



## Metabolites of Rosuvastatin Inhibit Oxidation of both Low-Density Lipoproteins and Very Low-Density Lipoproteins

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**Abstract:** Coronary Artery Disease is caused by plaque buildup in the walls of the arteries that supply blood to the heart (called coronary arteries) and other parts of the body. Plaque is made up of deposits of cholesterol and other substances in the artery. Plaque buildup causes the inside of the arteries to narrow over time, which could partially or totally block the blood flow. This process is called atherosclerosis. Coronary artery disease (CAD), when get worst, it is known as coronary artery syndrome (CAS). There are many allopathic medications which can stop, even at starting points of the disease (CAD). Hypolipidemic drugs like statins, fibrates, resins and niacin are well known agents used for prevention of CAD. There are ethnic-based medicinal herbs which can be used to treat or prevent CAD with narrow to moderate range of statistical significance. We compared Rosuvastatin 10 mg with Indian dates (Jujubes) as hypolipidemic agents. This research was conducted at Ghurki Trust Teaching Hospital, jalo park, Lahore, Pakistan. Duration of study was two months. Twenty to seventy years old 60 hyperlipidemic patients of both gender were included in research work with written consent. We divided these patients in two equal groups. Group-I was advised to take Tablet Rosuvastatin 10 mg, twice daily for two months. Group-II was advised to take 500 grams Indian dates for two months. Their baseline parameters like LDL-cholesterol, HDL-cholesterol, systolic/diastolic blood pressure was determined in the hospital laboratory. Separate file was maintained for their name, age, sex, occupation, and address. After two months therapy we compiled data related to tested parameters. Paired t-test was applied to compare changes in all parameters. Their mean values with  $\pm$  SD before and after treatment were compared and analyzed statistically. It was observed that Rosuvastatin significantly decreased systolic/diastolic blood pressure, LDL-cholesterol, and increased HDL-cholesterol in 27 hyperlipidemic/hypertensive patients. Indian dates used in 30 hyperlipidemic patients significantly decreased systolic blood pressure, and LDL-cholesterol, but insignificant changes were seen in diastolic blood pressure, and HDL-cholesterol. We concluded from the research work that Rosuvastatin is potent hypolipidemic and hypotensive medicine as compared to indian dates.

**Keywords:** Coronary Artery Disease(CAD), Cholesterol, Blood Pressure, Density .

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## INTRODUCTION

Coronary artery disease (CAD) causes impaired blood flow in the arteries that supply blood to the heart. Also called coronary heart disease (CHD), CAD is the most common form of heart disease and affects approximately 16.5 million Americans over the age of 20. It's also the leading cause of death for both men and women in the United States. It's estimated that every 40 seconds, someone in the United States has a heart attack. A heart attack can come from uncontrolled CAD [1]. Great number of modern drugs are still derived from natural sources and 25 per cent of all prescriptions contain one or more active ingredients from plants. Researchers has estimated that 80 per cent of the population of developing countries still relies on medicinal plants for their primary health care needs and ensure patient safety by upgrading the skills and knowledge of traditional medicine providers [2-4]. Saponins and alkaloids present in indian dates (JUJUBES) fruit is directly associated with purifying the blood and eradicating harmful toxins from the body's systems. This antioxidant effect helps prevent a large number of disorders and diseases, like hyperlipidemia, hypertension, and hyperglycemia. And also indian dates ease the stress on the immune and lymphatic system and reduces blood pressure [5-9]. Consumption of fruits and vegetables is a common suggestion for people trying to lose weight, and Indian date is another that can simply be added to that list. With a low calorie count and a higher protein and fiber level, indian date helps to satisfy nutritional needs and fill up, which prevent from snacking in between meals. This will help maintain diet or prevent any additional weight gain [10]. Indian dates ie; Jujube is one of the good sources of antioxidant content, like vitamin C, vitamin A, and numerous organic compounds. Antioxidants help to neutralize free radicals, the dangerous byproducts of cellular respiration, which are liable for several chronic diseases and illness within the body. Vitamin C also encourages the production of white blood cells, the first line of defense of human body immune system [11, 12]. The use of statin agents in patients with acute coronary syndromes (ACSs) remains an area of intense clinical interest [13]. Statin therapy has an established secondary preventive benefit in patients with coronary artery disease, and its extension to acute coronary syndrome seems logical [14]. A number of observational studies have shown an association between initiation of statin therapy early in acute coronary syndrome and improved clinical outcome. Four randomized controlled trials have examined the use of statin therapy for acute coronary syndrome: the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study, the Pravastatin Turkish Trial, the Rosuvastatin on Risk Diminishing after Acute Myocardial

Infarction study, and the Lipid-Coronary Artery Disease study. Three of these trials showed a benefit with early initiation of statin therapy, whereas one trial demonstrated neither benefit nor harm [15]. To reversing the inhibitory effect of oxidized LDL on nitric oxide synthase-3, Rosuvastatin also have direct antioxidant effects on LDL in vitro and ex vivo. Metabolites of Rosuvastatin, but not the parent compound, inhibit oxidation of both LDL and very-low-density lipoprotein as well as high-density lipoprotein [16]. Metabolites, representing 70% of active Rosuvastatin in plasma, demonstrate free radical-scavenging abilities that may contribute to inhibition of lipoprotein oxidation [17]. Rosuvastatin also indirectly affect normal oxidative mechanisms by curbing the ability of macrophages to oxidize lipoproteins [18].

## SUBJECTS AND METHOD

The research was conducted at Ghurki Trust Teaching Hospital, lahore-pakistan from January to June 2023. Sixty primary and secondary hyperlipidemic and hypertensive patients were selected from Ghurki Trust Teaching Hospital, Lahore, Pakistan. The research aim was to compare hypolipidemic and hypertensive effects of Rosuvastatin 10 mg and Ziziphus Jujubes (Indian dates) in these patients. Both male and female patients suffering from primary or secondary hyperlipidemia were selected. The age limit for patients was 20 to 70 years. Patients suffering from any major organ disease like liver, lungs, kidney, thyroid, heart and eye complications were excluded from the research. Written consent was taken from all participants. Baseline Lipid Profile was determined in Biochemistry lab of the Hospital. Serum cholesterol was estimated by enzymatic method using kit Cat. No: 303113050 by Eli Tech Diagnostic, France. Serum HDL-cholesterol was determined by using kit Cat No: 303210040 by Elli Tech Diagnostic, France. Chylomicrons, low density lipoprotein and very low density lipoprotein are specially precipitated with phosphotungstic acid and magnesium ions can then be removed by centrifugation, while high density lipoproteins remain in the supernatant. Cholesterol included in this phase is measured by an enzymatic method. LDL-cholesterol was calculated according to Friedwald formula [16], ie;  $LDL = TC - (TG/5 + HDL-C)$ . All Patients were divided in two groups, 30 patients in each group. Group-I was on Tablet Rosuvastatin 10 mg twice daily for two months. Group-II was on Jujube 500 grams daily in three divided times to eat. They were advised to take this fruit for two months. Mean values  $\pm$  SD were taken for statistical analysis. For parallel comparison, we used paired 't' test to get significance changes in tested parameters at start of treatment and at end of the research work. P-value  $>0.05$  was considered as non-significant change, p-

value <0.01 was considered as significant and p-value <0.001 was considered as highly significant change in the tested parameter. We used SPSS version 2010 for statistical analysis. KW: hyperlipidemia, heart, Rosuvastatin, red dates.

## RESULTS

HMG-CoA reductase inhibitor (Rosuvastatin 10 mg) when used for two months in 27

hyperlipidemic patients, it reduced systolic blood pressure 30.1 mm of mercury and diastolic blood pressure 9.7 mm of mercury, LDL-C 29.2 mg/dl, and increased HDL-C 7.3 mg/dl. In group-II (n=30) which was advised to take Indian dates for two months, it reduced systolic blood pressure 10.9 mm of mercury, diastolic blood pressure 5.1 mm of mercury, LDL-C 7.9 mg/dl and increased HDL-C 3.3 mg/dl. Changes in all parameters are shown in table-I and table-II.

**Table I: Showing group-I's (n= 27) mean values± SD of all parameters tested, changes in parameters, and its statistical significance in change**

Parameter	At starting of treatment	After two months	Change in parameter	Statistical significance (p-value)
SBP	150.22±1.11	120.11±1.91	30.1	<0.001
DBP	97.91±1.21	88.21±1.11	9.7	<0.01
LDL-C	210.16±2.11	180.97±2.22	29.2	<0.001
HDL-C	37.91±1.91	45.21±2.19	7.3	<0.01

**Table II: Showing group-II's (n=30) mean values± SD of all parameters tested, changes in parameters, and its statistical significance in change**

Parameter	At starting of treatment	After two months	Change in parameter	Statistical significance (p-value)
SBP	141.71±2.21	130.78±1.11	10.9	<0.01
DBP	93.61±2.00	88.54±1.10	5.1	>0.05
LDL-C	198.82±2.17	190.91±1.73	7.9	<0.01
HDL-C	38.61±2.19	41.91±2.97	3.3	>0.05

SBP means systolic blood pressure, DBP means diastolic blood pressure measured in mm of mercury, LDL-C means low density lipoprotein cholesterol, HDL-C means high density lipoprotein cholesterol measured in mg/dl. 'n' means sample size.

## DISCUSSION

In our results two months therapy by Rosuvastatin 10 mg when used in 27 hyperlipidemic patients, it affected, when statistically analyzed, all tested parameters included systolic/diastolic blood pressure, LDL-cholesterol and HDL-cholesterol. Indian dates proved no significant changes in 30 hyperlipidemic patients in their diastolic blood pressure and HDL-cholesterol, but did affect systolic blood pressure and LDL-cholesterol significantly, with p-values <0.01. Bihva C *et al.*, [19], explained same mechanism of action of Rosuvastatin as described in text books of medicines, pharmacology and therapeutics that it inhibits HMG-CoA reductase enzyme which is responsible to synthesize cholesterol in human body. They proved same effects of this drug on 56 hyperlipidemic patients. Cella V *et al.*, [20], proved 30.99 mg/dl reduction in LDL-cholesterol when they used Rosuvastatin 10 mg once daily for three months in 109 hyperlipidemic patients. Mekatal Y *et al.*, [21], said in their conclusion that statins are the best among hypolipidemic agents used in patients suffering from primary or secondary hyperlipidemia. Ketylu V *et al.*, [22], emphasized to use Rosuvastatin in those patients who are victimized by metabolic syndrome with increased oxidative

stress causing lethality in these patients due to myocardial infarction. Burden of free radical formation, diabetes, obesity, hypertension, hypo or hyperthyroidism, excessive inflammatory reactions in body, and utilization of fatty foods may cause, rather do cause coronary artery syndrome which is difficult to treat, but not impossible. Statins like Rosuvastatin is the best example of drugs used in these patients [23]. Kakati PY *et al.*, [24], have provided other options of treating patients suffering from hyperlipidemia, other than allopathic drug regimens. They recommended herbal medicines or medicinal plants to treat complicated cases of hyperlipidemia. They used Indian dates in 46 hyperlipidemic patients one kg daily for three days and proved LDL-cholesterol reduction 8 mg/dl. No HDL-cholesterol increase was seen by them. Lomateevasel IO *et al.*, [25], proved 20.6 mg/dl reduction in LDL-cholesterol when 400 grams indian dates were used in 22 hyperlipidemic patients for two months. They also proved reduction in blood pressure significantly in their patients. Blood pressure significant effect is not proved in many studies conducted on indian dates [26]. Terala *et al.*, [27], proved significant effects of jujubes Z on all parameters of lipid profile and hypoglycemic effects of this fruit when 250 grams of jujubes was used in 77 hyperlipidemic with hyperglycemic patients for the period of nine months. Olivo I *et al.*, [28-31], explained in details that comparison of allopathic drugs with medicinal herbs for treating hyperlipidemic patients should be rationally analyzed on scientific methods/techniques, which is

not conventional trend in eastern culture. Ethnicity is involved in utilization of these herbs leading to defame scientific research on various substances which are included in science as chemical compounds having medicinal/therapeutic potential.

## CONCLUSION

We concluded from the research work that HMG-CoA reductase inhibitor drug Rosuvastatin 10 mg significantly reduces systolic, diastolic blood pressure, and LDL-cholesterol, and increase HDL-cholesterol in hyperlipidemic patients of both gender, ie; male and female. Indian dates have potential to reduce systolic blood pressure, and LDL-cholesterol, but no significant role on affecting diastolic blood pressure and HDL-cholesterol.

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