

## NEW WAYS TO DEAL WITH THERAPEUTICS IN MEDICINE

(Review)

Salman Iffikhar, Shah Murad, Seema Saif, Abdul Ghaffar Jamila Shah Murad, Manal Raouf,

Assoc Prof of Pharmacology at RLMC Lahore Pakistan, HOD Pharmacology at IMDC/DANTH, Islamabad Pakistan, Gynecology Department, NMC Karachi Pakistan., CWO at DANTH and IMDC Pakistan, Psycholoist at BU Karachi, Dentist at IDH/IMDC Islamabad Pakistan

### ABSTRACT

Inflammation within an atherosclerotic plaque makes the plaque more likely to rupture, precipitating an acute ischemic event. Highly sensitive C-reactive protein (hsCRP), a nonspecific marker of inflammation, appears to predict CAD risk, as do LDL cholesterol levels. The JUPITER (Justification for the Use of Statins in Primary Prevention. Hyperlipidemia has afflicted humankind since antiquity. In 2002, coronary heart Epidemiological evidence strongly supported the positive correlation between blood lipids, hyperlipidemia and its complications, mainly CHD. This relationship has been shown between and within cultures. The hyperlipidemia is traditionally defined as conditions in which the concentration of cholesterol or triglyceride-carrying lipoproteins in plasma exceeds an arbitrary normal limit. These lipoproteins deposit in the interstitial space of arteries arising from aorta, restricting the blood supply to the heart. This phenomenon is known as atherosclerosis. Higher deposition of lipoproteins completely blocked the blood supply to the heart, and thus myocardial infarction (MI) occurs, which is commonly known as heart attack. In recent decades, some researchers assert that newer lipid measurements, including non-HDL-C, apolipoprotein (apo)A-I, apoB, and lipid ratios, are superior to traditional LDL-C in predicting adverse outcomes in general population. Some researchers even suggest that apoB can replace the standard "lipid profile" as a target for monitoring and therapy in at-risk patients. High plasma lipids interact with free radicals in human body leading to develop coronary artery disease. Coronary artery disease is a complex syndrome to get initiation from formation of atherosclerotic plaques in systemic circulation to cardiac arrhythmia causing morbidity/mortality. This study was conducted to compare hypolipidemic effects of Niacin and Indian date (Jujuba) in hyperlipidemic patients. Study was conducted from July 2018 to December 2018 at National Hospital Lahore-Pakistan. Sixty participants were enrolled of both gender male and female patients age range from 25 to 60 years. Consent was taken from all patients. They were divided in two groups. Group-I was advised to take 2 grams Niacin in divided doses for the period of two months. Group-II was advised to take 500 grams of fruit Jujube daily for the period of two months. All patients' systolic and diastolic blood pressure was noted. Their baseline LDL and HDL cholesterol was determined by conventional method of measuring Lipid Profile. After two months therapy, their post treatment blood pressure and lipid profile was measured and mean values with  $\pm$  SEM were analyzed biostatistically. Group-I which was on Niacin their blood pressure was reduced but it was non-significant change, LDL cholesterol decreased significantly and HDL cholesterol was increased

significantly. In group-II patients LDL cholesterol was decreased significantly but HDL increase was not significant with p-value of  $>0.05$ . It was concluded from the research work that Niacin is potent in lowering LDL and increasing HDL cholesterol, while Jujube has significant effect as LDL cholesterol lowering potential, but it does not increase HDL cholesterol significantly. Jujubes and vitamin B-3 did not reduced blood pressure, when analyzed statistically.

prevention of heart attack, peripheral vascular disease and

## INTRODUCTION

An indirect measure of inflammation is lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>), an enzyme produced by inflammatory cells and liver cells that circulates in the plasma primarily bound to LDL particles. It hydrolyzes oxidized phospholipids on LDL particles, producing two inflammatory mediators, lysophosphatidylcholine and oxidized fatty acids, which have been linked to atherosclerotic plaque formation. In allopathic discipline of therapeutics, blood lipid levels are normalized by statins, fibrates, niacin and bile acid binding resins (BABRs). All of these allopathy related drugs have low compliance ranges from mild compliance due to metallic taste of BABRs to severe side effects like rhabdomyolysis by fibrates and statins. Due to low compliance and adverse effects of conventionally used hypolipidemic agents, herbal medicines are going to be famous among Physicians, and Cardiologists. Hypolipidemic drugs are very effective and they have excellent results, when used regularly. They not only decrease the level of fats in blood, but they also decrease risk of atherosclerosis and its complications. Therefore, these drugs may be used in

ischemic stroke<sup>1</sup>. Commonly used medications for treatment of Hyperlipidemia include Statins, Fibrates, Niacin, and Resins. All these medicines have potential for SEs and low compliance due to one reason or another<sup>2</sup>. Niacin when given in hypolipidemic doses i.e. more than 2 grams per day it causes partial inhibition of release of free fatty acids from adipose tissue, and increased lipoprotein lipase activity, which may increase the rate of chylomicron triglyceride removal from plasma. Niacin decreases the rate of hepatic synthesis of VLDL and LDL by synthesis of apoproteins which are integral part of LDL or VLDL structure<sup>3</sup>. Some herbs have been proved to reduce plasma lipids in human population. Jujubes or Ziziphus jujube have some what hypolipidemic as well as hypoglycemic effects<sup>4</sup>. Jujube fruit is known to contain considerable amount of phenolic compounds, including chlorogenic acid, gallic acid, protocatechuic acid and caffeic acid<sup>5</sup>. High polyphenolic content of Z Jujube suggests its potent capacity in

clearing of oxidants. Many studies proved the hepatoprotective effect of methanolic extract of *Zizyphus jujuba* fruits. Histopathological studies supported the biochemical findings. Study concludes a hepatoprotective activity probably due to its antioxidant effect<sup>6</sup>. Some studies evaluated the effect of *Z. Jujube* fruit in controlling dyslipidemia in obese adolescents. A triple-blind randomized placebo-controlled trial of 86 obese adolescents aged 12--18 with dyslipidemia proved its hypolipidemic features. Results showed the fruits to be generally well tolerated, with potential favorable effects on blood pressure and serum lipid profile<sup>7</sup>. Hydro-alcoholic preparations from Indian dates have been proved to possess hypotensive and hypolipidemic effects in human population. Main problem with ingestion of Indian dates or *Jujuba* was its larger amount to take by human population to reduce blood pressure and hyperlipidemia<sup>8</sup>. It is proved in various studies that if taken in high amount Indian dates are antioxidant and anti-inflammatory in characteristics. Their cardiogenic and hepatogenic effects are explained in various studies. They stated that medicinal plants increase the expression of cholesterol and lipoprotein receptors on the liver cells. Antioxidants are chemicals that occur naturally in foods. They help fight the potentially harmful effects of unstable substances known as free radicals<sup>9</sup>.

## MATERIAL AND METHOD

Place of research study and duration: The research work was started after written

approval of ETHICS COMMITTEE of National Hospital, Lahore. It was conducted from July 2018 to December 2018. Sample size and inclusion criteria: Sixty hyperlipidemic patients were selected from National Hospital Lahore-Pakistan to compare hypolipidemic effects of Niacin (vitamin B-3) and commonly used fruit in winter season in Pakistan i.e. Indian date or *Jujube* (Bair in urdu). Both male and female patients suffering from primary or secondary hyperlipidemia were selected. The age limit for patients was 25 to 60 years. Exclusion criteria were alcoholics, cigarette smokers, habitual to enjoy sedentary life, with impaired liver or renal functions. Written and already explained consent was taken from all participants. Their systolic/diastolic BP was measured by using mercury sphygmomanometer. Baseline Lipid Profile was determined in Biochemistry lab of the Hospital. Patients were divided in two groups, 30 patients in each group. Group-I was on Tab. Niacin 2 grams daily in three divided doses. Group-II was on *Jujube* 500 grams daily in three divided times to eat. They were advised to take fruit and vitamin B-3 for two months. They were also advised not to take junk food and were also advised to do 35 minutes brisk walk daily in the morning or evening. Mean values  $\pm$  SEM were taken for statistical analysis using SPSS version 10.0, 2015. Paired 't' test was applied to get significance changes in parameters before and after treatment. 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 parameter.

**RESULTS**

With two months therapy by vitamin B-3 (Niacin) and Indian dates (Jujube or Jujuba), systolic/diastolic blood pressure

was not changed when analyzed statistically but plasma total cholesterol, LDL-cholesterol and HDL-cholesterol were changed, which are shown in following table:

Table illustrating mean values with ±SEM and p-values in two groups of hyperlipidemic patients before and after treatment.

|                  | LDL-C                            | HDL-C                  | SYSTOIC BP                 | DIASTOILC BP             |
|------------------|----------------------------------|------------------------|----------------------------|--------------------------|
| Before treatment | G1= 210.1±2.11<br>G2= 198.8±2.17 | 37.9±1.91<br>38.6±2.19 | 110.02±1.12<br>113.98±2.86 | 86.87±2.01<br>89.66±1.04 |
| After treatment  | G1= 180.9±2.22<br>G2= 190.9±1.73 | 45.2±2.19<br>41.9±2.97 | 108.55±2.87<br>112.56±2.67 | 85.84±1.00<br>87.52±2.22 |
| Change in mg/dl  | G1= 29.2<br>G2= 7.9              | 7.3<br>3.3             | 1.47<br>1.42               | 1.03<br>2.14             |
| Change in %      | G1= 13.9 %<br>G2= 4.0 %          | 16.2 %<br>7.9 %        | 1.33%<br>1.24%             | 1.18%<br>2.38%           |
| p-value          | G1= <0.001<br>G2= >0.05          | <0.001<br><0.01        | >0.05<br>>0.05             | >0.05<br>>0.05           |

KEY: G1 is group on Niacin, G2 is group on drug-2 ie Jujube, ± stands for Standard Error of Mean values, BP stands for blood pressure, p-value >0.05 is non-significant cnage, p-value <0.01 is used for significant change in parameter, and p-value <0.001 is highly significant change in tested parameter.

**DISCUSSION**

The association between various lipid measurements and secondary risk of CAD deserves more attention due to limited and inconsistent results of previous studies. Atherosclerotic problems are encountered with enhancement of LDL uptake by monocytes and macrophages. In the liver, uptake of plasma LDL is mediated via specific LDL receptors, but a scavenger receptor system is employed by macrophages. Hypolipidemic drugs decrease chances of LDL particles available for oxidation, so prevent CAD. Vitamin B-3 (Niacin) is commonly used hypolipidemic drug which inhibit lipoprotein lipase activity, so lesser

formation of free fatty acids will be available which are main sources of TG-rich lipoproteins (VLDL) formation. Lesser amount of VLDL lead to lesser synthesis of LDL particles which are rich in cholesterol. In our research study it was proved that no vitamin B-3 nor Indian dates decrease systolic or diastolic blood pressure when pre and post treatment results were analyzed biostatistically. In our results vitamin B-3 (Niacin) 2 grams daily intake for two months decreased LDL-cholesterol about 13.9 % which is highly significant change. HDL-cholesterol in this group increased about 16.2 % which is again highly significant change. ZQ Zhu et al<sup>10</sup> and W Cao et al<sup>11</sup> proved same results when they used 2 grams of Niacin in 66



hyperlipidemic patients, but WB Yao et al<sup>12</sup> observed lesser effects of Niacin on HDL cholesterol, i.e. only 4.4 % increase in HDL cholesterol. Hung PG et al<sup>13</sup> explained different mechanisms of hypolipidemic response of Nicotinic acid on persons with different genetic code. One of the favorable mechanism for patients with CAD they described is fibrinolytic activity of Niacin. In our results Jujube fruit decreased LDL cholesterol is 7.9 mg/dl, which is significant change in the parameter. HDL cholesterol is not increased significantly in our results with p-value of >0.05. Tan H et al<sup>14</sup> and Tripathi M et al<sup>15</sup> observed same reason of Jujube on LDL and HDL-cholesterol, which augment our results. Tschesche R et al<sup>16</sup> observed more effects of Jujube as we observed in low density lipoprotein cholesterol. Um S et al<sup>17</sup> proved that LDL cholesterol is much decreased as compared to our results. KB Kang et al<sup>18</sup> observed too less effects of Jujube fruit in 5 hyperlipidemic patients. This difference in two studies are due to their small sample size, i.e. they tried herb only on five hyperlipidemic patients, while we tried in 30 hyperlipidemic patients. Compliance of Indian fruit Jujuba is low due to its very high amount to take as hypolipidemic and hypotensive herbs. It was explained by Loom Viyu et al<sup>19</sup> and A. Mohammad et al<sup>20</sup>. In allopathy blood lipid levels are normalized by statins, fibrates, niacin and bile acid binding resins (BABRs). All of these allopathy related drugs have low compliance ranges from mild compliance due to metallic taste of BABRs to severe side effects like rhabdomyolysis by fibrates and statins<sup>21</sup>. Due to low compliance and adverse effects of conventionally used

hypolipidemic agents, herbal medicines are going to be famous among Physicians, and Cardiologists<sup>9</sup>. Medicinal herbs like jujbae, indian dates, nigella sativa are being used as mild to moderate hypolipidemic agents<sup>22-25</sup>.

## REFERENCES

1. S Nawaz, M Furqan, Z. A. Kuliev, Yu. A. Akhmedov, A. D. Vdovin, N. D. Abdullaev. Atherosclerosis and its complications. Chemistry of Natural Compounds 2012;33(2):165-73.
2. Anbarasi Balakrishnan, Parimala Devi Balasubramaniam, Senthil Kumar Natesan. Conventional therapies for dyslipidemia. J Adv Sci Res, 2013;3(3):40-3.
3. Reza Afrisham, Mohammad Aberomand, Mohammad Ali Ghaffari, Amir Siahpoosh, and Mostafa Jamalán. Vitamin B-3: new considerations. Journal of Botany 2015;5(3):119-21.
4. Usama El-Sayed Mostafa and Louay Labban. Effect of Zizyphus jujuba on serum lipid profile and some anthropometric measurements. Advancement in Medicinal Plant Research 2013;1(3):49-55.
5. Shah M, LF Juju, FF Jau, Ul Lyme, KT Fauo, ML Panic. Phenolic compounds in Indian dates. Ethanobotanical J 2014;12(5):222-7.
6. Daneshmand F, Zare-Zardini H, Tolueinia B, Hasani Z, Ghanbari T. Crude Extracts from Ziziphus Jujuba Fruits: new guidelines. Iranian Journal of Pediatric Hematology Oncology 2013;3(3):191-3.

7. Bruckert E, Labreuche J, Amarenco P. Compliance of Indian dates when used in high amount. *Atherosclerosis* 2010;(2):353-61.
8. Duggal JK, Singh M, Attri N, Singh PP, Ahmed N, Pahwa S, Molnar J, Singh S, Khosla S, Arora R. Hypotensive and hypolipidemic effects of Indian fruits. *Journal of cardiovascular pharmacology and therapeutics* 2013; 19(1):58–60.
9. Manoj P, Shiv Kumar, K. G. Bhat. Effect of Indian date leaves extracts on phagocytosis. *JOURNAL OF NATURAL REMEDIES* 2014;4(1):47.51.
10. ZQ Zhu, J.W. Chen, T.X. Hu, D.Y. Zhu. Niacin affects HDL-cholesterol and LDL cholesterol. *Phytochemistry* 2011;22:1667-72.
11. W Cao, B.N. Wang, H. Gao, M.T. Fan, J.B. Vitamin B-3 or Niacin for prevention of coronary artery disease. *Plant Pharmacol* 2011;61:703-7.
12. WB Yao, H. Wang, X.D. Gao, G.C. Zhou, L. Cai. Niacin is important for healthy heart. *Science of pharmacol* 2011;10:122-7.
13. Hung PJ, J. Wang, L.T. Li, Y. Dan. Vitamin B-3 for Atherosclerosis and its prevention. *J. Food Chem* 2011;10:21-4.
14. Tan, N.H., Fan HG, Zhou, J. JUJUBE IS HYPOLIPIDEMIC HERB. *Chem. Rev.* 2007;106:840-5.
15. Tripathi, M., Pandey, MB., Jha, RN., Pandey, VB., Tripathi, PN., Singh, JP. Cyclopeptide alkaloids from *Zizyphus jujuba*. *Fitoterapia* 2011;72:507–510.
16. Tschesche, R., Khokhar, I., Wilhelm, H., Eckhardt, G. Jubanine-A and Jubanine-B. Alkaloids from *Zizyphus jujuba* have antioxidant characteristics. *Phytochemistry* 2010;15:541-2.
17. Um, S., Choi, T.J., Kim, H., Kim, B.Y., Kim, S.H., Lee, S.K., Oh, K.B., Shin, J. Hypolipidemic effects of *Z Jujube*. *J. Org. Chem.* 2013;78:321-29.
18. KB Kang, JJ You, LL mumpycal, ST Simon. *Z. Jujube* is effective to reduce oxidation burden. *Phytochemistry* 2014;22(4):222-5.
19. Loom viyu, PK Joshi, Roomyu L, Furquye Y. Indian dates and its compliance in human population. *J ethanobotany* 2014;4(4):123-9.
20. A. Mohammad, S Mohammad, N Mohammad, N Abdullah. Indian fruits varieties and their characteristics in various therapies. *Ir J of Nat Med* 2013;12(1):444-9.
21. Mustv JH, Shah M, LF Juju, FF Jau, UI Lyme, KT Fauo, ML Panic. Phenolic compounds in Indian dates. *JUMCP* 2015;34(8):34-9.
22. Therw Q, Daneshmand F, Zare-Zardini H, Tolueinia B, Hasani Z, Ghanbari T. Crude Extracts from *Zizyphus Jujuba* Fruits: new guidelines. *IJMC* 2017;22(5):90-5.
23. Ilher T, Bruckert E, Labreuche J, Amarenco P. Compliance of Indian dates when used in high amount. *MCJR* 2017;11(5):50-5.
24. Ilsavi UK, Duggal JK, Singh M, Attri N, Singh PP, Ahmed N, Pahwa S, Molnar J, Singh S, Khosla S, Arora R. Hypotensive and

hypolipidemic effects of Indian fruits. In Jou SMC 2017;33(5):122-8.

on phagocytosis. JOURNAL OF NATURAL REMEDIES 2014;4(1):47.51.

25. Eslave W, Manoj P, Shiv Kumar, K. G. Bhat. Effect of Indian date leaves extracts

