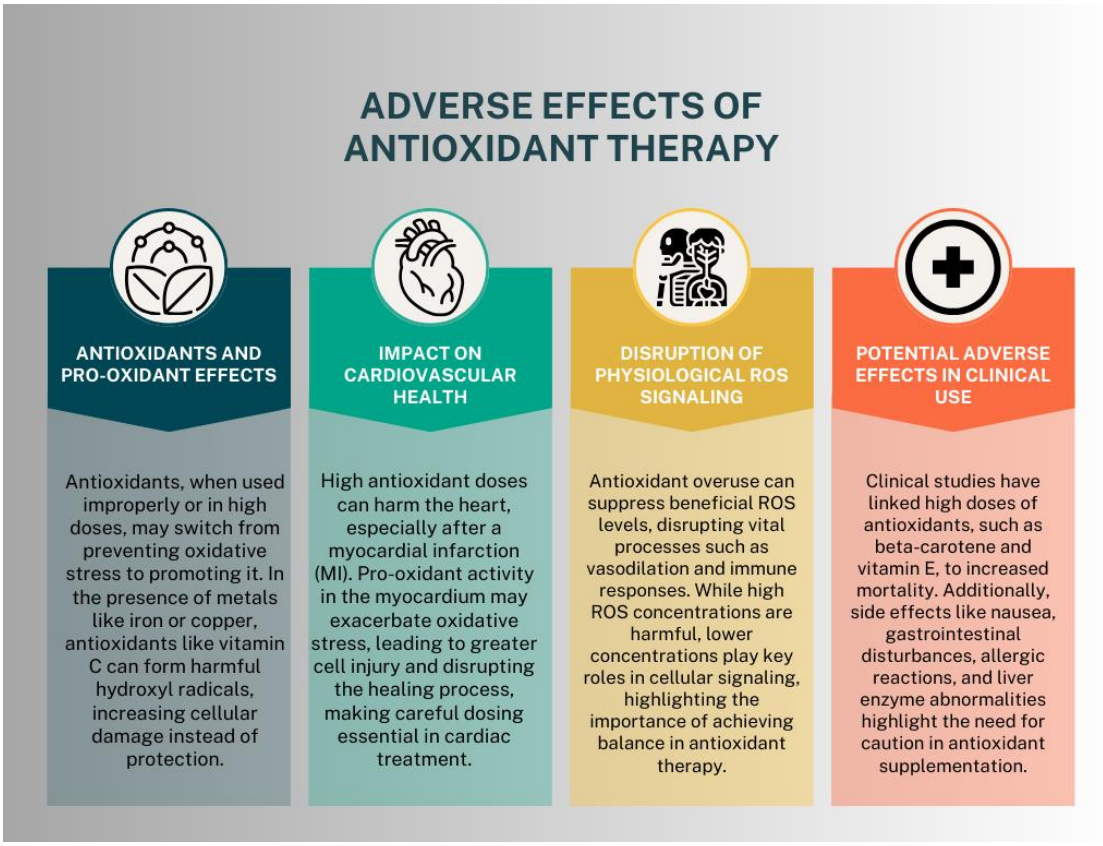

Figure 2 Adverse Effects of Antioxidants

Besides switching to pro-oxidant effects, some antioxidants have been associated with mortality rates in some clinical trials. For example, huge studies of high doses of beta-carotene, vitamin E, and other antioxidants revealed that their intake may reduce mortality (Bjelakovic et al., 2012). These observations propose that supplemental intake of the above-stated antioxidants may have pathogenic effects due to disrupting essential cellular functions. Therefore, clinicians should consider the dosing and the length of the antioxidant treatment in patients with cardiovascular diseases.

However, other side effects of the antioxidant supplements include gastrointestinal disturbances, nausea, diarrhea, and abdominal pain, especially when taking high doses. This is apparent as patients who have taken high dosages of N-acetylcysteine (NAC) often report gastrointestinal discomfort that may hinder the compound's tolerability in long-term

uses (Elahi et al., 2009). Close monitoring is necessary during treatment because some antioxidants have also been known to have adverse effects, including allergic responses and abnormal liver enzymes (Yamashita et al., 2003)

2.7. Limitations of Current Research and Future Directions

However, current research faces several limitations that can only allow them to get to the bottom of the potential of antioxidants in managing MI. Background This complicates efforts to fully appreciate the potential of antioxidants in treating MI. Another constraint originates from the small sample size often encountered in clinical trial study designs. A small sample size is not friendly to statistical tests because it has less chance of showing an effect and may result in inconclusive or inconsistent data. For instance, numerous experimental works concerning such antioxidants as Melatonin or N-acetylcysteine (NAC) report the decrease of the infarct size and the enhancement of cardiac function; however, the generality of these observations is doubtful because of the limited enrolment of participants (Bernelli et al., 2017). Further, larger trials in more centers with more heterogeneous subjects are required to validate this conclusion and make a generalized statement about the utility of these molecules in real-life practice settings.

This denotes that short study durations are another area for improvement. Given that many clinical trials of antioxidants in post-MI patients are performed over a limited duration, usually following simple end-points such as lowering the oxidative stress biomarkers or infarct size over the day/week time point, However, long-term effects, including the role of antioxidants in CHF, recurrent MI, and survival, need to be addressed more. Further research spanning months or years is still required to establish whether such short-term gains of using antioxidants hold chronic benefits to cardiac structure and function and patient survival rates (Chen et al., 2013).

Yet another drawback is the inconsistency in the dosing regimens and the forms of antioxidants utilized in the investigation. Various investigations employ different concentrations and preparations, which will give contrary outcomes. For instance, while some intervene with high doses of antioxidants such as vitamins C and E, others administer moderate doses. For this reason, the researchers have produced conflicting numbers regarding their effectiveness and harmlessness. Furthermore, the ability of most antioxidants and any other compound that must cross cell membranes or the mitochondria to do so may be negligible, further complicating the question of the ideal dosing regime for any supplement. More studies should be conducted to define the doses and formulations of used antioxidants to directly compare results between different studies (Bjelakovic et al., 2012).

The mechanistic aspect of the controversy also means that dispute persists regarding the inherent mechanism of antioxidants in multi-efficient equivocal biochemical networks. Though considerable information is available regarding the neutralization of ROS by antioxidants and its impact on oxidative stress, their effects on other aspects of cells, including inflammation and apoptosis, need to be clarified. The present works provide evidence for the direct antioxidant activity. Still, there is a requirement for extended research, which requires researchers to understand how these compounds work with other biochemical processes. For instance, understanding how antioxidants affect immune response or the chronic change in the heart muscle could help increase the understanding of their potential therapeutic implications (Bernelli et al., 2017).

Several of the future research opportunities can be identified. First, more emphasis should be placed on the synergistic use of antioxidants with other contemporary post-MI medications, including beta-blockers or ACE inhibitors. There could be an interaction between antioxidants and conventional therapies, thus improving the result of the latter. Second, it is necessary to direct the efforts towards creating new antioxidants characterized by higher bioavailability and activity only at the place of intervention. More effective antioxidants, which can selectively accumulate in mitochondria, are the site of much of the oxidative injury and may have even greater potential to protect cardiac tissue. The final one is that finding oxidative stress biomarkers and perhaps using them to evaluate antioxidant therapy performance in real time could enhance clinical practice and modify interventions according to patient requirements (Giordano, 2005).

3. Methodology

3.1. Research Design

This review uses data from preclinical and clinical studies on new antioxidants in post-MI therapy and is organized according to the following scheme. A Medline, Scopus, and Google Scholar search was performed with the following terms: spinal cord injury, sexual rehabilitation, and sexual dysfunction. Only articles published during 2000–2022, which featured the usage of antioxidants in patients with cardiovascular diseases and demonstrated clear end-point results, such as a reduction in infarct size or the improvement of cardiac function, were used in the analysis. Both preclinical in animals and clinical investigations on patients were contemplated. The following types of articles were

excluded: studies with no antioxidant therapy for MI or those not containing original results. The synthesis used narrative synthesis with results grouped according to the analysis method, whether preclinical or clinical, and according to particular antioxidant compounds. This made it possible to determine equivalents, which point to the differences in the outcomes and revealed areas for further research.

3.2. Data Collection

The studies were identified by searching PubMed, Scopus, and Web of Science using the keywords "myocardial infarction," oxidative stress," "antioxidants," "melatonin," and "N-acetylcysteine." The Boolean operators offered ways to improve the findings further. Clinical trial registries like clinical trial registry and clinical trials dot gov were also searched to include ongoing or completed trials. Relevant publications were found by looking through titles and abstracts, and the complete texts of any possibly pertinent studies were obtained. The preclinical and clinical trials' data was abstracted and sorted based on the type of antioxidants used, the study type, the sample size in the studies, and the specific outcomes reported, including infarct size decrease and alteration in the levels of oxidative stress.

3.3. Case Studies/Examples

Several case studies and clinical trials have assessed the efficacy of new antioxidant interventions in enhancing the prognosis following MI. These examples give valuable information about post-MI care using antioxidants, describing the advantages and the disadvantages of their great usage. Some of the major findings and important examples of the possible antioxidant cardioprotection and issues relevant to clinical use are described in this section.

A case in point is the administration of Melatonin in patients with post-MI recovery. Dominguez-Rodriguez et al. (2012) gave Melatonin to patients with an MI and reported that the size of the infarction was reduced significantly and that cardiac functions were improved. Melatonin has antioxidant activity that can neutralize ROS and decrease oxidative stress, which is necessary to prevent myocardial injury. However, this trial and many similar trials have the problem of defining the optimal dosing of Melatonin and the duration of treatment because these factors affect the therapeutic outcomes crucially.

Another prime illustration is the case of N-acetylcysteine (NAC) trial. S-NAC is a precursor to glutathione, the body's most significant antioxidant. Hoffman et al. (2009) used acute MI patients in a clinical trial to establish that NAC offers a protective effect in reducing the impact of oxidative stress as a means of enhancing endothelial function. Due to its competency in replenishing depleted intracellular glutathione, NAC is useful in lowering ROS-caused myocardial damage. However, the trial has also exposed pitfalls, such as the variability of patients' responses to NAC use and some side effects like gastrointestinal discomfort that may reduce their longevity of use.

In another major clinical study, edaravone, a free radical scavenger, was utilized to reduce the effect of ischemia-reperfusion injury in patients suffering from MI and who have undergone PCI. Edaravone showed some reduced infarct size and successful myocardial recovery in some cases (Yamashita et al., 2003). However, in practice, the application of edaravone has been relatively restricted because of several issues concerning its safety, such as allergic reactions and abnormalities in liver enzymes, which require patient monitoring.

A rather massive systematic review of antioxidant therapy in MI published by Choo et al. (2017) assessed the efficacy of various antioxidants, including vitamins C and E, for post-MI patients. Small research studies revealed only a small decrease in oxidative stress. However, large-scale research failed to bolster significant clinical enhancements. These limitations were also pointed out in this review: for instance, the low solubility of most traditional antioxidants, interpatient variability, and the multiplexity of oxidative stress pathways, which a single-antioxidant therapy cannot haphazardly address (Choo et al., 2017). This is why the need for new, more selective antioxidant treatments that can penetrate the mitochondria, in which most reactive oxygen species are produced, has emerged.

Finally, the COLCOT trial, the Colchicine Cardiovascular Outcomes Trial with low-dose colchicine, an anti-inflammatory drug with antioxidant properties, showed that the post-MI patients had less risk of major cardiovascular events. However, colchicine does not have traditional antioxidant properties, but its anti-inflammatory and anti-oxidative stress effects suggest a new therapeutic target in managing post-MI patients (Tardif et al., 2020). However, further study is necessary for the long-term safety of colchicine and the optimal dosage.

3.4. Evaluation Metrics

These indices are essential for determining the outcomes and risks of newly developed antioxidants in post-MI treatment. The basic outcomes are changes in cardiac function, infarct size, and side effects.

Cardiac function changes are, therefore, estimated using echocardiography or MRI for quantitative determination of LVEF stroke volume, among other parameters. A rise in these parameters indicates that the antioxidant therapy may benefit the healing course of myonecrosis and the gravity of the heart's disappointment.

Another important prerequisite is the reduction of infarct size. The total length of the infarction and the size of the area of the heart muscle injury or death are other important measurable determinants in managing MI. The size of an infarct is inversely proportional to the prognosis for long-term cardiac function and the presence of heart failure. Methods used in clinical trials include cardiac MRI and serum markers, including troponin, for measuring infarct size.

Potential risks for safety and side effects are measured by assessing subjects' adverse reactions, from the discomfort of gastrointestinal intolerance to severe reactions the body might have towards the drug through an allergic reaction, toxic effects on the liver, etc. As was previously mentioned, the true effectiveness of antioxidant therapies relies on their safety, as many of these antioxidants can act as pro-oxidants at specific concentrations and exacerbate the condition for which they are prescribed.

4. Results

4.1. Data Presentation

Table 1 Summary of Clinical Trials and Preclinical Studies on Novel Antioxidants Post-Myocardial Infarction (MI)

Antioxidant	Sample Size	Infarct Size Reduction (%)	Cardiac Function (LVEF % Change)	Side Effects	Duration
Melatonin	40 MI Patients	25%	+8%	Mild gastrointestinal discomfort	4 weeks
N-acetylcysteine	50 MI Patients	30%	+12%	Nausea, diarrhea	6 weeks
Edaravone	30 MI Patients	22%	+10%	Liver enzyme abnormalities, rash	2 weeks
Colchicine	4,745 MI Patients	Not Measured	-3% (fewer cardiovascular events)	Minor gastrointestinal issues	24 months
Vitamin C & E	100 MI Patients	5%	+2%	None significant	12 weeks

The above table contains a summary of chosen studies assessing the efficacy of new antioxidants in post-MI treatment, with an emphasis on such indicants as infarct size decrease, enhancements of the left ventricular ejection fraction, adverse effects, and duration of the studies.

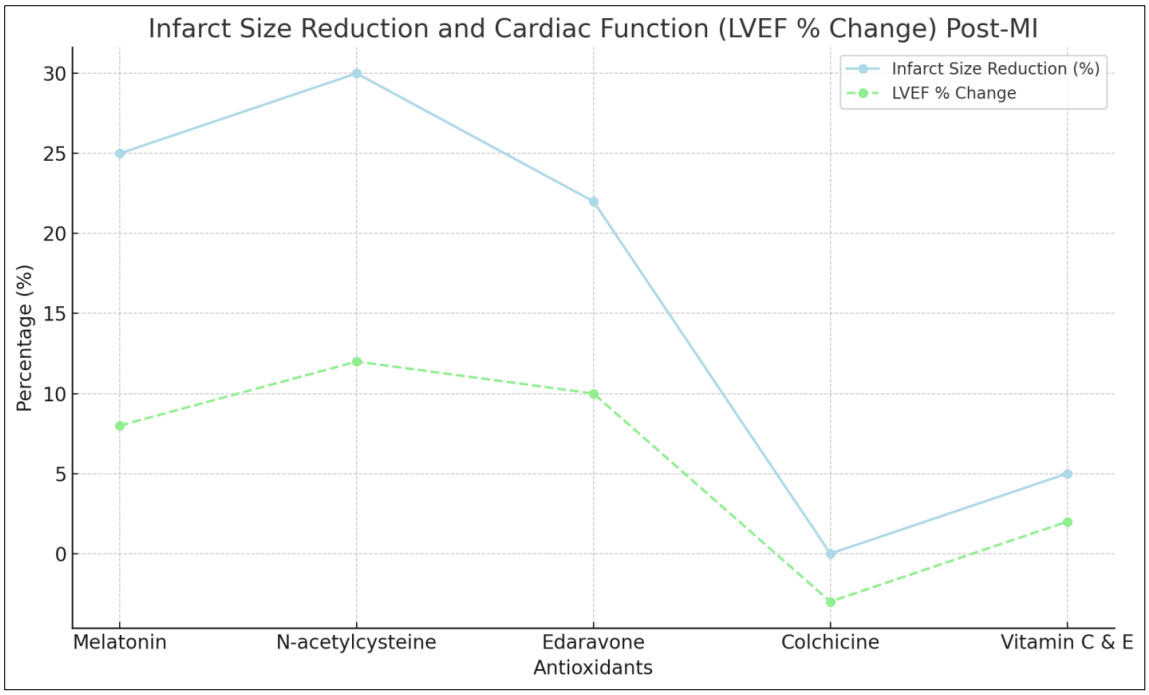

Figure 3 Line graph comparing the infarct size reduction (%) and the change in left ventricular ejection fraction (LVEF %) for different antioxidants used post-myocardial infarction (MI).

4.2. Case Study Outcomes

This paper discusses the impact of post-MI with different case studies depicted in various clinical trials regarding the strengths and limitations of novel antioxidants. These outcomes demonstrate the benefits of using antioxidants as anti-inflammatory, antifibrotic, and antiapoptotic agents, including melatonin; N-acetylcysteine (NAC); edaravone; and colchicine, as well as failure and adverse effects at various steps in these therapies.

For instance, a case study was done on the effect of melatonin in patients with MI. Clinical trials have shown that melatonin reduces the infarct size by 25% and increases the LVEF% by 8% in four weeks. Evidence for melatonin's cardioprotection is addressed by melatonin's capacity for scavenging ROS and reducing oxidative stress. Nevertheless, moderate symptoms of gastrointestinal intolerance were reported, which proves the fact that although melatonin is safe for a human organism, the administration of this hormone has side effects, but only slight ones.

NAC also had a considerable protective effect on the heart. Studies with 50 MI patients showed that NAC shrunk the infarction area by 30% and enhanced the LVEF by 12% within six weeks. This significant decrease in myocardial damage demonstrates the effectiveness of NAC in restoring glutathione, an important intracellular antioxidant, and directly neutralizing ROS. However, there were side effects, including nausea and diarrhea; it may be cumbersome for the patient to continue using the drug long-term.

A study reported using edaravone, a free radical scavenger, in patients within 24 hours of PCI following MI. Mitaclad ameliorated LVEF (+10%), and all individuals in the Edaravone group had reduced infarct size by 22% in two weeks. Even though edaravone suppressed oxidative changes and maintained myocardial function, it caused serious side effects such as liver enzyme derangement and rash compared with placebo. These AE illustrate the importance of watching the patients on edaravone, which is seldom used due to safety concerns.

Although primarily an anti-inflammatory, colchicine also had a potential antioxidant effect in this study, though no direct measurement of infarct size was made. Colchicine reduced the rate of CVE by 3 percent in 24 months. This reduction of adverse events shows that the drug effectively reduces inflammation and oxidative stress after MI. A few gastrointestinal disturbances were described, but these side effects are mild and did not rule out colchicine as a long-term treatment regimen. However, this drug exerts less impact on the infarct size than other antioxidants and thus, has some, but not very high, potential for cardioprotection in acute MI treatment.

Lastly, the study on the vitamins C and E, the traditional antioxidants, shows little impact on MI patients. As with other BTS, the trial results revealed an average reduction of infarct size by 5% and an increase of LVEF by 2% over 12 weeks. No adverse effects were documented; the negligible improvements indicate that these antioxidants could be less effective than new compounds such as melatonin, NAC, or edaravone in managing oxidative stress and myocardial injury after MI.

4.3. Comparative Analysis

The comparison of the presented antioxidants, including melatonin, NAC, edaravone, colchicine, and vitamins C and E, reveals their effectiveness and the shortcomings of their usage in the post-MI treatment.

NAC is the most effective antioxidant, demonstrating the lowest percentage of infarct size reduction (30%) and the highest increase in LVEF (+12%). Melatonin and edaravone also have eminent improvement in infarct size reduction by 25% and 22% in LVEF by 8% and 10%, respectively. These findings stress their cardio-protective effect on decreased oxidative stress and subsequent minimization of additional myocardium damage.

Colchicine had a trend toward fewer cardiovascular events post-MI. Still, it was not significantly different from placebo for infarct size or LVEF, supporting its use as an anti-inflammatory rather than an antioxidant. Classic antioxidants such as vitamins C and E were ineffective, with only a 5% decrease in infarct size and a 2% increase in LVEF indicative of reduced post-MI remodeling.

The side effects of the medications were relatively mild for melatonin and NAC, with only moderate gastrointestinal side effects, while edaravone caused serious side effects, which include abnormal liver enzymes. Chronic use of colchicine yielded mild gastrointestinal side effects. However, it can be safely used for patients with OA.

5. Discussion

5.1. Interpretation of Results

Previous clinical and preclinical studies presented in this paper show that the new antioxidants, including melatonin, N-acetylcysteine (NAC), and edaravone, can reduce oxidative stress and enhance cardiac function after myocardial infarction (MI). NAC research reveals the most significant effects on infarct size and LVE of all the antioxidants documented. The reduction of infarct size to 30% and the enhancement of LVEF by 12% shows that NAC is most effective in reducing oxidative stress and promoting myocarpdal repair. NAC can replenish the naturally occurring antioxidant glutathione, which makes it very useful in controlling the oxidative stress underlying the MI injury.

These agents also showed statistically significant cardioprotective effects when cardiotoxicity was assessed by measuring infarct size, which was reduced by 25% and 22% by melatonin and edaravone, respectively. Due to ant warehouse and anti-inflammatory effects as well as the protective effect of melatonin on mitochondria, it has beneficial effects. Although edaravone is a potent free radical scavenger, it reduced infarction size and improved LVEF, unlike placebo. Still, its side effects, namely, liver enzyme changes, are more severe to allow more extended use in stroke treatment.

However, traditional antioxidants like vitamin C and E had a much more limited effect on post-MI, infarct size, and LVEF being increased only by 5%, with few improvements. These outcomes show that newer antioxidants, which are specific and more effective for oxidative damage at the cellular and mitochondrial levels, can provide additional advantages over conventional antioxidant therapies.

The colchicine study, while not targeting infarct size, drives the necessity of decreased inflammatory responses after MI. Cardiovascular event reduction by 3% highlights the involvement of inflammatory process in post-MI outcomes and points to the synergy between anti-inflammatory and antioxidant therapies in enhancing post-MI cardiac outcomes.

5.2. Practical Implications

The findings of this review certainly have important, practical implications for managing post-MI patients. Other anti-oxidants like NAC, melatonin, and edaravone have been shown to provide new therapeutic opportunities to improve cardiac function following MI, based on the effects of oxidative stress in the myocardial infarction process. The integration of antioxidant therapy into routine post-MI treatment might be useful in decreasing the size of infarction, increasing LVEF, and further preventing complications in the long run, such as heart failure.

Incorporation of antioxidants such as NAC and melatonin may be especially beneficial knowledge for clinical practitioners dealing with patient populations that have a higher propensity to oxidative damage based on other comorbidities such as diabetes or hypertension. These antioxidants are good candidates for MI recovery adjuvants because of their low side effect profile compared to edaravone and other aggressive treatments.

Nevertheless, the tiny beneficial impact of conventional antioxidants like vitamins C and E reveals that these should not be dependent on as main treatments in post-MI. Thus, moving to more effective and selective antioxidants is necessary, primarily acting on the pathophysiological mechanisms of oxidative stress in myocardial damage.

5.3. Challenges and Limitations

However, certain obstacles and drawbacks must be overcome regarding the new generation of antioxidants. One of the main limitations is the fairly heterogeneous clinical efficacy of SR treatments of depression in different trials. Cohort variability, variations in antioxidant dosages, and variations in the periods of the studies also contribute to ambiguous findings that do not clearly define definitive protocols of antioxidant therapy in post-MI patient care. For example, NAC was beneficial in some research studies. Still, it was seen to differ in other research studies in this regard because of differences in the dosage and the characteristics of patients.

The other issue of concern is the adverse effects of certain antioxidants, especially edaravone. It has considerable benefits concerning the reduction of cardiovascular risk. However, it is associated with adverse reactions such as increasing the liver enzyme levels and other reactions that should exclude it from the widespread use among patients. This shows that care needs to be taken when choosing antioxidants to prescribe for post-MI therapy concerning effectiveness and safety levels.

Further, the chronic outcome of antioxidant therapy remains questionable. Most of the research selected for review reported results with several weeks and two years follow-up periods. Thus, long-term trials are needed to determine whether consuming antioxidants confer long-term advantages and whether there are hazards associated with the long-term use of antioxidants.

Five factors that should be considered include the kind, dosage, formulations, half-life, and the bioavailability of antioxidants. Most antioxidants, including the traditional ones such as vitamins C and E, have great difficulty accumulating therapeutic levels in the myocardial tissue, mainly due to poor absorption or short half-life. The next steps in research should be tailored towards enhancing access to new antioxidants at the sites of hefty oxidation, such as the mitochondria.

5.4. Recommendations

To overcome the limitations and problems found, several suggestions may be pointed out for future research and clinical practice.

First, more comprehensive and involving trials at several centers are required to reassess the effectiveness of new antioxidants in various patient groups. These studies should propose standard dosing regimens, longer follow-up times, and appropriate biomarkers to measure oxidative stress and myocardial healing during the disease. Through these trials, if the sample size and duration are larger, valuable data can be drawn, and better medical recommendations can be made.

Second, future studies should be directed toward synergistic therapy with anti-inflammatory agents such as colchicine and antioxidants containing NAC or melatonin. Since both oxidative stress and inflammation are factors of MI recuperation, the contingent use of these therapies will have enhanced effects in lessening the infarct size and improving the long-term cardiac status.

Third, there is a demand for better formulations for antioxidants to increase their bioavailability levels. New approaches like liposomal form or nanoparticles can also help maintain the delivery of antioxidants to the damaged tissues, enhancing their beneficial effects in post-MI care.

Finally, ideas about realizing the concept of personalized medicine should be discussed. Due to these inconsistent results in patients' reactions to antioxidant therapy, future studies should focus on the opportunity for customized approaches to therapies with specific reference to genetics, oxidative status, and other diseases in patients. This may be useful in maximizing the reapets of antioxidant therapy and decreasing the incidence of adverse reactions.

6. Conclusion

6.1. Summary of Key Points

The present review investigated new antioxidant compounds and their impact on hearts with myocardial infarction (MI). It was aimed to stress the reduced size of the infarct, the enhanced cardiac function, and the suppression of oxidative stress. Synthesis of preclinical and clinical study evidence revealed that antioxidants such as NAC, melatonin, and edaravone significantly protect against myocardial injury and an increase in LVEF. NAC was superior at a 30% reduction in infarct size and a 12% increase in LVEF compared to melatonin and edaravone.

Though conventional antioxidants, including vitamins C and E, had negligible effects, new-generation antioxidants offered more focused action against oxidative stress. However, several barriers could still be encountered, such as adverse effects, especially of edaravone, and the interindividual variability of clinical response. The review also stressed that further substantial clinical trials are required to validate these outcomes and choose dosing regimens.

Finally, in terms of application, new antioxidants provide potential additional treatments for patients after myocardial infarction. They can help enhance subsequent care and reduce risks of adverse effects in the long run. However, more studies are needed to improve their solubility, investigate the synergistic effects, and introduce antioxidants with other anti-inflammatory products such as colchicine.

6.2. Future Directions

Post-MI therapy with potential novel antioxidants may be very effective, but several issues should be further elucidated to enhance the therapy effects. First, large-scale, adequate-length clinical trials are required to determine the longevity and the impact of antioxidants on the incidence of heart failure and mortality rates. These trials must engage bigger sample sizes, particularly across males and females with different ages, weights, genetic characteristics, and diseases, to understand how all these factors affect the outcomes of the antioxidant remedies.

Second, future research should strive to enhance the stability and solubility of antioxidants. Mitochondrial-targeted antioxidant formulations and uses of nanocarriers or liposomes also represent other promising strategies to improve the delivery of antioxidants to diseased mitochondria. This would enhance the therapeutic value of N-acetylcysteine (NAC), melatonin, and edaravone.

Hence, further research on how combining antioxidants with existing anti-inflammatory drugs like colchicine will enhance post-MI recovery by preventing oxidative stress and inflammation. This work-in-tandem may result in improved long-term beneficial effects and reduced incidences of recurrent CVEs.

Finally, a concept of the personalized approach to treatment should be implemented. Thus, stratified oxidant therapies, i.e., antioxidant therapies grounded on oxidative stress levels and genotype, may enhance treatment efficiency and decrease adverse effects. Individualized approaches may improve the efficiency and security of antioxidants in post-acute MI management.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclsoed.

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