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Effect of *Picrorhiza kurroa* Royle ex Benth ethanolic root extract on Cardio protection against methotrexate induced myocardial infarction in rats

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ABSTRACT: The purpose of this research was to examine whether *Picrorhiza kurroa* Royle ex Benth (ERPK) root extracts could prevent Methotrexate (MTX)-induced heart damage in rats. Methotrexate (20 mg/100g, s.c.) was administered twice at 24-hour intervals to the animals. Analysis of electrocardiogram (ECG) parameters, serum marker enzymes, and cardiac histology were used to determine cardio-protective efficacy. P wave, QRS complex, and R-R interval all increased significantly (P< 0.001) after pretreatment with 200 and 400mg/kg of ERPK, whereas heart rate, QT interval, and cardiac cycle remained within acceptable ranges. All of the diagnostic indicators assessed for ERPK were significantly (P <0.05; P< 0.001) lower in that group than in the MTX-treated group. The protective function of ERPK was substantiated by histological examinations of cardiac tissue alterations. These findings imply that ERPK therapy before MTX plays a crucial role in preventing MTX-induced myocardial infarction in rats.

Keywords: *Picrorhiza kurroa*, Methotrexate, ECG, Marker enzyme, Cardioprotective.

INTRODUCTION

Ischaemic heart illnesses, particularly acute myocardial infarction (MI), continue to be the major cause of death in both developed and under developing countries, as observed during the course of the previous quarter century (Mochizuki *et al.,* 1998; Zhu *et al.,* 1998). According to the World Health Organisation (WHO), ischemic heart disease (IHD) will overtake cancer as the top cause of death in the world by the year 2020 (Lopez *et al.,* 1998). IHD is currently the leading cause of both morbidity and mortality around the world. Ischemic heart disease (MI) is caused by chronic myocardial ischemia, which leads to the death of myocytes and occurs when blood supply is cut off to part of the heart (White 1996). Methotrexate (MTX) induced myocardial necrosis is a well-known standard model that was developed by Wexler in 1978 in order to investigate the beneficial effect that various medicines have on cardiac dysfunction (Wexler 1978).

Antineoplastic agents, such as methotrexate, are utilised in the treatment of a wide range of malignancies, as well as severe cases of psoriasis, rheumatoid arthritis, and juvenile rheumatoid arthritis. According to research carried out by Perez-Verdia and colleagues in 2005, the cytotoxic effects of MTX not only kill cancer cells but also have an effect on critical organs like the heart(Perez-Verdia *et al.,* 2005). MI that is produced by MTX in rats has been shown to be accompanied by hyperglycemia, hyperlipidaemia, and an increase in serum creatinine phosphokinase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase activity (Demiryilmaz *et al.,* 2012; Jahovic *et al.,* 2004). The formation of extremely cytotoxic free radicals through auto-oxidation of catecholamine has been suggested as one of the contributing elements in the cardiac damage that has been attributed to the drug methotrexate. This mechanism is postulated to explain how the drug causes the damage. It is of the utmost significance to bring the overall mortality rate down and to stop people from having heart attacks.

Studies conducted in the laboratory shown that continuous administration of MTX led to an increase in the size of myocardial infarcts, cardiac hypertrophy, and a reduction in cardiac function. Because of the potential for unpleasant responses and side effects, their application is frequently restricted. On the other hand, there is a burgeoning interest in the use of complementary and alternative medicine for the long-term prevention of heart attacks in individuals who are at high risk for developing the condition. An alternative therapy for ischemic heart illnesses can be derived from a wide variety of plants and the active components found within them, with just minor adverse effects. In addition, the plant kingdom contains a store of biologically active chemicals that are relatively unknown, particularly in the context of cardiovascular disorders. The purpose of the current study was to explore the cardio-protective effects of ethanolic root extracts of *Picrorhiza kurroa* in MTX-induced

alterations in electrocardiographic, serum marker enzymes, and histopathological abnormalities.

Picrorhiza kurroa Royle ex Benth. (Scrophulariaceae) is a small perennial herb that can be found growing at an elevation ranging from 3,000 to 5,000 metres (Mehra *et al.,* 1968; Subedi *et al.,* 2000). It is primarily found in the Himalayan region. The plant's leaves are ovate in shape, and their margins are finely serrated. Since ancient times, the leaf, the bark, and the underground components of the plant, particularly the rhizomes, have all been utilised extensively in the Ayurvedic medical practises that are practised in India. According to Atal *et al.,* the traditional use of *Picrorhiza kurroa* includes the treatment of conditions related to the liver, the upper respiratory tract, fevers, dyspepsia, chronic diarrhoea, scorpion stings, and cancer (Atal *et al.,* 1986). It has been established that the plant have the ability to prevent DNA damage (Russo *et al.,* 2001). In spite of the fact that it possesses antioxidant, anti-inflammatory, and immunomodulatory properties, the effect that it has on the liver is what makes it so valuable. Since ancient times, people have been using the rhizomes of the *Picrorhiza kurroa* plant to treat dyspepsia, which is caused by an imbalance in the digestive secretions (Krishnamurthy 1969).

MATERIAL AND METHODS

Drugs and chemicals: ECG Electrodes were obtained from Biopac in Santa Barbara, California, and methotrexate hydrochloride (MTX) was purchased from Sigma Chemical Company in St. Louis, Missouri, in the United States. Pentobarbitone and anaesthetic ether were also utilised in this study along with sodium carboxy methyl cellulose (Na-CMC) sourced from Loba Chemie in Mumbai, India. All of the compounds were of a grade suitable for analytical usage.

Experimental animals: For the purpose of the study, male Wistar rats weighing between 150 and 200 g were employed. The inbred rat colonies were acquired from Venkateshwara Enterprises in Bangalore, which is located in India. They were exposed to controlled environments consisting of temperature (23±2º C), humidity (50±5%), and light-dark cycles lasting 12 h. The animals were housed in sanitised polypropylene cages that contained sterile rice husk as a bedding material. Following this, the animals were randomised into several experimental and control groups. They were provided with an unlimited supply of water and the normal feed of pellets at all times. The CPCSEA regulation was followed in terms of both the care given to the laboratory animals and the care given to the experimental animals, both of which were authorised by the Institutional Animal Ethical Committee (IAEC). We chose to conduct our research on male rats since previous research by Stauss found that female rats are less likely to experience cardiovascular problems (Stauss *et al.,* 1994).

Plant material: The research used *Picrorhiza kurroa* root powder that was dried and purchased from Herbo Nutra in Uttar Pradesh, India, in the month of August 2021.

Preparation of extract: Extensive extraction with Ethanol (95%) from dried root powder in a Soxhlet apparatus. The extracts were concentrated using a rotary flash evaporator at a low temperature and pressure, then freeze dried and placed in a desiccator for safekeeping. Distilled water was used to make a suspension of EEPK in Sodium carboxy methyl cellulose (Sod. CMC) to evaluate the plant's cardioprotective properties.

Induction of Myocardial Ischemia: The rats were split up into six different groups of six. Methotrexate (20 mg/100g injected subcutaneously twice at an interval of 24 h) dissolved in normal saline was used to produce Myocardial ischemia in Group II rats (Al-Taher *et al.,* 2020), whereas Group I served as a control. On days 29 and 30, after receiving *Picrorhiza kurroa* root extract (100, 200, and 400 mg/kg) for 30 days (Ghani 2003), rats in Groups III, IV, and V were given Methotrexate (20 mg/100g subcutaneously twice at a 24-hour interval).

Measurement of ECG: ECGs were collected using a computerised data collecting system (Biopac MP 35, Santa Barbara, California) on the 30th day of extract/vehicle therapy after the rats were anaesthetized with light anaesthetic ether (24 hours after the second MTX injection). Bi-polar standard lead-I, lead-II, and lead-III were used for the recordings. Lead II has the most distinct individual waves compared to Lead I and Lead III in all cases of myocardial infarction. Lead II was used as the sole ECG monitoring lead.

Biochemical analysis: In order to estimate marker enzymes, blood was drawn from the retro-orbital plexus after an electrocardiogram was recorded (Zaijun Zhang *et al.,* 2009). Aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, triglyceride, and total cholesterol levels were all measured with standardised kits.

Histopathological Studies: Thiopental sodium injections were used to euthanize the animals (CPCSEA annexure 6). After removal, the hearts were washed in saline and placed in 10% buffered formalin for preservation. Haematoxylin and eosin were used to stain the heart tissue after it was kept in 10% buffered formalin, paraffin embedded, and sectioned at 5 mm. Histological alterations were analysed by observing these sections under a microscope.

Statistical Analysis: Six rats were used in each group, and the results are presented as means SEM. Statistical significance was established using one-way analysis of variance (ANOVA) and Tukey's multiple comparisons test.

RESULTS AND DISCUSSION

ECG parameters: *Picrorhiza kurroa's* impact on electrocardiogram (ECG) readings Electrocardiographic patterns from both the control and experimental animals are shown in Figures 1A through 1F. While ECGs from control and ERPK (100, 200, and 400mg/kg)-treated rats were normal, those from MTX (100mg/kg)-treated rats showed significant elevation in the ST segment,

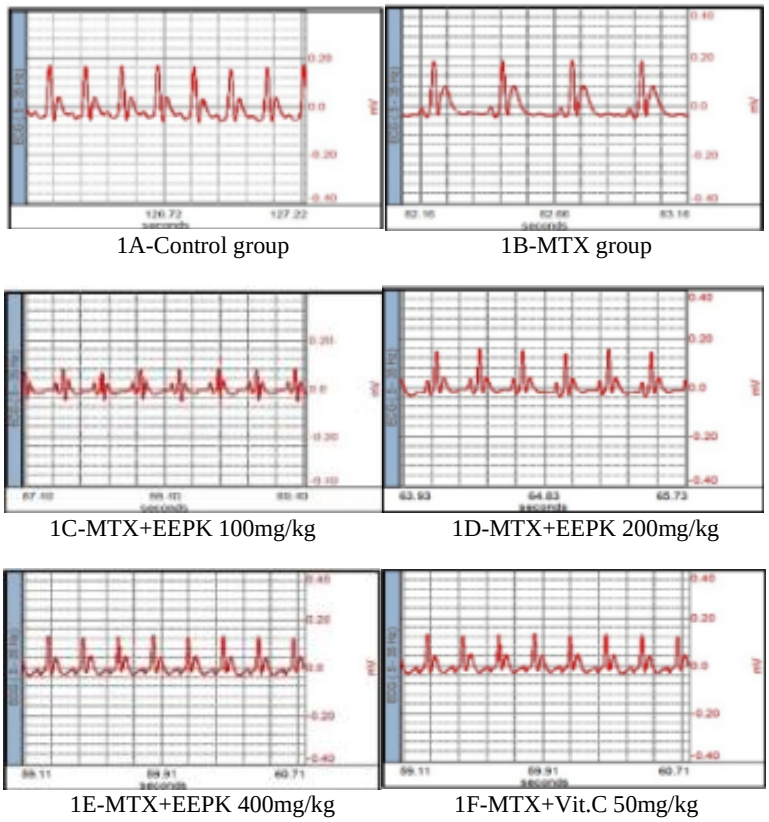
reduction in the P wave, QRS complex, and R-R interval, as well as an increase in heart rate, prolongation of the QT interval, and an increase in cardiac cycles. Normal ECG pattern with a mild elevation in the ST segment was observed in rats pretreated with ERPK at 100, 200, and 400mg/kg. The P wave, QRS complex, and R-R interval all showed statistically significant ($P < 0.001$) changes as a result of treatment, although the heart rate, QT interval, and cardiac cycle were all kept close to normal, particularly at high dose. Table 1 and Fig. 1 show the experimental animals' heart data, including P waves, QRS complexes, QT intervals, R-R intervals, heart rates, and cardiac cycles.

Effect of *Picrorhiza kurroa* on serum marker enzymes: Serum myocardial damage marker enzyme levels (AST, ALT, LDH, CK, CK-MB, Troponin, triglycerides, and total cholesterol) were considerably (p 0.001) higher in MTX-treated rats compared to normal control rats (Table 2). Compared to the MTX-only treated group, all of the diagnostic markers were significantly lower in the group that received pretreatment with ERPK at 100, 200, and 400 mg/kg for 30 days. In contrast to the normal control group, however, ERPK treatment at 100, 200, or 400 mg/kg had no effect on the levels of any of these marker enzymes.

Table 1. Effect of *Picrorhiza kurroa* root extracts on ECG parameters in Methotrexate induced Myocardial infarction in rats.

Groups	P Wave	QRS Complex	Q-T Interval	R-R Interval	Heart rate	Cardiac cycle
Control	0.03850±0.0014	0.04292±0.0009	0.08500±0.0033	0.1879±0.0033	345.2 ±4.87	0.1221±0.0037
MTX -20mg/kg	0.03175±0.0007[a]	0.03492±0.0001[a]	0.09944±0.0019[a]	0.1218±0.0021[a]	424.9±6.90[a]	0.1361±0.0027[a]
MTX+Vit.C-50mg/kg	0.03831±0.0014	0.04212±0.0009[b]	0.08584±0.0033[b]	0.1795±0.0033[b]	353.2±4.87[b]	0.1227±0.0041[b]
EEPK100mg/kg	0.03481±0.0011[b]	0.03984±0.0005[b]	0.08960±0.0012[b]	0.1823±0.0013[b]	377.0±9.35[b]	0.1278±0.0018[b]
EEPK200mg/kg	0.03692±0.0011[b]	0.04089±0.0004[b]	0.08870±0.0026[b]	0.1841±0.0027[b]	359.0±6.35[b]	0.1254±0.0026[b]
EEPK400mg/kg	0.03774±0.0011[b]	0.04201±0.0004[b]	0.08653±0.0016[b]	0.1862±0.0011[b]	351.4±7.25[b]	0.1233±0.0014[b]

The data were expressed as Mean ± S.E.M for six rats in each group. Statistical comparisons were performed by one-way ANOVA followed by Tukey's post-test, The ECG parameters are expressed in seconds (sec) and the Heart rate as Beats per Minute (BPM). a $P < 0.001$ compared with control, b $P < 0.001$ compared with MTX treated group.



1A-Control group 1B-MTX group

1C-MTX+EEPK 100mg/kg 1D-MTX+EEPK 200mg/kg

1E-MTX+EEPK 400mg/kg 1F-MTX+Vit.C 50mg/kg

Fig. 1. Effect of ethanolic root extracts of *Picrorhiza kurroa* (EEPK) onECG parameters in Methotrexate induced cardiotoxicity in rats.

Histopathological studies: Myocardial tissue from both control animals and those given *Picrorhiza kurroa* showed histopathological evidence of the membrane's obvious integrity and the absence of inflammatory cell infiltration upon histopathological evaluation (Fig. 2A). Heart tissue recovered from MTX-treated mice showed

localised lesions (molten staining, muscle fibre disintegration, and confluent retrogressive lesions) in varying degrees (Fig. 2B). Hyaline necrosis, vacuolar alterations, and significant sequestering mucoid oedema were also observed in MTX-treated rats. Vacuolar changes, oedema, capillary dilatation, and leukocyte infiltration were all significantly reduced in the ERPK 100, 200, and 400 mg/kg pre-treatment groups compared to the MTX given group (Fig. 2C, D, and E).

When dealing with ischemic heart disorders, oxidative stress is a crucial consideration. Extensive research (Hevener *et al.,* 2002; Dhalla *et al.,* 2000) points to a negative involvement of ROS in cardiovascular disease. Methotrexate, a well-known cardio-toxic agent, destroys myocardial cells, resulting in the release of cytosolic enzymes that serve as diagnostic markers of myocardial tissue damage. These include lactate dehydrogenase (LDH), transaminases (ALT and AST), and creatine kinase (CK), CK-MB, and Troponin. Changes in plasma membrane integrity and/or permeability are reflected by the concentration of these cellular enzymes in the blood. Reductions in lactate dehydrogenase, glutamic oxalacetic transaminase, and creatine kinase levels after therapy with drugs such naringin, silibinin, and squalene suggest that these drugs stabilise membranes (Sabeena *et al.,* 2004; Sawyer *et al.,* 2002; Rajadurai *et al.,* 2006; Gürgün *et al.,* 2008).

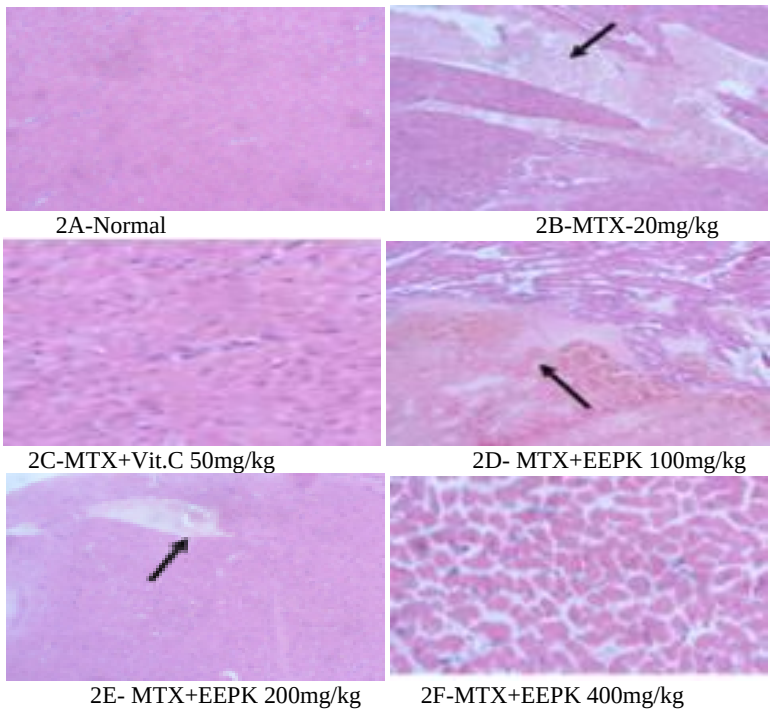


Fig. 2. Effect of ethanolic root extracts of *Picrorhiza kurroa* (EEPK) on histopathological studies in Methotrexate induced cardiotoxicity in rats.

Significant increases in AST, ALT, LDH, CK-MB, Troponin, and CK were seen in the present study in MTX-treated rats. In addition, consistent with a previous publication, increased levels of these enzymes are a marker of the severity of MTX-induced cardiac membrane necrosis. Serum marker enzyme elevations caused by MTX were significantly decreased after pretreatment with ERPK at doses of 100, 200, and 400 mg/kg, with the exception of CK. Its influence on preserving membrane integrity may be responsible for the decrease in enzyme levels by limiting the leaking of these molecules. The 1-adrenergic receptor is widely believed to be the primary mediator of Methotrexate-induced cardiac damage. Loss of membrane integrity, induction of heart contractile dysfunction and myocyte toxicity, and the eventual production of myocardial are all caused by the acute stimulation of beta-adrenergic receptors, which also rapidly generates reactive oxygen species, reduces total cellular antioxidant capacity, down regulates copper-zinc superoxide dismutase enzyme activity, protein, and mRNA, and lowers glutathione level (Rathore *et al*., 1998).

In this research, we discovered that *Picrorhiza kurroa* extracts prevented myocardial functional and structural harm caused by Methotrexate by restoring normal levels of diagnostic marker enzymes. According to recent epidemiological research (Srivastava *et al.,* 2007), people who don't get enough of particular nutrients are more likely to develop chronic degenerative disorders. Vegetable and fruit consumption has been shown to lessen the risk of cardiovascular disease, although the mechanisms underlying this protective impact are not well understood. Antioxidant levels in the blood are thought to be crucial, though. Studies showing a correlation between antioxidant flavanol intake and a lower risk of death from coronary heart disease in men over the age of 65 lend credence to this theory. Epidemiological research indicates that consuming foods rich in flavonoids (quercetin, catechin, and epicatechin), which are found mostly in red wine but also in fruits and

vegetables, is inversely linked with the development of coronary heart disease (Padmanabhan *et al.,* 2007, Paritha *et al.,* 1996). They have been linked to this impact because of their antioxidant properties. Therefore, the flavonoids in ERPK, which are well-known free radical scavengers, may be responsible for the observed myocardial protective effect.

Myocardial infarction is often diagnosed based on the presence of specific abnormalities in an electrocardiogram. Patients suffering from acute myocardial ischemia and rats subjected to Methotrexate-induced myocardial infarction both showed ST-segment elevation (Seneviratine *et al.,* 1999; Peacock *et al.,* 2007). Compared to controls, MTX-treated rats had significantly different ECG patterns. The typical findings were a weakening of the P wave, a slowing of the QRS complex and R-R intervals, a lengthening of the QT interval, and a slower heart rate. The ST segment was likewise significantly elevated, and so was the heart rate. One possible explanation for these changes is that damaged myocardium gradually loses its cell membrane (Rajadurai *et al.,* 2007). Pre-treatment with *Picrorhiza kurroa* fractions significantly prevented Methotrexate-induced ST-segment elevation, suggesting its cell membrane protective properties, as revealed in the present study. Ischemia can be detected by the presence of certain electrocardiographic alterations, such as an elevated Q wave or ST segment. Ischemia-related pathogenic Q waves were not detected in the current investigation. Francis Morris *et al.,* found that only in individuals with serious heart disorders (such as ischemia or infarction) did patients exhibit a pronounced Q wave (Francis Morris *et al.,* 2003). An increase in ST has been linked to oxidative stress-induced damage to cellular membranes (Holland *et al.,* 1977; Kela *et al.,* 1980). ERPK at doses of 100, 200, and 400mg/kg prevented the abnormal ECG pattern and immediate lethal consequences caused by MTX by protecting the cell membranes.

Histopathological examinations provided additional confirmation of the electrocardiographic and biochemical findings. Myocardial tissue from negative controls showed clear membrane integrity on histopathology testing. The hearts of healthy control rats showed no evidence of invasion by inflammatory cells. Focal lesions in several sections were seen in the MTX group, and they consisted of moulted staining and fragmentation of muscle fibres with confluent retrogressive lesions, hyaline necrosis, and sequestering mucoid oedema. Focal lesions, muscle fibre fragmentation, and retrogressive lesions with hyaline necrosis were all suppressed in the MTX-treated group after pretreatment with ERPK at 100, 200, and 400 mg/kg. ERPK treated groups at 200 and 400 mg/kg showed decreased inflammatory cell density, demonstrating the additional cardio-protective action exerted by *P. kurroa*. However, normal rats treated with ERPK at 200 and 400 mg/kg p.o) showed no signs of toxicity on heart structure. Subendocardial ischemia, hypoxia, necrosis, and fibroblastic hyperplasia were induced by a higher dose of Methotrexate, followed by decreased myocardial compliance and inhibition of diastolic and systolic function. These pathological changes are similar to those seen in human myocardial infarction (Karthick and Prince, 2006).

CONCLUSIONS

The present investigation demonstrated that fractions of the root of *Picrorhiza kurroa* protected myocardium from the structural and functional damage caused by Methotrexate. ERPK was shown to include flavonoids, tannins, and phenolics in the phytochemical analyses. The existence of these bioactive components and their synergistic capabilities may account for the cardio-protective activity of ERPK. The cardio-protective activity may also occur because beta-adrenergic receptor stimulation is inhibited, which reduces the production of reactive oxygen species and keeps the myocardial membranes healthy. The present study's findings support the use of *Picrorhiza kurroa* as a cardio-protective agent by showing that its extracts restored normal levels of electrophysiological, biochemical, and histopathological parameters in experimental rats given Methotrexate.

FUTURE SCOPE

The promising results identified in this study can be continued with the isolation of the active constituents responsible for the activity and it may be tested both in-vitro and in-vivo methods to find out the new and effective cardioprotective agent.

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Conflict of interest. None.

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