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Original article

Maslinic acid and gallic acid protective efficacy on lipids, lipoproteins and lipid metabolizing enzymes against isoproterenol administered cardiotoxicity: An *in vivo* and *in silico* molecular docking evidences

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ABSTRACT

Objective: The current study designed to investigate the protective efficacy of maslinic acid (MA) and gallic acid (GA) against isoproterenol (ISO) administered cardiac toxicity in rats by exploring *in vivo* and *in silico* approaches.
Methods: The animals were divided into five different groups. The individual animal groups were orally pretreated with MA (15 mg/kg) and GA ((15 mg/kg) for 7 days and ISO administered subcutaneously on 8th and 9th days to induce MI. Blood, heart and liver were collected from sacrificed animals and used for biochemical analysis.
Results: The results represented significant decrease in the levels of high density lipoprotein cholesterol, lipoprotein lipase and lecithin cholesterol acyl transferase whereas significant increase in the levels of total cholesterol, triglycerides, low density lipoprotein cholesterol, very low density lipoprotein cholesterol and HMG-CoA reductase in ISO (85 mg/kg) treated rats. However, pretreatment of ISO treated rats with MA and GA markedly brought all the parameters such as lipids, lipoproteins and lipid metabolic marker enzymes to near normal level indicating the ameliorating effect of MA and GA against MI. Further, the investigation extended to *in silico* analysis to study the interaction of MA and GA with the key lipid metabolizing enzymes by using Gold 3.0.1 software. The molecular docking studies revealed that HMG-CoA reductase, LPL and LCAT formed strong enzyme ligand complexes with MA and GA.
Conclusions: MA and GA exhibited protective efficacy against ISO administered cardiotoxicity and the results further supported by molecular docking studies.

1. Introduction

Myocardial infarction (MI) also known as heart attack, is the world's population leading cause of death. It occurs due to the improper blood supply to the heart muscle that implies to the necrosis of myocardium. Multiple risk factors like sedentary lifestyle, stress, smoking, alcohol consumption, obesity, diabetes and blood pressure are suitable causes of MI. Asides, hypercholesterolemia, hyperlipidemia and hypertriglyceridemia together lead to the development of atherosclerosis and MI (Yang et al., 2008). It is also evidenced that the key lipid metabolizing enzymes HMG-CoA reductase and lipoprotein lipase (LPL) takes a crucial part in the progression of MI. Lecithin cholesterol acyl transferase (LCAT) is an enzyme that esterifies the cholesterol on the surface of high density lipoprotein cholesterol (HDL-C) and leads to the formation of giant HDL-C particles which protects from cardiovascular diseases (CVD) (Shaik et al., 2018).

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Isoproterenol (ISO) is a powerful potent β-adrenergic agonist that has intense chronotropic and inotropic properties. It causes severe stress in cardiac tissue and develops necrosis of heart muscle (Liu et al., 2009). Several mechanisms have been proposed by which ISO causes MI. ISO enhances the free radical formation which causes increased lipid peroxidation (LPO). This increased LPO causes infarct-like necrosis of the heart muscle (Prince and Rajadurai, 2005). The heart failure subsequent to MI has been proved to be connected with the deficiency of antioxidants and augmented myocardial oxidative stress (Hill and Singal, 1996).

Bioinformatics is the computational technique applied to solve the biological difficulties by structural prediction and molecular docking studies of biomolecules like genes, nucleic acids and proteins. Docking software is useful in the evaluation of drug design and in the prediction study of drug binding to the active site of enzyme. Depending on the molecular docking results, designers have the feasibility to refine the molecules of drugs.

CVD prevention is associated with the utilization of fruits and green vegetables that enriched with natural antioxidants. The ameliorative property of plants may be due to triterpenoids. The triterpene compounds represented different physiological activities including anti-atherosclerotic, anti-inflammatory, anti-cancer, anti-diabetic, antiulcerogenic, hypolipidaemic and hepatoprotective (Dzubak et al., 2006). Maslinic acid (MA), a natural triterpenoid extensively distributed in aerial parts of medicinal plants such as leaves and fruits (Montilla et al., 2003). MA has been reported for many pharmacological properties like antioxidant, anti-hyperlipidaemic, anti-hyperglycemic and anti-inflammatory activities. In our earlier studies we reported the cardioprotection of MA and Gallic acid (GA) on antioxidant enzyme paraoxonase (Hussain Shaik et al., 2012) and myocardial membrane bound ATPase enzymes (Shaik et al., 2020). This study has been planned to discover the protective efficacy of MA and GA on lipid metabolizing enzymes against ISO administered cardiotoxicity by analyzing *in vivo* and *in silico* approaches.

2. Material and methods

2.1. Chemicals and drugs

The active compound MA was purchased from Cayman chemical company, United States of America. ISO and GA were procured from Sigma chemicals, United States of America. All other chemicals and reagents used were analytical grade.

2.2. Animals and experimental procedure

The rats of Albino Wistar strain weighing around 150 g were acclimatized to standard animal house conditions for one week. Standard food provided and water *ad libitum*. The animal experimental study got approval from Institutional Animal Ethics Committee, Sri Krishnadevaraya University, India with registration number "Ref.No. 470/01/a/CPCSEA".

The rats categorized into 5 groups contained 8 in each group.

1. Control animals
2. Animals fed with 15 mg/kg MA
3. Animals subcutaneously injected with 85 mg/kg ISO
4. Animals fed with 15 mg/kg MA + ISO
5. Animals fed with 15 mg/kg GA + ISO

The rats orally pretreated with MA for 7 days by dissolved in sodium carboxymethyl cellulose (0.05%), whereas saline used to dissolve the positive control GA. The control group and ISO group rats were treated with sodium carboxymethyl cellulose. ISO was dissolved in distilled water and subcutaneously injected on 8th and 9th days to induce MI. All animals sacrificed on 10th day by cervical decapitation. Blood, heart and liver samples were collected for biochemical analysis.

2.3. Biochemical estimations

The lipids and lipoproteins such as total cholesterol (TC), triglycerides (TG), and HDL-C in heart tissue were assayed by using standard diagnostic kits. The following formulae used to calculate the levels of very low density lipoprotein cholesterol (VLDL-C) and low density lipoprotein cholesterol (LDL-C).

$$\mathrm{VLDL-C} = \mathrm{TG}/5;\ \mathrm{LDL-C} = \mathrm{TC} - (\mathrm{HDL-C} + \mathrm{VLDL-C}).$$

LCAT activity was assayed in serum (Nagasaki and Akanuma, 1977). Lipoprotein lipase (LPL) activity was assayed in heart and liver tissue homogenate (Shirai and Jackson, 1982). 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase enzyme activity was assayed in heart, liver and serum (Rao and Ramakrishnan, 1975). The protein level was measured by Lowry et al. (n.d.).

2.4. Molecular docking studies

Molecular docking of MA and GA with HMG-CoA reductase, LPL and LCAT was performed. Structures prepared by obtained the crystal structure from protein data bank (HMG-CoA-1HW9 Istvan and Deisenhofer, 2001; LPL-6E7K Birrane et al., 2019; LCAT-4X96 Glukhova and Tesmer, 2015). For docking, active sites of these enzymes were predicted using Castp server (Andrew et al., 2003). MA and GA compound structures constructed and optimized in Chemsketch software (ChemSketch, 2020). The statins occupied in the binding sites of enzymes were eliminated. The chain A of enzymes opted and hydrogen atoms were incorporated into the enzymes for molecular docking studies. The binding orientation of MA and GA in enzyme structures were studied by performing molecular docking method using GOLD (Genetic Optimization of Ligand Docking) version 3.0.1 program (Jones et al. 1997). The best energetically conformation of the compound was identified and after docking, individual binding poses were calculated the interactions with the protein. All the protein and ligand structural images were generated using PyMol (http://www.pymol.org) (DeLano, 2006).

2.5. Statistical analysis

All results data was statistically analyzed by one way analysis of variance (ANOVA) and Duncan's Multiple Range (DMR) test. The comparison among groups considered statistically significant at $p < 0.05$.

3. Results

Table 1 represents MA and GA protective effect on cardiac lipids and lipoproteins in control and ISO treated rats. ISO significantly increased ($P < 0.05$) the concentrations of TC, TG, LDL-C, and VLDL-C whereas significantly decreased ($p < 0.05$) the concentrations of heart HDL-C when compared with those of normal rats. Pretreatment with MA (15 mg/kg) to ISO injected rats decreased the levels of heart TC, TG, LDL-C, and VLDL-C, whereas the levels of HDL-C in heart of ISO-induced myocardial infarcted rats increased when compared with untreated ISO-induced myocardial infarcted rats. GA (15 mg/kg) also decreased the levels of heart TC, TG, LDL-C, and VLDL-C, whereas the levels of heart HDL-C increased significantly ($p < 0.05$). MA (15 mg/kg) alone not exhib-

Table 1
Protective effect of maslinic acid (MA) and gallic acid (GA) on lipid profile in heart of isoproterenol (ISO) induced cardiac toxicity in rats.

Groups	TC (mg/dL)	TG (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)	HDL (mg/dL)
Control	5.4 ± 0.4[a]	4.3 ± 0.3[a]	2.0 ± 0.4[a]	0.8 ± 0.07[a]	2.5 ± 0.3[a]
MA (15 mg/Kg bw)	5.1 ± 0.4[a]	4.2 ± 0.3[a]	1.7 ± 0.3[a]	0.8 ± 0.06[a]	2.5 ± 0.1[a]
ISO (85 mg/Kg bw)	10.2 ± 0.4[b]	7.3 ± 0.4[b]	7.2 ± 0.6[b]	1.4 ± 0.08[b]	1.5 ± 0.1[b]
MA (15 mg/Kg bw) + ISO	6.3 ± 0.2[c]	5.0 ± 0.2[c]	2.9 ± 0.4[c]	1.0 ± 0.04[c]	2.3 ± 0.2[a]
GA (15 mg/Kg bw) + ISO	7.0 ± 0.2[d]	5.9 ± 0.1[d]	3.5 ± 0.1[d]	1.1 ± 0.03[d]	2.2 ± 0.1[a]

Values are mean ± S.D. (n = eight rats). Values not shared a common superscript (a, b, c and d) differ significantly from each other ($p < 0.05$, Duncan's multiple range test).

ited any significant change in lipids and lipoproteins in comparison with control rats.

Fig. 1 shows the effect of MA and GA on serum LCAT in control and ISO administered rats. Serum LCAT levels decreased significantly ($p < 0.05$) in ISO administered rats when compared with control rats, while MA (15 mg/kg) pretreatment and GA (15 mg/kg) pretreatment increased the levels of LCAT significantly ($p < 0.05$) as compared to ISO-induced myocardial infarcted rats.

Fig. 2 represents the effect of MA and GA on the activity of LPL in heart and liver of control and ISO administered rats. Animals injected with ISO exhibited significant ($p < 0.05$) decrease in the activity of LPL when compared to control rats. Oral administration of MA (15 mg/kg) and GA (15 mg/kg) to ISO-induced MI rats increased the activity of LPL significantly ($p < 0.05$) when compared to ISO alone administered rats.

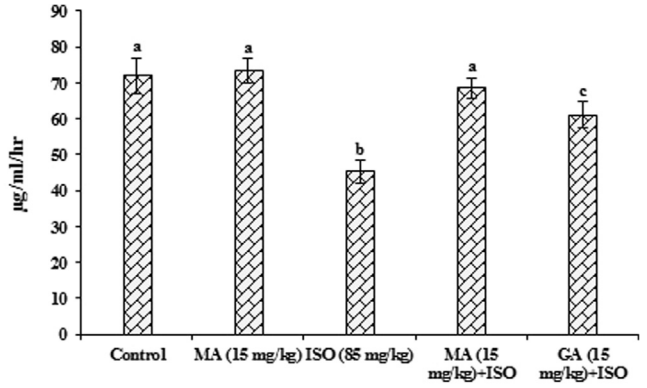


Fig. 1. Protective effect of maslinic acid (MA) and gallic acid (GA) on lecithin cholesterol acyl transferase (LCAT) in heart of isoproterenol (ISO) induced cardiac toxicity in rats. Values are mean ± S.D. (n = eight rats). Values not shared a common superscript (a, b and c) differ significantly from each other ($p < 0.05$, Duncan's multiple range test).

Fig. 3 reveals the effect of MA and GA on HMG-CoA reductase activity in heart, liver and plasma of rats. The enzyme in heart, liver and plasma decreased significantly ($p < 0.05$) in ISO administered rats when compared to control rats. MA (15 mg/kg) pretreatment to ISO group showed significant ($p < 0.05$) rise and GA (15 mg/kg) pretreatment to ISO group also showed significant ($p < 0.05$) rise in the activity of HMG-CoA reductase when compared with ISO alone administered group. The low ratio of HMG-CoA/mevalonate represents the high activity of HMG CoA reductase enzyme and vice versa.

Fig. 4 A and B illustrated the molecular docking studies of the active compounds MA and GA with the enzyme HMG-CoA reductase. From the molecular docking of MA into active site of HMG-CoA reductase (Table 2), hydrogen bond observed between the hydroxyl group (H44) of MA and oxygen atom of ARG452, and other hydrogen bond noticed between hydroxyl group of LEU509 and oxygen atom (O5) of MA. In docking of GA with HMG-CoA reductase (Table 2), hydrogen bond observed between the hydroxyl group of ARG86 and oxygen atom (O3) GA, and other hydrogen bond noticed between hydroxyl group of LYS88 and oxygen atom (O4) of GA.

Fig. 5 A and B showed the docking studies of the active compounds MA and GA with LPL enzyme. MA docked with hydrogen bond forming between the hydroxyl group of CYS54 and oxygen atom (O3) of LPL enzyme. Also Molecular docking of GA into active site of LPL showed hydrogen bond between the hydroxyl group of CYS54 and oxygen atom (O3) of GA as MA.

From the Fig. 6 A and B, it was confirmed that MA and GA are the active inhibitor compounds of the enzyme LCAT. In docking studies of MA with LCAT, hydrogen bond is observed between the hydroxyl group of ARG99 and oxygen atom (O3) of MA. Another hydrogen bond formed between oxygen atom of GLU37 and oxygen atom (O3) of MA. In docking studies of GA with LCAT, two hydrogen bonds observed between the hydroxyl groups of GLU37 and oxygen atom (O3) of GA. Another hydrogen bond

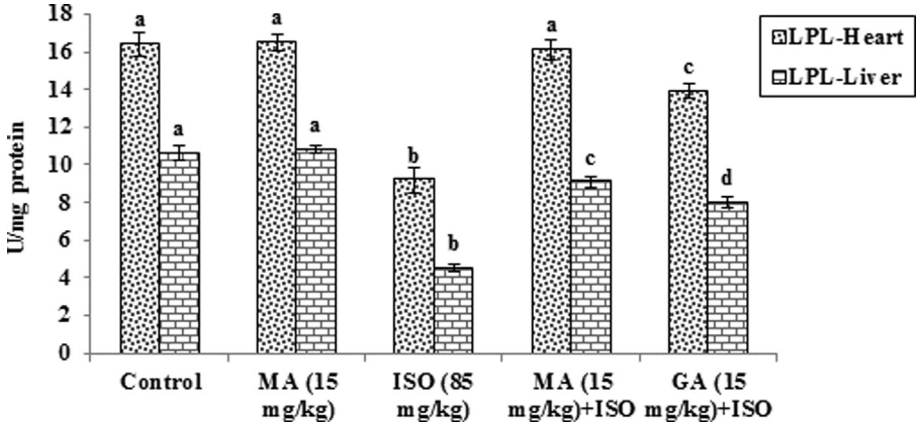


Fig. 2. Protective effect of maslinic acid (MA) and gallic acid (GA) on lipoprotein lipase enzyme in heart and liver of isoproterenol (ISO) induced cardiac toxicity in rats Values are mean ± S.D. (n = eight rats). Values not shared a common superscript (a, b, c and d) differ significantly from each other ($p < 0.05$, Duncan's multiple range test).

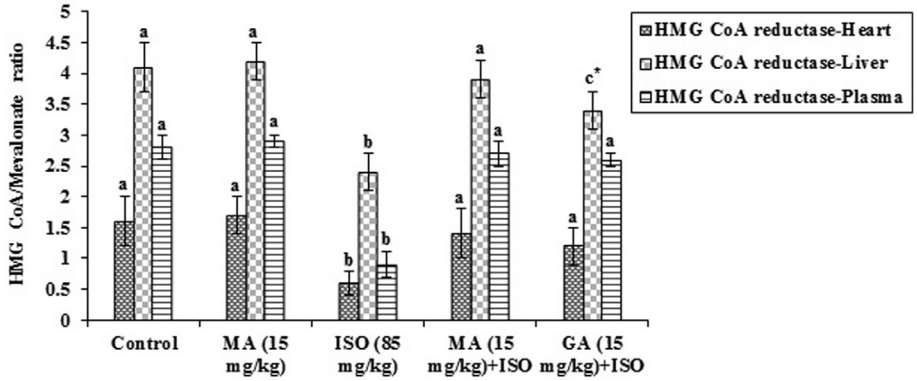


Fig. 3. Protective effect of maslinic acid (MA) and gallic acid (GA) on HMG-CoA reductase enzyme in heart, liver and plasma of isoproterenol (ISO) induced cardiac toxicity in rats. Values are mean ± S.D. (n = eight rats). Values not shared a common superscript (a, b and c) differ significantly from each other ($p < 0.05$, Duncan's multiple range test). * Group not significantly differs with MA (15 mg/Kg) + ISO treated group.

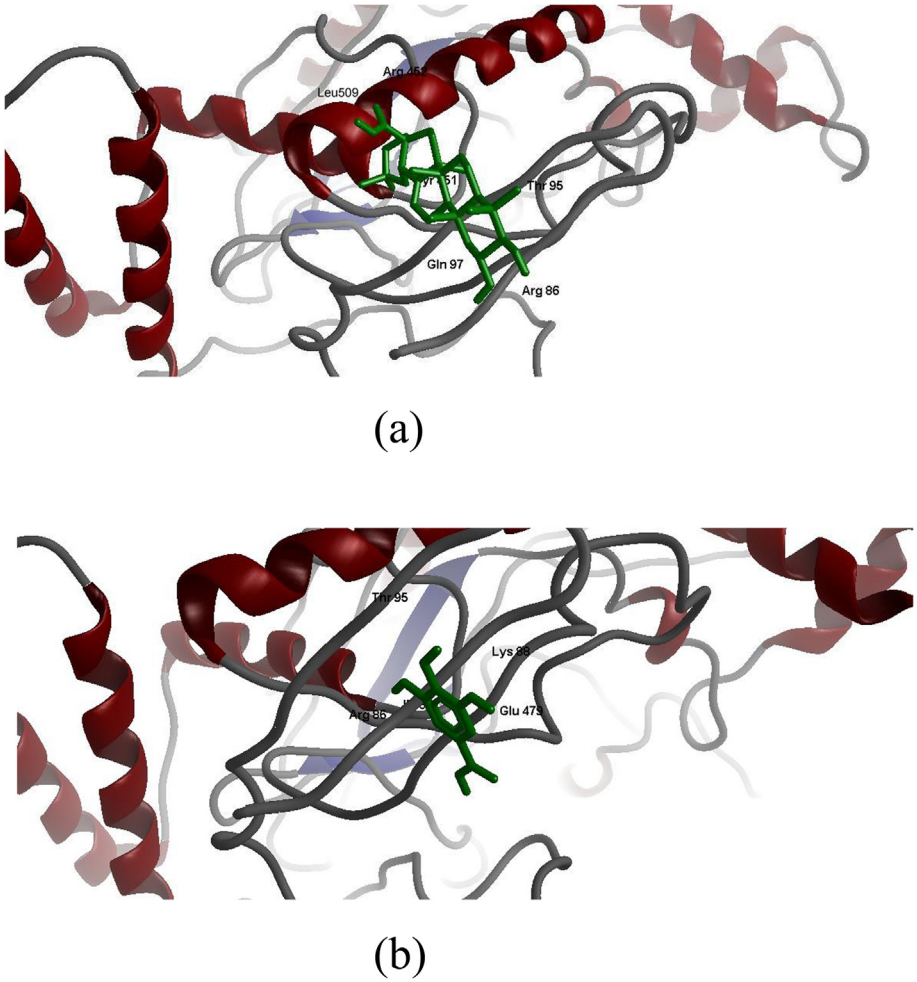


Fig. 4. A and B. Molecular Docking of maslinic acid (MA) and gallic acid (GA) with HMG-CoA reductase enzyme.

formed between hydroxyl group of LYS105 and oxygen atom (O5) of GA.

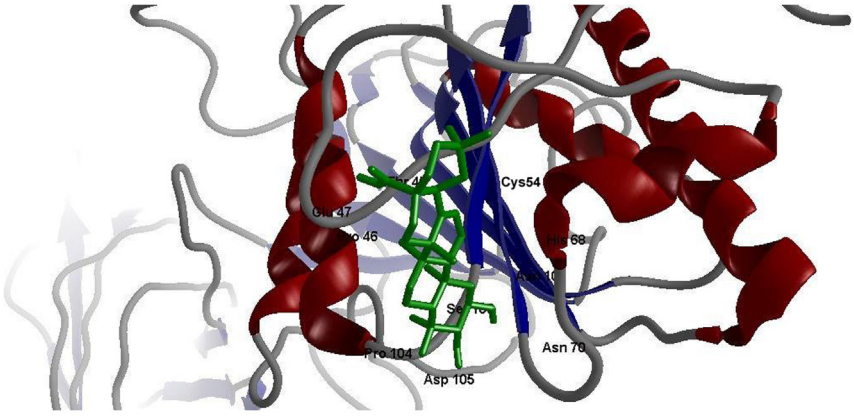
4. Discussion

ISO induced MI considered to be highly advantageous when compared with physical occlusion of coronary artery where ISO exerts intense inotropic and chronotropic actions to induce MI and also there is a possibility of reperfusion after ISO administration (Saeed and Ahmed, 2006). ISO induced MI in rats is a well-established model to analyze to protective effect of cardioprotective drugs (Zhou et al., 2008).

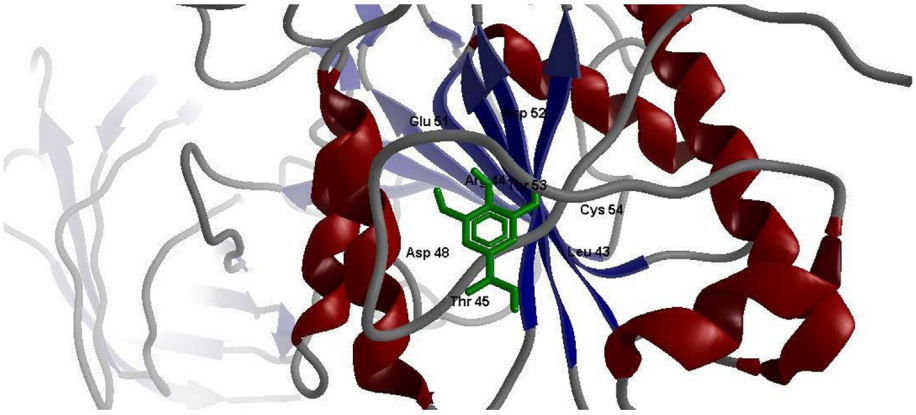
Lipids and lipoproteins are independent risk factors for CVD. Lipid profile is a crucial factor in the progression and pathogenesis of MI. Hypercholesterolemia and hypertriglyceridemia are considered to be the major risk factors in developing the MI. In our results

Table 2
Docking score of maslinic acid (MA) and gallic acid (GA) with the binding of enzymes HMG-CoA reductase, lipoprotein lipase (LPL) and lecithin cholesterol acyl transferase (LCAT).

Enzyme	Molecule/Ligand	Number of Hydrogen Bonds	Atoms		Bond Length (Å)	Docking Score (Kj/mol)
			Protein	Molecule		
HMG-CoA reductase	MA	1	ARG452(H)	1(O)	1.820	−108.65
			LEU-509(O)	5(O)	1.45	−107.26
	GA	2	ARG86(H)	3(O)	2.350	−105.45
			LYS88 (H)	4(O)	2.365	−105.65
LPL	MA	2	CYS54(H)	3(O)	1.125	−118.35
	GA	2	CYS54(H)	3(O)	1.426	−111.32
LCAT	MA	1	ARG99 (H)	3 (O)	1.342	−128.43
			GLU37 (H)	3 (O)	1.242	−118.35
	GA	1	GLU37 (H)	3 (O)	1.272	−126.40
			LYS105(H)	5(O)	1.284	−123.58



(a)



(b)

Fig. 5. A and B. Molecular Docking of maslinic acid (MA) and gallic acid (GA) with lipoprotein lipase (LPL) enzyme.

the levels of TC, TG, LDL-C and VLDL-C were increased in heart whereas the levels of HDL-C in heart were decreased in ISO treated rats. Previously described that rise in cardiac cholesterol in ISO administered rats is due to augmented absorption of LDL-C by myocardial membranes from the blood circulation (Anandan et al., 2007). The noticed rise in TGs might be due the reduced activity of LPL and reduced uptake of TGs from blood circulation (Sushama Kumari et al., 1990). Rats pretreated with MA and GA showed decreased content of heart TC, TG, LDL-C, VLDL-C and increased content of HDL-C indicating the beneficial effects MA and GA in reducing hyperlipidemia caused by ISO administration which may be due to MA and GA anti-hypercholesterolemic and anti-hyperlipidemic activity.

The results represented that MA and GA raised the activity of LCAT in ISO treated rats. It is proposed that LCAT promotes the process Reverse Cholesterol Transport (RCT) which considered as antiatherogenic mechanism (Glomset et al., 1966). In this process HDL molecules removed the excess amount of cholesterol from the cells and excreted by delivered to liver (Glomset, 1968). MA and GA raised the levels of LCAT which directly raises the levels

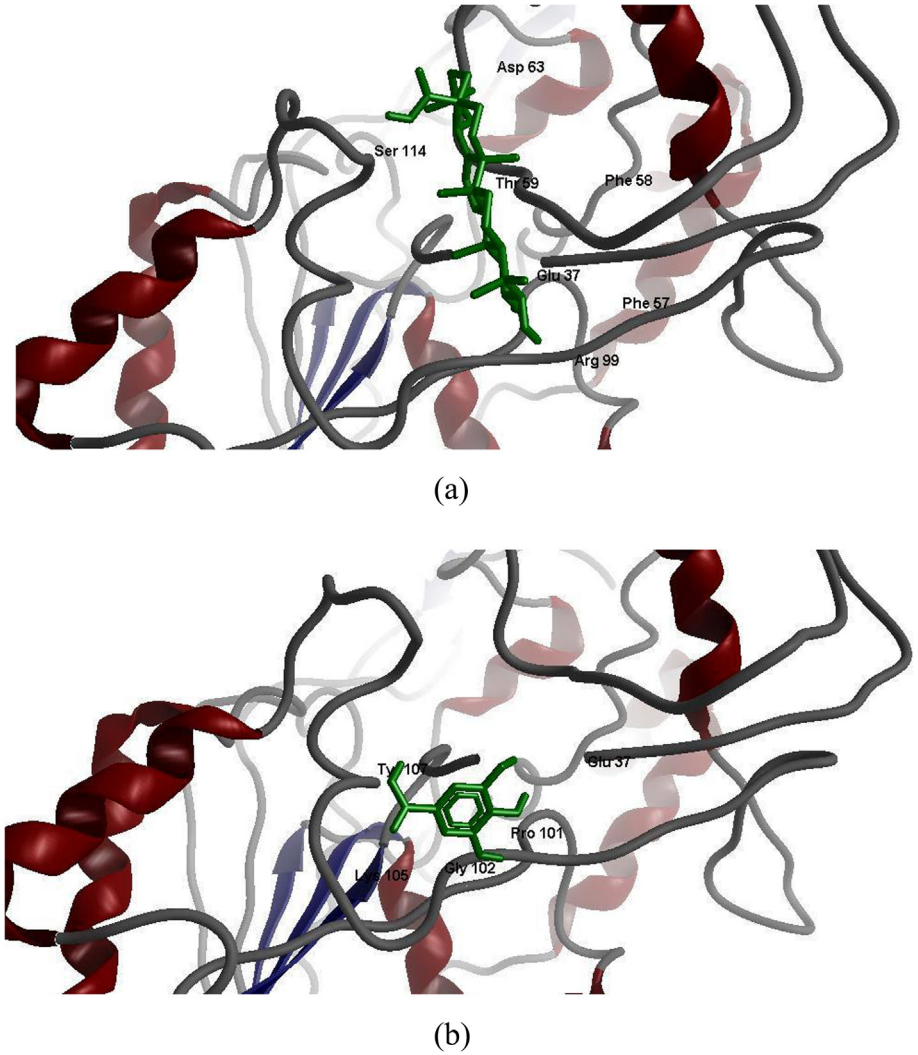


Fig. 6. A and B. Molecular Docking of maslinic acid (MA) and gallic acid (GA) with lecithin cholesterol acyl transferase (LCAT) enzyme.

of HDL-C in ISO treated rats. HDL molecule is heterogeneous and contains several different lipoprotein particles. HDL-C accommodating apoA-I considered as more effective in RCT (Barbaras et al., 1988). LCAT activity is highly enhanced by consisting the potent cofactor ApoA-I, and the activity of LCAT is sensitive with modulating the size of apoA-I. The diet induced atherosclerosis has been prevented by the overexpression of LCAT in transgenic rabbits (Hoeg et al., 1996). MA and GA pretreatment accelerated the activity of LCAT in ISO administered rats. Thus, the noticed acceleration of LCAT might be due to the obstacle of LPO in MA and GA pretreated ISO induced rats.

The TGs like chylomicrons and VLDL-C in plasma lipoproteins hydrolyzed by LPL and causes changes in lipoprotein metabolism which stimulates hepatic removal of lipoproteins. Based on the earlier reports it is considered as, an increased levels in LPL are anti-atherogenic and the decreased levels in LPL are atherogenic (Miesenbock et al., 1993; Reymer et al., 1995). It is reported that several LPL-deficient patients have developed relatively advanced atherosclerosis (Kareem et al., 2009). In our report pretreatment with MA and GA enriched the activity of LPL in ISO treated rats. This is due to the acceleration of LPL activity by MA and GA.

HMG-CoA reductase is a key metabolic enzyme of cholesterol biosynthesis. The significant increased activity of HMG-CoA reductase in heart, liver and plasma of ISO treated rats was noticed in this study. The increased activity leads to the development of atherosclerosis by accumulating cholesterol in the form of foam cells (Berliner and Heinecke, 1996). Cellular cholesterol homeostasis is an important factor in the eradication of MI. Our results showed that pretreatment of MA and GA regulated the biosynthesis of cholesterol by the inhibition of HMG-CoA reductase in ISO treated rats. Thus, the reduced quantity of cholesterol in MA and GA treatment might be correlated to the reduced HMG-CoA reductase activity in ISO treated rats. The potent antioxidant property of MA and GA (Shaik et al., 2020) indirectly supports to the reduction of lipid levels, by the inhibition of LPO.

The present *in vivo* studies are also supported with molecular docking results of *in silico* studies where MA and GA showed the effective binding with the enzymes HMG-CoA reductase, LPL and LCAT by which it regulates the activity of these enzymes. Molecular docking study conveyed that MA and GA are the excellent ligand molecules towards HMG-CoA reductase, LPL and LCAT enzymes. The inhibition of HMG-CoA reductase enzyme by MA and GA might be due to strong hydrogen bonds formation between ligand and amino acids of enzyme which insisted to the inhibition of enzyme. It is evidenced from this study that, the inhibition of HMG-CoA reductase and regulation of LPL, LCAT by MA and GA leads to reduction in the biosynthesis of cholesterol. The RMSD value of the best hit (with the lowest L_RMSD) based on shape complementarity. The root mean squares deviation (RMSD) between the C-alpha atom of the template and the model was

0.89 Å, indicating close homology. The generated pdb file analyzed for their binding conformations. Analysis was based on E total or free energy of binding, lowest docked energy, and calculated RMSD values. Free binding energy between the model and template was 0.92 Å, which again showed the close homology. The results obtained from protein–ligand docking algorithms are in general satisfactory. The total clusters of docking conformations, with the top 30 docked molecules showed negative binding energies. Cluster one shows the following results, Energy −1.873230e + 02, RMS −1.00. IC50 Values were all within range. Among all docking conformations cluster rank 10 i.e., solution16 gave the best predicted binding free energy of −1.6083 kcal mol − 1 of HMG-CoA reductase and regulation of LPL, LCAT by MA and GA.

5. Conclusions

In conclusion, MA and GA revealed protective efficacy of anti-hypercholesterolemic, anti-hyperlipidemic and lipid metabolism regulatory activities. Furthermore, the molecular docking studies confirmed that the compounds MA and GA effectively act on the key lipid metabolizing enzymes and offered cardioprotection.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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