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Additive and antagonistic effects of selected polyphenols on biochemical indices of isoproterenol-induced toxicity in Wistar rats

Grace Jadesola Oyinbogbola, Mary Tolulope Olaleye, Aanuoluwapo Ruth Adetuyi, Ibrahim Olabayode Saliu, Afolabi Clement Akinmoladun*

Department of Biochemistry, School of Life Sciences, The Federal University of Technology, Akure, Nigeria.

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ABSTRACT

Drug-induced toxicity negatively affects the quality of life and predisposes to mortality from health-related causes. This study investigated the effects of selected phenolic compounds on isoproterenol (ISP)-induced toxicity related to liver and heart functions in rats. Male Wistar rats were treated with 20 mg/kg quercetin, 50 mg/kg catechin, 100 mg/kg coumaric acid, combined doses of the polyphenolic compounds, or 2.5 mg/kg ramipril, for 12 consecutive days and administered with 100 mg/kg ISP on the last 2 days of the treatment. Serum triglyceride (TG) and cholesterol (CHOL) levels, and activities of alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), and creatine kinase (CK) were evaluated after the treatment. Fasting blood sugar (FBS) and reduced glutathione (GSH) levels were also determined. Results revealed increased TG, CHOL, ALP, AST, ALT, LDH, CK, and FBS but decreased GSH levels in the ISP-toxified group compared with the control group. Both the individual and the combined phenolics ameliorated biochemical changes occasioned by ISP administration, with the combined phenolics appearing more potent in ameliorating imbalances in the lipid and FBS levels. Quercetin/catechin ameliorated ISP-induced increase in TG and CHOL levels by 72% and 90% ($P < 0.05$), respectively. These results indicate that the individual phenolics and their appropriate combinations are protective in ISP-induced toxicity.

1. INTRODUCTION

Drug-induced toxicity is a major challenge and may affect various biological processes involving single or multiple target organs. The heart and liver are two of the most commonly observed target organs of drug toxicity [1]. Cardiotoxicity contributes to myocardial infarction (MI) which is a leading cause of mortality worldwide. MI ranks top in the list of non-communicable diseases responsible for mortality in many countries [2,3]. It results from reduced oxygen supply to the myocardium insufficient to meet metabolic demand, occasioning myocardial hypoxia, and followed by several biochemical cascades including free radical damage, alterations in cardiac markers, and pro-inflammatory cytokines. Pathophysiological mechanisms of MI include oxidative stress, calcium overload, myocardial and endothelial injury, contractile dysfunction, and eventual cell death either by necrosis or apoptosis or both [3,4]. Drug-induced liver injury can be caused by numerous pharmaceutical agents, dietary, and herbal supplements and is a major cause of concern in drug development and therapy because of the liver's important role in biotransformation. The mechanisms by which many drugs cause hepatic injury are elusive, but several hypotheses exist [5,6].

*Corresponding Author:
Afolabi Clement Akinmoladun,
Department of Biochemistry, School of Life Sciences, The Federal University of Technology, P.M.B. 704, Akure - 340001, Nigeria.
E-mail: acakinmoladun @ futa.edu.ng

Isoproterenol (ISP)-induced myocardial damage is an established model for investigating the protective effects of bioactive agents on cardiac function [7]. At high doses, ISP exerts rigorous trauma to the myocardium causing the development of infarct-like lesion [8]. It depletes the energy stock of the myocytes, producing structural and biochemical aberrations [9]. Injury to cardiomyocytes occurs through calcium overload, coronary hypotension, depletion of energy stores, excessive generation of free radicals, and hypoxia [10]. Biochemical alterations induced by ISP include disturbances in circulating lipid levels which leads to coronary artery disorder [11].

Natural products such as phytochemicals have been reported to protect against drug-dependent toxicity [12-14]. Polyphenols are a large family of natural compounds that are widely distributed in plants and have been credited with diverse biological activities [15-17]. The two major classes of polyphenols are flavonoids and phenolic acids. Some of the reported biological activities of these polyphenolic compounds are antioxidant and radical scavenging, anti-inflammatory, cardioprotective, neuroprotective, and anticancer properties [15,18-20]. The antioxidant and radical scavenging activity of phenolics may be the most important function that underlies many of their biological actions in the body. Oxidative damage is implicated in most disease processes and epidemiological, clinical, and laboratory researches on antioxidants suggest their beneficial effects in the prevention and treatment of a number of these diseases. Individual polyphenols and polyphenol-rich phytoextracts can be

utilized in preventative and treatment protocols for cardiovascular disease and other diseases [21-24].

Interactions of two or more phytochemicals can modify bioavailability and the ultimate biological effects of individual components. Mixtures of pure bioactive compounds or phytochemical-containing plant extracts could provide additive or subtractive effects on efficacy against oxidative stress, inflammation, and other pathological conditions. The bioavailability of phytochemicals can be affected by the presence of other components in the matrix, for example, there could be interactions among phytochemicals during intestinal absorption, thereby influencing their activity [25,26]. Influence of interactions among polyphenolic compounds, especially flavonoids and phenolic acids, is a subject of continuing interest conceivably due to their preponderance in the diet and their health benefits [27,28].

The present study was designed to investigate the protective property of the flavonoids, quercetin, and catechin and the phenolic acid, coumaric acid, and whether their combinations could offer a protective synergism against ISP -induced toxicity in experimental rats. The heart is a primary target organ for ISP toxicity while the liver is the major organ responsible for metabolizing xenobiotics [29]. Therefore, the effects of ISP and the polyphenols on markers related to heart and liver functions were assessed. Ramipril, which belongs to a class of drugs called angiotensin-converting enzyme inhibitors (ACEIs), was used as the reference standard drug in this study. ACEIs are used for the treatment of heart-related conditions such as high blood pressure, heart failure, heart attack, and for preventing kidney failure due to high blood pressure and diabetes [30,31].

2. MATERIALS AND METHODS

2.1. Chemicals

Catechin, quercetin, ISP, 5,5′-dithiobis (2-nitrobenzoic acid), sulphosalicylic acid, and trichloroacetic acid were obtained from Sigma-Aldrich (St. Louis, MO, USA). All other reagents were of analytical grade. Assay kits for alkaline phosphatase (ALP) activity, aspartate aminotransferase (AST) activity, alanine aminotransferase (ALT) activity, cholesterol (CHOL) level, triglyceride (TRIG) level, lactate dehydrogenase (LDH) activity, and creatine kinase (CK) activity were obtained from Randox Laboratories Limited (Antrim, UK).

2.2. Experimental animals

Male Wistar rats (250 ± 40 g) were bred in the animal house of The Federal University of Technology, Akure, Nigeria. They were maintained under standard environmental conditions and natural darkness and light cycle. Experiments were approved by the University's Research Ethical Committee, Centre for Research and Development, with approval number FUTA/ETH/21/04. Handling and use of animals conformed to the NIH Guide for the Care and Use of Laboratory Animals, 2011.

2.3. Experimental Design

Animals were divided into nine groups with six animals per group. Doses of administered phenolics, ramipril, and ISP were based on previous reports [32-36].

Animals in Group I received distilled water only throughout the experiment and served as the control while Group II animals received distilled water for 12 consecutive days and were administered with ISP (100 mg/kg, i.p.), on the 11th and 12th day at 24 h interval. Animals in Groups III, IV, and V were orally administered with 20 mg/kg quercetin, 50 mg/kg catechin, and 100 mg/kg coumaric acid, respectively, for 12 consecutive days and on the 11th and 12th day received ISP at 24 h interval. Animals in Groups VI, VII, and VIII were orally coadministered with quercetin/catechin, quercetin/coumaric acid, and coumaric acid/catechin, respectively, for 12 consecutive days and on the 11th and 12th day received ISP at 24 h interval. Group IX animals were administered with ramipril (2.5 mg/kg) orally for 12 consecutive days and on the 11th and 12th day received ISP (i.p.) at 24 h interval.

2.4. Biochemical Estimations

The determination of fasting blood sugar (FBS) was performed before decapitation which was carried out 24 h after the last administration. The FBS of each animal was determined using Acuchek glucometer with strips supplied by the manufacturer following the manufacturer's instructions. The FBS was determined after withdrawing food overnight from the animals.

Animals were anesthetized with ether and blood samples were collected through cardiac puncture. For serum preparation, blood was collected into clean plain tubes and allowed to stand for 1 h. Serum was prepared by centrifugation at 3000 x *g* for 30 min at 25°C. The clear supernatant obtained was used for the estimation of serum enzymes and other biochemical indices.

Activities of ALP, AST, ALT, CK, and LDH, and the concentrations of TRIG and CHOL were determined using assay kits obtained from Randox Laboratories Limited (Antrim, United Kingdom) following the instructions of the manufacturer. GSH level was assayed following the previously reported method of Beutler *et al*. [37].

2.5. Statistical Analysis

Data obtained were analyzed by one-way analysis of variance followed by Duncan's Multiple Range Test using SPSS 11.09 for windows. The significance level was set at $P < 0.05$.

3. RESULTS AND DISCUSSION

ISP administration caused deleterious alterations to biochemical parameters. These changes were abated by treatment with the polyphenolic compounds.

In Table 1, administration of ISP caused a significant increase

Table 1: Serum activities of alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase of experimental animals, administered isoproterenol, and treated with polyphenolic compounds.

Group	ALP (U/L)	AST (U/L)	ALT (U/L)
Control	15.34±1.15^{b}	9.82±0.64^{a}	3.96±0.95^{bc}
Isoproterenol	41.83±4.76^{e}	16.43±1.00^{e}	5.31±0.44^{c}
Quercetin	10.31±1.89^{a}	11.60±0.62^{ab}	4.82±1.20^{c}
Catechin	20.24±2.85^{c}	12.12±0.69^{bc}	3.17±0.36^{ab}
Coumaric acid	16.05±3.05^{bc}	12.46±2.05^{bc}	5.23±0.60^{c}
Quercetin/coumaric acid	36.81±3.77^{d}	14.90±2.18^{de}	4.48±1.88^{bc}
Quercetin/catechin	13.73±2.50^{ab}	14.43±2.40^{cde}	2.00±1.03^{a}
Coumaric acid/catechin	37.19±3.65^{d}	13.33±2.95^{bcd}	7.85±1.13^{d}
Ramipril	39.61±7.12^{de}	19.03±2.42^{f}	7.13±1.69^{d}

Values are expressed as mean±SD, n= 6; values with same superscript down a column are not statistically different from each other (P>0.05). ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

($P < 0.05$) in ALP activity compared with the control. Pre-treatment with quercetin, coumaric acid, and a combination of quercetin and catechin restored ALP activity to normal control levels. However, pre-treatment with ramipril and a combination of quercetin and coumaric acid was not effective in reversing the ISP-dependent elevation in ALP activity. ISP administration to experimental rats caused a significant increase ($P < 0.05$) in serum AST activity compared with the control. Quercetin restored elevated AST activity to near-normal control value while pre-treatment with ramipril could not reverse the ISP-dependent elevation in serum AST level.

In the same vein, the ISP -administered group showed a significant increase ($P < 0.05$) in serum ALT level compared with the control. Pre-treatment with quercetin, catechin, coumaric aid, quercetin/coumaric acid, and quercetin/catechin before ISP administration ameliorated the ISP -induced elevation in serum ALT level.

Administration of ISP to experimental rats resulted in a significant increase (137.37 ± 11.80 U/L) in serum LDH activity compared with the control (73.98 ± 8.45 U/L) ($P < 0.05$). Pre-treatment with single and combined phenolic compounds as well as ramipril reversed ISP-induced elevation in serum LDH activity [Figure 1]. Quercetin and catechin were less effective than other treatments. Only quercetin reversed ISP-induced increase in CK activity while catechin and ramipril also showed notable ameliorative effect [Figure 2].

Figure 3 shows that ISP administration caused a significant increase in glucose level compared with the control. Pre-treatment with ramipril did not ameliorate the ISP-induced elevation in blood glucose. Catechin, quercetin/coumaric acid, and coumaric acid/catechin pre-treatments were very effective in lowering the FBS level while the effects of quercetin, coumaric acid, and quercetin/catechin were not statistically different from the ISP control group ($P > 0.05$).

Reduced glutathione (GSH) level was markedly depleted by ISP administration (99.00± 2.4 µg/ml in ISP-challenged group compared to 966.67 ± 73.36 µg/ml in the control group, ($P < 0.05$). The treatment with ramipril and the phenolics significantly ameliorated the ISP-induced reduction in GSH level with the quercetin treated group recording the highest GSH level [Figure 4].

Table 2 shows the concentration of TRIG and CHOL in all groups. TRIG level increased (1.31 ± 0.11 mmol/l) significantly on ISP administration compared with the control (0.51 ± 0.05 mmol/l) ($P < 0.05$). Pre-treatment with both individual and combined phenolics reversed ISP-induced elevation in TRIG level while pretreatment with ramipril was not effective. The serum level of CHOL in ISP intoxicated rats (8.47 ±0.29 mmol/dl) was significantly higher ($P < 0.05$) compared with the control (1.53 ± 0.01 mmol/dl). Pre-treatment with both individual and combined phenolics as well as ramipril significantly reduced the effect of ISP on CHOL level with groups pre-treated with catechin and quercetin/coumaric acid (1.44 ± 0.17, 1.33 ± 0.03 mmol/dl) showing a reversal of CHOL level to the normal control level.

The toxicity of ISP was confirmed by the results of this study. The significant increase in the level of enzymatic indices related to heart and liver toxicity (CK, LDH, ALP, AST, and ALT) supports reports of its cardio and hepatotoxicity and could be secondary events following ISP -induced lipid peroxidation of cardiac and hepatic membranes, with a consequent increase in enzymatic leakage from cardiac myocytes

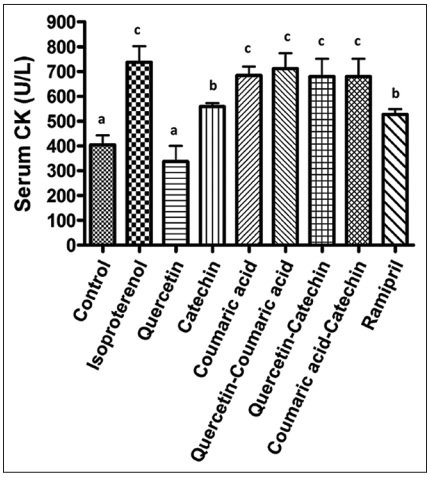

Figure 2: Serum creatine kinase activity of rats administered isoproterenol and pretreated with polyphenolic compounds and their combinations. Values are presented as mean±SD, *n*=6; bars with the same letters are not statistically different (*P*>0.05).

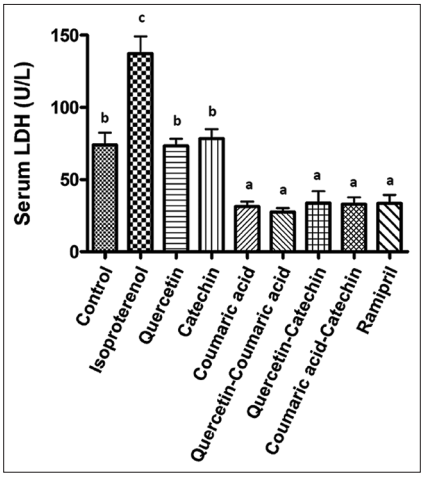

Figure 1: Serum lactate dehydrogenase activity of rats administered isoproterenol and pretreated with polyphenolic compounds and their combinations. Values are presented as mean±SD, *n*=6; bars with the same letters are not statistically different (*P*>0.05).

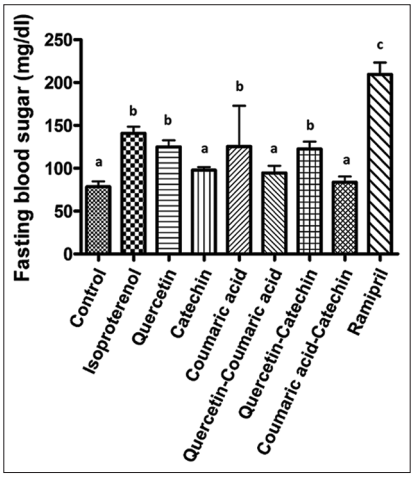

Figure 3: Fasting blood sugar concentration of rats administered isoproterenol and pre-treated with polyphenolic compounds and their combinations. Values are presented as mean±SD, *n*=6; bars with the same letters are not statistically different (*P*>0.05).

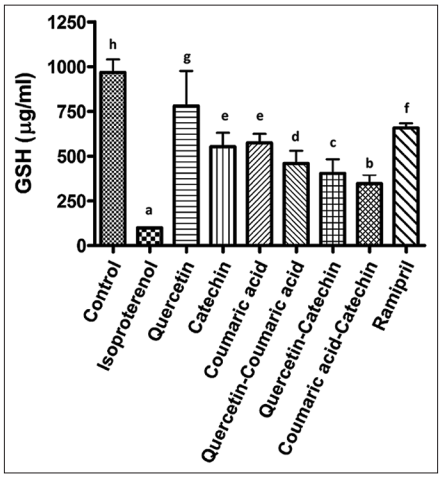

Figure 4: Serum reduced glutathione concentration of rats administered isoproterenol and pre-treated with polyphenolic compounds and their combinations. Values are presented as mean±SD, *n*= 6; bars with the same letters are not statistically different (*P*>0.05).

Table 2: Serum triglyceride and cholesterol levels of experimental animals administered isoproterenol and treated with polyphenolic compounds.

Group	Triglyceride (mmol/l)	Cholesterol (mmol/l)
Control	0.51±0.05^{bc}	1.53±0.01^{b}
Isoproterenol	1.31±0.11^{d}	8.47±0.29^{f}
Quercetin	0.58±0.07^{c}	2.51±0.18^{c}
Catechin	0.56±0.06^{c}	1.44±0.17^{b}
Coumaric acid	0.6±0.08^{a}	3.07±0.16^{d}
Quercetin/coumaric acid	0.46±0.10^{bc}	1.33±0.03^{b}
Quercetin/catechin	0.37±0.05^{ab}	0.82±0.69^{a}
Coumaric acid/catechin	0.54±0.05^{bc}	2.08±0.02^{c}
Ramipril	1.55±0.39^{e}	3.97±1.22^{e}

Values are expressed as mean±SD, (n=6).Values with the same superscript down a column are not statistically different from each other (*P*>0.05).

and hepatocytes. In ISP -induced MI, the release of cellular cardiac enzymes such as CK and LDH is correlated with changes in plasma membrane integrity and/or permeability as a response to β-adrenergic stimulation. This might be due to damage inflicted on the sarcolemma by the β-agonist, rendering it leaky [38].

The observed elevation in serum activities of the cytosolic enzymes in ISP-treated rats is indicative of toxicity since they are released into bloodstream on membrane damage and serve as the diagnostic markers of tissue damage [38-40]. Pre-treatment with quercetin, catechin, and coumaric acid and their combinations prevented the increase in serum CK, LDH, AST, and ALT induced by ISP suggesting that these polyphenols may have a potential protective effect against ISP -induced cardiac and liver damage.

Liver abnormalities have been reported as a feature of cardiac diseases and heart failure [41,42]. Evidence has been adduced for associations between key serum liver function tests and cardiovascular disease risk. Combined heart and liver dysfunctions coexist in the setting of the main heart and liver diseases because of complex cardiohepatic interactions [43-45]. This could be observed in the results of ALP, AST, and ALT, which are markers of hepatocellular injury [46-49]. The significant increase in serum ALP, AST, and ALT activities of ISP control rats is indicative of damage to the liver and ameliorative effect shown by pre-treatment with the polyphenolics agrees with the well-reported hepatoprotective activity of polyphenolic compounds [50-53].

GSH is a major intracellular antioxidant in the heart and liver. The deficiency of GSH puts the cell at risk for oxidative damage. GSH not only protects cell membranes from oxidative damage but also helps to maintain the sulfhydryl groups of many proteins in the reduced form, a requirement for their normal function. GSH depletion is linked to several disease states including cancer, neurodegenerative, hepatic, and cardiovascular diseases. Cardiac and hepatic injuries are mediated and potentiated by oxidative stress involving a reduction in the level of antioxidants including GSH [54-57]. In the present study, the reduction noticed in the level of GSH of ISP-toxified rats may be due to severe oxidative stress. The observation that the decrease in GSH level arising from ISP administration was ameliorated in polyphenolic-pretreated animals further support the antioxidant property of phenolics.

The liver plays a central role in lipid metabolism, serving as the center for lipoprotein uptake, formation, and export to the circulation. Alterations in hepatic lipid metabolism can contribute to the development of chronic liver disease. Furthermore, lipid profiles are commonly used for the evaluation of cardiovascular risk [58-61]. The hypertriglyceridemia and hypercholesterolemia observed in ISP-toxified rats implied hepatic impairment and a potential cardiovascular problem. The ameliorative effect of the polyphenols on ISP-induced dyslipidemia is an indication of their beneficial bioactivities. Dyslipidemia is usually associated with hyperglycemia and abnormal glucose levels are associated with dysfunctions of various organs including the heart and liver. The observed effect of the polyphenols on glucose level is a further indication of their protective property.

This study demonstrates that the phenolics when used individually and in combinations ameliorated ISP-induced toxicity in Wistar albino rats to different degrees. In general, the treatment with the single phenolics appeared to be more effective in correcting ISP-induced aberrations in the activity of the studied enzymes and the GSH level, while the combined treatments appeared more potent in ameliorating imbalances in the lipid and FBS levels. For instance, quercetin ameliorated ISP-induced increase in ALP and AST activities by 75% and 29% ($P < 0.05$), respectively, while quercetin/catechin ameliorated ISP-induced increase in TG and CHOL levels by 72% and 90% ($P < 0.05$), respectively. Among the single phenolics, the approximate order of effectiveness is coumaric acid <catechin<quercetin, while for the combined phenolics, it is coumaric acid/catechin< quercetin/coumaric acid <quercetin/catechin. Ramipril was not effective in ameliorating ISP-induced alterations to hepatotoxicity indices, TRIG level, and FBS level but appreciably ameliorated ISP-induced increase in CHOL level, LDH activity, and the ISP-induced decrease in GSH level.

4. CONCLUSION

These results support the beneficial effect of ramipril in cardiovascular problems but indicate that it may not be effective in addressing associated liver dysfunctions in cardiovascular events. The results of this study suggest that individual phenolics and their appropriate combinations may be better than synthetic drugs in the management of cardiovascular diseases. A limitation of the present investigation is the absence of post-treatment study of the test compounds. Future investigation of post-treatment effects of the compounds and their molecular mechanisms of action will provide interesting details on their efficacy.

5. AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors requirements/ guidelines.

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7. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

8. ETHICAL APPROVALS

Experiments were approved by The University's Research Ethical Committee, Centre for Research and Development (CERAD), with approval number FUTA/ETH/21/04. Handling and use of animals conformed to the NIH Guide for the Care and Use of Laboratory Animals, 2011.

9. DATA AVAILABILITY

Data will be made available upon reasonable request to the corresponding author.

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