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Cardioprotection conferred by rooibos (*Aspalathus linearis*): A mini review to highlight a potential mechanism of action

A number of cardioprotective interventions have been identified throughout the years, and these include the use of natural antioxidants in sources like rooibos (*Aspalathus linearis*) tea. Recent studies have demonstrated that rooibos (either its isolated components or the crude rooibos extract/tea) confers cardioprotection in diabetic cardiomyopathy and myocardial ischaemic injury. In addition, a clinical study has shown that regular rooibos consumption reduces the risk for cardiovascular disease in adults. However, rooibos is currently not considered an official treatment against cardiac disease, mainly because the underlying mechanisms for rooibos-induced cardioprotection are not fully elucidated. Physiological actions of rooibos must be well investigated before rooibos can be used in a clinical setting as adjunct treatment for patients with heart disease. Thus, research to delineate the underlying mechanisms of rooibos-induced cardioprotection is key. In the light of the aforementioned, the available literature on rooibos-induced cardioprotection is reviewed here, highlighting the fact that rooibos preserves and maintains cardiac energy homeostasis. It is postulated that rooibos activates an AMPK-GLUT-4 glucose oxidation (cardiac energy-shortage sensing) pathway to shift cardiac energy usage, thereby conferring cardioprotection.

Significance:

- It is hypothesised that rooibos may alter the way in which the human heart uses energy and oxygen, in order to protect the heart against disease. The heart's mitochondria are responsible for the heart's energy processes, and therefore are most likely involved in rooibos-induced cardioprotection.

- Cardioprotection conferred by rooibos is likely via an AMPK-GLUT-4 glucose oxidation pathway.

- The mechanism of cardioprotection is important for future studies investigating how rooibos alters cardiac mitochondria.

- The more information gathered about the underlying mechanisms of rooibos, the easier it will be to recommend rooibos as an official cardioprotective intervention in patients with heart disease.

Introduction

Cardioprotection is the manipulation of cellular processes with various therapeutic interventions to protect the heart before, during or after disease.[1-3] These interventions include pre- and post-conditioning[4-6], remote ischaemic conditioning[4-6], and intake of antioxidants melatonin[7,8] and rooibos (*Aspalathus linearis*)[9,10]. Rooibos is an endemic South African fynbos plant species that grows exclusively in the Cederberg mountain region.[11,12] Research investigating rooibos mainly describes the multiple biological effects of the two forms of rooibos leaf extracts: unfermented green and fermented rooibos.[13] Bioactive components within rooibos extracts/tea are categorised as polyphenols and flavonoids[14,15] and are responsible for the anti-inflammatory, anti-cancer[16,17] and antioxidant properties[13,18], of rooibos. Considering that polyphenols and flavonoids have a well-documented role in cardioprotection[19,20], rooibos extract is a possible candidate for cardioprotection[21,22].

Cumulative evidence suggests that either the individual rooibos components[9,23,24] or the crude rooibos extract/tea confers cardioprotection against heart disease in diabetes[10] and heart attacks[25]. In one recent study, rooibos conferred cardioprotection in rats that were on antiretroviral therapy and displayed myocardial ischaemic damage.[26] However, in all these aforementioned studies, the mechanisms underpinning the rooibos-induced cardioprotection were not fully understood. Considering that rooibos is reported as a cardioprotective strategy for patients with heart disease[21,22], the underlying mechanisms of rooibos-induced cardioprotection should be better understood. Without this understanding, in addition to a lack of evidence on the active ingredient(s) and safety/toxicity for patients taking heart disease medication[27], rooibos may not pass clinical standards as a cardioprotective intervention for heart disease patients. If more information were gathered about the physiological mechanisms of rooibos, there would be a solid scientific foundation for the recommendation of rooibos as an effective cardioprotective intervention in patients with heart disease.

Considering the variety of bioactive components present in rooibos tea, it is likely that more than one component of rooibos contributes to cardioprotection. Additionally, these different components may activate different, yet synergistic, molecular pathways to bring about cardioprotection. This likelihood complicates the understanding of the underlying mechanisms of rooibos-induced cardioprotection. However, over the years, multiple studies have highlighted isolated mechanistic aspects related to rooibos-induced cardioprotection. To this end, a review paper is necessary to provide a novel perspective on current evidence, and to highlight a possible underlying mechanism for rooibos-induced cardioprotection. This elucidation of possible mechanisms might be useful for the design of future studies.

Overview of cardiac energy substrate utilisation in cardioprotection

Cardiac energy substrate utilisation plays a key role in cardiomyopathies[28,29] and cardioprotection[30,31]. In diabetes[32,33], high blood glucose (hyperglycaemia) as well as high glucose uptake without simultaneous glucose utilisation/oxidation,

induces toxic effects on the heart[34,35]. It induces this toxicity by activating programmed cell death (apoptosis of cardiomyocytes)[36] and thereby contributes to diabetic cardiomyopathy[37]. In this case, a sensible approach is to increase glucose oxidation, a pathway that can reduce the amount of glucose entering cardiomyocytes.[38] This approach limits cardiomyocyte apoptosis and confers cardioprotection.[39,40] Against this background, several therapeutic interventions modulate cardiac energy substrate utilisation in favour of glucose oxidation[39,40], in order to confer cardioprotection.

Another dimension to the negative impact of hyperglycaemia on the heart, is that it increases the production of toxic molecules called reactive oxygen species[41] that contribute to oxidative damage in the heart during hyperglycaemia. Therefore, in theory, a therapeutic intervention that can (1) increase myocardial glucose oxidation and (2) reduce reactive oxygen species, would accelerate glucose breakdown and thus limit the toxic effects of hyperglycaemia on the heart (Figure 1, green side).
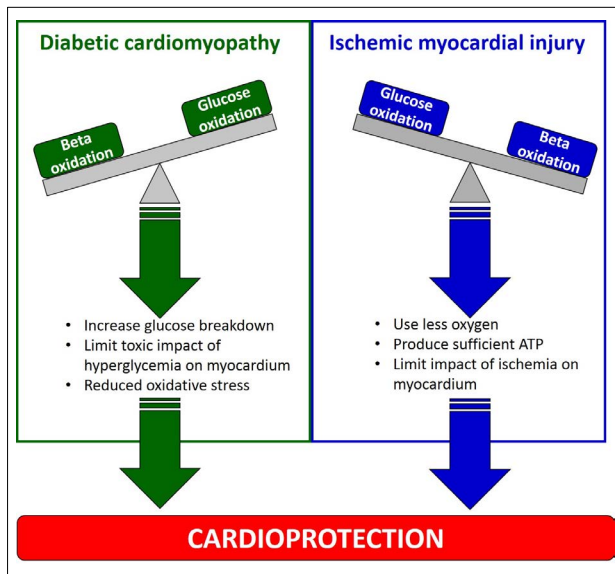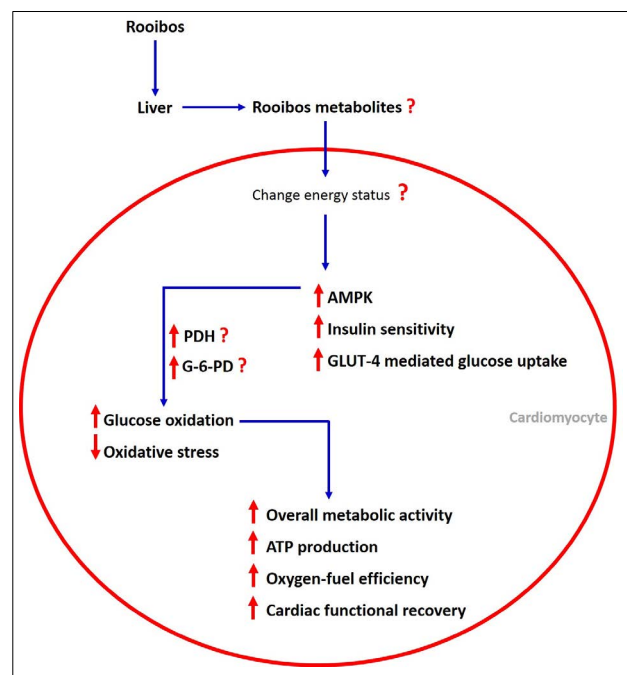

ATP, adenosine triphosphate

Figure 1: This figure demonstrates the role of glucose- and beta-oxidation in mitigating diabetic cardiomyopathy and myocardial ischaemic injury. In diabetic cardiomyopathy, hyperglycaemia induces toxic effects on the myocardium (heart muscle) and, therefore, increased uptake and breakdown of glucose alleviates the impact of hyperglycaemia. During myocardial ischaemia, increased myocardial glucose oxidation is a better fuel option, as it produces sufficient ATP with an oxygen sparing effect. Shifting of myocardial energy metabolism toward glucose oxidation, irrespective of whether diabetic cardiomyopathy or ischaemia-reperfusion is present, promotes cardioprotection.

In the case of a heart attack (myocardial ischaemia), oxygen availability to the myocardium is markedly reduced.[2] The heart normally generates energy through both glucose oxidation and fatty acid oxidation, while the latter uses less oxygen for the production of a similar amount of energy (adenosine triphosphate, ATP).[42] Thus, if fatty acid (beta) oxidation is elevated during a heart attack and not altered, the already limited oxygen will be used to produce ATP, which will produce more severe ischaemic effects on the heart.[29,43] Therefore, increased glucose oxidation during myocardial ischaemia is considered a better pathway as it produces sufficient ATP with an oxygen sparing effect.[29,43] In keeping with this logic, previous reports have demonstrated that in myocardial ischaemia, pharmacological modulation of cardiac energy metabolism (how the heart uses glucose or fatty acids as energy) confers cardioprotection mainly because it increases glucose oxidation.[31,44,45] Furthermore, other reports have demonstrated that a shift in cardiac energy substrate utilisation toward glucose oxidation (irrespective of whether cardiomyopathy is from hyperglycaemia or ischaemia) contributes to cardioprotection[43,46] (Figure 1, blue side).

Evidence that rooibos shifts cardiac energy substrate utilisation

A number of studies have demonstrated a link between rooibos and changes in energy substrate utilisation in the liver[47] and skeletal muscle[48]. A recent study showed that rooibos reduced hepatic insulin resistance by modulating adenosine 5′ monophosphate activated protein kinase (AMPK) pathways.[49] One research group was able to demonstrate that rooibos increases liver activity of adenosine AMPK.[48] Similarly, rooibos is able to increase AMPK activity, glucose oxidation[48], mitochondrial activity and ATP production in muscle[50]. AMPK is also the main sensor for cardiac energy status[51], and thus this effect of rooibos on AMPK was also recently demonstrated in the heart[9,10,52]. Taken together, these findings demonstrate the ability of rooibos to modulate cardiac energy substrate utilisation.

Rooibos also preserves and maintains cardiomyocyte ATP production[9] and improves cardiac functional recovery[25] by enhancing glucose oxidation[9]. From these data, it can be inferred that rooibos alters AMPK activity to enhance myocardial glucose uptake via glucose transport-4 (GLUT-4)[48] in order to promote myocardial glucose oxidation (Figure 2).

AMPK, 5' AMP-activated protein kinase; GLUT-4, glucose transporter-4; RB, rooibos; ATP, adenosine triphosphate; PDH, pyruvate dehydrogenase complex; G-6-PD, glucose six phosphate dehydrogenase

Figure 2: This figure demonstrates that, after oral consumption, rooibos is metabolised in the liver, and after metabolism, metabolites are circulated to the heart. Upon entering cardiomyocytes, rooibos metabolites may change cardiomyocyte energy status and increase AMPK activity and GLUT-4 mediated glucose uptake. Subsequently, glucose oxidation is increased and beta-oxidation reduced (Randle Cycle), and, because of the antioxidant properties of rooibos, oxidative stress is mitigated. In concert, these changes increase metabolic activity (through increased ATP production, less oxygen used, increased functional recovery) and ultimately contribute to rooibos-induced cardioprotection. Therefore, this figure depicts the postulated hypothesis that rooibos confers cardioprotection via an AMPK-GLUT4 glucose oxidation pathway.

As a consequence of the feedback inhibition of increased glucose oxidation on beta-oxidation (also referred to as the Randle relationship)[37], rooibos may reduce fatty acid uptake/oxidation[9]. In concert, these processes allow the myocardium to have a reasonably high cardiac mitochondrial activity, and consume less oxygen in order to produce sufficient ATP production (Figure 2). Although not tested, this hypothesis could explain the enhanced

myocardial functional recovery after ischaemia-reperfusion[25], and the preserved cardiomyocyte ATP production[9] as previously reported. Therefore, in Figure 2, a hypothesis is depicted contending that rooibos may alter the overall cardiomyocyte energy status, and act via an AMPK-GLUT-4 glucose oxidation pathway to confer cardioprotection. Future studies could investigate this hypothesis, and test whether rooibos extracts are able to activate this pathway to execute its favourable impact on cardiac energy substrate utilisation, and confer cardioprotection.

Furthermore, considering that pyruvate dehydrogenase[53,54] and glucose-6-phosphate dehydrogenase[55] are regulators of glucose oxidation, it should also be investigated whether rooibos modulates these enzymes in order to activate this AMPK-GLUT-4 glucose oxidation pathway. Merely enhancing myocardial glucose oxidation may not solely account for rooibos-induced cardioprotection – other factors, such as reduced apoptosis signalling[9,10,23,25] mitochondrial connexin-43[56] and cardiolipin[57], G-protein-coupled receptor kinase-2[58] and the reduction of reactive oxygen species[21,59] may also contribute. There is a need for therapeutic interventions that confer cardioprotection, particularly those that can be consumed through dietary intake of rooibos. However, the cardioprotective properties of rooibos are not well described and the exact underlying mechanisms remain to be delineated.[60] Therefore, ongoing research is necessary to aid in the understanding of how rooibos confers cardioprotection and studies investigating the underlying mechanisms should be a priority. The identification of these underlying mechanisms would contribute to the body of knowledge on rooibos-induced cardioprotection, and possibly facilitate the use of rooibos as an accepted cardioprotective intervention in the clinical setting.

Conclusions

Studies on rooibos-induced cardioprotection, particularly those studies using models of diabetic cardiomyopathy and myocardial ischaemic injury, were reviewed. Based on the evidence presented and discussed in this review, it is hypothesised that rooibos may alter myocardial energy status, acting via an AMPK-GLUT-4 glucose oxidation pathway to confer cardioprotection. Future studies could further investigate this hypothesis and the activation of the proposed pathway in a suitable experimental model of cardiomyopathy.

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