Anti hyperlipidemic and hepatoprotective effects of native date fruit variety "*Aseel*" (*Phoenix dactylifera*)

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Abstract: Diet rich in saturated fats and sugars have been associated with obesity, insulin resistance, hyperlipidemia and fatty liver disease. Especially high serum lipid levels are directly connected to the progression of cardiovascular disorders, which are the leading cause of death all over the world. Date palm fruit *(Phoenix dactylifera)* is known for numerous health benefits however little information is available about *in vivo* clinical and preclinical benefits, hence antihyperlipidemic and hepatoprotective potential of native date variety *Aseel* has been assessed in hyperlipidemia induced albino rats. Forty adult male albino rats were divided into five groups with 8 animals in each group. One group was kept as normal control while remaining four groups were fed high fat high sugar diet for 8 weeks; from this one group was reserved as disease control while two groups as treated which received 300 and 600mg/kg of date fruit suspension. The fourth group served as positive control and received standard drug atorvastatin in the dose of 2.1mg/kg. After 14 days serum lipid profile, hepatic profile and fasting blood sugar were determined for all groups. Fasting blood sugar, cholesterol, triglycerides, LDL and VLDL along with cholesterol- HDL and LDL-HDL ratio were significantly decreased at 300 mg/kg without any increase in liver enzymes as observed in positive control group. Animals received 600 mg/kg also revealed significant decline in fasting blood sugar, triglyceride, VLDL and alkaline phosphatase. Hence present results demonstrate ameliorative role of date fruit in hyperlipidemia and fatty liver however more studies are required to gain insight into the possible mechanism of action and confirmation of these effects on human subjects.

Keywords: Hyperlipidemia, *Phoenix dactylifera*, anti-hyperlipidemic, euglycemic.

INTRODUCTION

High fat and sugar diet is directly associated with obesity, insulin resistance, hyperlipidemia and fatty liver disease (Massiera *et al.,* 2010). These metabolic changes may lead to cardiovascular diseases, hypertension, liver fibrosis and diabetes mellitus (Panchal and Brown, 2011). In particular, increased lipid levels in blood are directly related with the progression of cardiovascular disorders like atherosclerosis, angina and myocardial infarction which is the leading cause of death all over the world (Verlecar *et al*., 2007 and Wong, 2014).

Hyperlipidemia is categorized by the increased blood levels of lipids and lipoproteins that eventually lead to atherosclerosis and coronary heart diseases. Among all other major illnesses, coronary heart diseases are considered as the most persistent cause of morbidity and mortality (Naghavi, 2015). Risk factors like diet with high sugars and saturated fatty acid, hypertension, family history, age and life style have major part in the development of coronary artery disease (Mendis *et al.,* 2011).

Moreover, increased sugar and lipid rich di*et al*so tend to disturb hepatic functions that end in the development of fatty liver. Excessive lipid deposition in liver, oxidative stress and pro-inflammatory cytokines mutually promote complications like fibrosis and liver cirrhosis (Mastroianni *et al.,* 2014). Hence administration of high fat and high sugar diet has been used extensively in laboratory animals for the induction of metabolic syndrome including obesity, insulin resistance, hyperlipidemia and fatty liver disease (Chun *et al.,* 2010 and Kohli *et al.,* 2010).

Long term use of anti-hyperlipidemic drugs has been associated with few adverse effects most importantly gastrointestinal upsets, general weakness, hepatic enzyme elevation and headache (Bellosta and Corsini, 2012 and Naci *et al.,* 2013), thus there is a need for the development of safer and effective alternates.

P. dactylifera, generally recognized as date palm is a vital plant in the Southeast Asia and North Africa most importantly in Middle Eastern region (Al Farsi and Lee, 2008 and Zaid, 1999). Date palm plays significant role in these cultures especially fruits are used as an important source of diet in infertile areas (Zaid, 1999).

Date fruit contains about 70% carbohydrates in the form of sucrose and fructose**.** 100gm flesh can provide approx 314 kcal of energy. Dietary fibers, protein and fats are also present but in lesser quantities (Al Farsi and Lee, 2008). They also contain ascorbic acid, riboflavin, thiamine, biotin and folic acid along with other fat soluble vitamins. The fruit is also rich in minerals like iron, calcium, phosphorus, potassium, copper and zinc (Ali and Khamis, 2004, Al Farsi *et al.,* 2005).

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Traditionally dates had been used as general body strengthener, tonic, aphrodisiac and fertility enhancer (Khare, 2007 and Zaid, 1999). Its use has also been associated with the treatment of hypertension and diabetes (Tahraoui *et al.,* 2007). In Ayurveda, date fruit is claimed to have anti-cough, expectorant, demulcent and diuretic effects (Khare, 2007). Regular consumption of dates is considered valuable for cold, cough, burning sensation, nephropathy, gastropathy, bronchitis and rheumatism (Khare, 2007 and Selvam, 2008).

P. dactylifera (Aseel) variety is among one of the predominant commercial date varieties in Pakistan (Markhand, 2010) and is considered to be a most important variety of Khairpur district Sindh. *Aseel* is an excellent semi-dry date with suitable fruit size (Khushk *et al.,* 2004). The proximate composition and mineral profile of *Aseel* variety have been summarized in table 1 (Jamil *et al.,* 2010).

Recent studies showed that hyperlipidemia and associated complications can be managed by modulating nutritional habits, particularly diet rich in polyphenols, flavonoids and antioxidants have antiatherogenic effects (Wilcox *et al.,* 1999 and Shin *et al.,* 1999). Different varieties of date fruits have shown promising antioxidant, anti-inflammatory and anti-hyperlipidemic properties in previous studies however no *in vivo* experimental studies have been conducted to evaluate pharmacological effects of Pakistan native date variety *Aseel*. Therefore *Aseel* variety has been selected in present study to evaluate its anti-hyperlipidemic and hepatoprotective potential in hyperlipidemia induced adult albino rats.

MATERIAL AND METHOD

Selection of animals

Forty adult male albino rats (250-300 gm) were bought from the animal house of Hussein Ibrahim Jamal (HEJ) Research institute of Chemistry, University of Karachi, Pakistan. The animals were kept in the animal house of the Pharmacology Department, Faculty of Pharmacy following ethics of biomedical research on animals, Helsinki Resolution specifications, 1964 (Carlson *et al.,* 2004). The study was permitted by the Board of Advanced Studies and Research University of Karachi. The rats were kept in a well-ventilated room in metal cages and allowed to acclimate for 1 week before the experiment. The rats were retained under regular laboratory conditions (25 °C, 60-70 % relative humidity and a 12-h light/dark cycle).

Preparation of oral date suspension

Fresh date fruit (*Aseel variety, Rutab stage*) was purchased from Khairpur local market and were identified by Prof. Dr. Anjum Parveen, Director, Plant Conservation Center, University of Karachi and given G. H. NO. 92189. Oral date fruit suspension was prepared by grinding 50gm of date fruit flesh with 100ml of distilled water till a uniform suspension is formed. This suspension was then kept in refrigerator at -4°C to avoid microbial and fungal contamination and used within 3 days. Date fruit was given as oral suspension since it carries all the ingredients of date fruit with ease of oral administration to laboratory animals.

Induction of hyperlipidemia

After one week of accommodation all rats were separated into five groups; control group was given standard laboratory diet and remaining four groups were given high fat and high sugar di*et al*ong with standard diet for 54 days according to body weight. High fat diet was prepared by mixing vanaspati ghee and coconut oil in the ratio of 3:1 v/v and was given to rats daily in the dose of 3 ml/kg, while high sugar diet was given as 10% fructose added to drinking water provided ad libitum (Munshi *et al.,* 2014).

Experimental design

Forty rats were equally divided in to five groups, one group served as normal control was given normal laboratory diet and distilled water; however four hyperlipidemia induced groups were sequentially fed on distilled water, date fruit suspension (two groups) and standard drug atorvastatin. One hyperlipidemic group was only given distilled water and designated as hyperlipidemic control; two groups received date fruit suspension in the doses of 300 and 600 mg/kg and were designated as treated, while fourth group was given atorvastatin in the dose of 2.1 mg/kg and designated as positive control; drugs and distilled water were given to all groups for 14 days.

Sample collection

7 ml blood samples were collected on 15th day after completion of dosing period from over-night fasted animals by cardio puncture technique. Serum was instantly separated through centrifugation at 4000 rpm for 10 min. Serum lipid profile (Cholesterol, triglycerides, HDL, LDL, VLDL) hepatic profile (ALP, AST, ALT, γGT, total bilirubin) and FBS was assessed within 3 hours of sample collection on Humalyzer 3000 automatic analyzer using standard reagents kits supplied by Human Gmbh Germany. Cholesterol/HDL ratio and LDL/HDL ratio have been determined using standard formula.

STATISTICAL ANALYSIS

Data entry and analysis were performed using Superior Performance Statistical Software (SPSS) version 20 IBM 2014. Data were presented as mean ± standard error of the mean with 95% confidence interval. ANOVA followed by post-hoc was performed for the comparisons of values with control. Values of $P \leq 0.05$ were considered as significant and $P \leq 0.005$ as highly significant.

Table 1: Composition and mineral profile of *Phoenix dactylifera* (Adopted from Jamil *et al*, 2010)

S. No	Parameter	Proximate Quantity
1	Moisture (%)	7.20±0.34
2	Ash (%)	2.19±0.05
3	Crude protein (%)	41.25±2.05
4	Crude lipid (%)	9.05±0.42
5	Carbohydrate (%)	40.22±2.01
6	Total oxalate (g/100ml)	0.54±0.04
7	Crude fiber (%)	86.08±3.95
8	Energy value (Kcal/100 g)	352.33
9	Sodium (mg/g)	3.13±0.15
10	Lithium (mg/g)	6.15±0.25
11	Potassium (mg/g)	8.88±0.35
12	Zinc (mg/g)	0.05±0.001
13	Calcium (mg/g)	0.45±0.01
14	Chromium (mg/g)	0.05±0.01
15	Magnesium (mg/g)	0.27±0.001
16	Manganese (mg/g)	0.02±0.001
17	Copper (mg/g)	0.31±0.01
18	Nickel (mg/g)	0.074±0.001

Table 2: Effect of *P. dactylifera* on lipid profile

S#	Parameter	Normal control (Distilled water)	Hyperlipidemic control (Distilled water)	Positive control (Atorvastatin)	*P. dactylifera* 300 mg/kg	*P. dactylifera* 600 mg/kg
1.	Cholesterol mg/dl	54.50±8.64**	97.50±17.31	57.75±6.82**	73.00±9.10*	91.75±16.50
2.	Triglycerides mg/dl	46.25±6.39**	83.25±14.31	34.50±7.87**	36.75±2.66**	52.00±8.78**
3.	HDL mg/dl	39.00±5.81	45.00±6.97	46.25±6.74	50.75±6.06	48.50±16.40
4.	LDL mg/dl	11.00±2.62**	43.50±14.51	14.00±2.93**	14.00±2.51**	33.75±17.88
5.	VLDL mg/dl	9.0 ±1.31**	16.75±4.23	6.75±1.58**	7.50±0.53**	10.50±1.77**
6.	Choles./HDL	1.4±0.06**	1.90±0.40	1.26±0.09**	1.44±0.05*	1.99±0.40
7	LDL/HDL	0.28±0.05	0.86±0.37	0.30±0.05**	0.27±0.04**	0.66±0.13

Table 3: Effect of *P. dactylifera* on hepatic profile and fasting blood sugar

S#	Parameter	Normal control (Distilled water)	Hyperlipidemic control (Distilled water)	Positive control (Atorvastatin)	*P. dactylifera* 300 mg/kg	*P. dactylifera* 600 mg/kg
1.	ALP (U/L)	274.10±51.39	352.0±80.76	226.50±70.03*	288.40±48.67	224.62±83.94*
2.	ALT (U/L)	77.20±11.55	84.10±11.98	103.70±16.61	58.30±14.3*	78.82±24.65
3.	AST (U/L)	134.52±16.40	166.40±24.30	202.10±19.84*	177.65±18.60	185.07±31.59
4.	γGT (U/L)	1.37±0.49	1.70±0.51	2.50±0.82	1.27±0.28*	1.72±0.31
5.	Tot Bili. (mg/dl)	0.23±0.04	0.20±0.075	0.77±0.21**	0.12±0.46*	0.30±0.13
6.	FBS (mg/dl)	156.80±6.05*	186.3±24.70	136.0±22.5**	153.4±26.10*	121.40±10.26**

n=8 values are mean ± S.E.M
*P≤0.05 significant as compared to disease control
**P≤0.005 highly significant as compared to disease control

RESULTS

Table 2 shows the comparison of cholesterol, triglycerides, HDL, LDL, VLDL levels and cholesterol-HDL and LDL-HDL ratio in treated and positive control groups against normal and hyperlipidemic control groups. Present results demonstrates that animals treated with high fat high sugar diet initially exhibited significant increase in cholesterol, triglycerides, LDL and VLDL as compare to normal control however there was significant decline in lipid profile when hyperlipidemia induced animals were treated with date fruit suspension and atorvastatin.

There was a significant decline in cholesterol and highly significant decline in triglycerides, LDL and VLDL in animals received 300mg/kg *P. dactylifera* as compared to hyperlipidemic controls, these results were almost similar to positive control group. The cholesterol/HDL and LDL/HDL ratio were also significantly decreased at 300mg/kg however HDL was insignificantly increased. In animals received 600mg/kg date fruit suspension there

was significant decrease in serum triglycerides and VLDL as compared to hyperlipidemic control group.

Table 3 demonstrates the results of alkaline phosphatase, AST, ALT, γGT, total bilirubin and fasting blood sugar (FBS) in treated and positive control groups against normal and hyperlipidemic control groups.

In comparison to normal and hyperlipidemic control groups, there was significant decrease in ALP and FBS in animals treated with atorvastatin and *P. dactylifera*, however there was marked decrease in ALT and total bilirubin levels of *P. dactylifera* treated animals on the contrary ALT and total bilirubin levels were found to be elevated in positive control group showing hepatotoxic effect of atorvastatin. Thus significant decrease in FBS, ALT, γ-GT and total bilirubin by *P. dactylifera* as compared to hyperlipidemic control group reveals its hepatoprotective effect.

DISCUSSION

Current study is first ever *in-vivo* study conducted to evaluate pharmacological effects of Pakistani date variety *Aseel.* Instead of using aqueous or organic solvents, whole fruit was evaluated by using oral suspension to determine the impact of all constituents and not fractions. This study revealed that moderate consumption of dates on regular basis as dietary component is more beneficial as high consumptions tend to decrease the positive impacts of dates. It also revealed positive effects on lowering atherogenic index and risk of heart attack, which is a very vital in the scenario of growing incidence of CVD in Pakistan. More importantly it also revealed that *Aseel* fruit did not produce hyperglycemia rather it was associated with decrease fasting blood sugar levels in dose dependent manner and showed better safety profile over Statins since *Aseel* fruit consumption did not raised hepatic inflammatory markers like Statins.

Hyperlipidemia is an established risk factor for cardio vascular disorders (CVD), particularly atherosclerosis. CVD is one of the chief reasons for premature death and is likely to be the most significant cause of death worldwide (Verlecar *et al.,* 2007 and Naghavi, 2015).

Worldwide remarkable increase in obesity, metabolic syndrome, and non-alcoholic fatty liver disease (NAFLD) has been associated with the increased use of processed food and beverages containing high sugar, salt and saturated fatty acids. NAFLD is regarded as the hepatic manifestation of the metabolic syndrome that includes hyperlipidemia, insulin resistance and fatty changes in liver and believed to be the most common cause of chronic liver disease in the world. These conditions if left untreated, may lead to cirrhosis and hepatocellular carcinoma (Massiera *et al.,* 2010).

CVD and NAFLD both are connected with raised cholesterol consumption, hence there is need to keep plasma cholesterol levels within permissible limits. This can be achieved through diet control, exercise and use of anti-hyperlipidemic drugs. Statins seems to be most valuable drugs in the management of hypercholesterolemia and atherosclerosis (Nielsen *et al.,* 1993 and Byington *et al.,* 1995). However there are issues of compliance due to frequent adverse effects associated with the use of statins (Bellosta and Corsini, 2012 and Naci *et al.,* 2013).

Hence dietary manipulation may play a vital role in the management of hyperlipidemia that works through lowering of raised sugar and cholesterol levels. Date fruits being rich in phytochemicals like phenolic acids, sterols, carotenoids, procyanidins, anthocyanins and flavonoids may be a solution in such condition. Dietary fiber present in dates may also be helpful in lowering of LDL and glucose by decreasing its absorption through gastrointestinal tract (Rahmani *et al*., 2014).

Hence current research investigates the possibility of *Aseel* fruit in suppressing induced hypercholesterolemia as efficiently as atorvastatin in rats. The study also focuses on hyperlipidemia associated changes especially raised hepatic inflammatory markers, fasting blood sugar, Cholesterol-HDL ratio and LDL-HDL ratio following daily oral administration of *Aseel* date fruit suspension for 14 days.

Results of present study demonstrates significant decrease in FBS, cholesterol, triglycerides, LDL and VLDL at 300 mg/kg *P. dactylifera* which were comparable to standard drug atorvastatin, however *Aseel* fruit was not associated with elevation of hepatic inflammatory biomarker. The Cholesterol-HDL ratio and LDL-HDL ratio were also significantly reduced at 300mg/kg against hyperlipidemia control group however it was noted that animals treated with 600mg/kg only demonstrate significant decline in triglyceride and VLDL levels where as all other lipid parameters were insignificantly altered. These finding are in accordance with the previous studies suggesting that phytoactive ingredients of dates *(P. dactylifera)* effectively reduces hypercholesterolemia and type 2 diabetes (Jung *et al.*, 2006).

Flavonoids and Vitamin C are richly present in date fruit (*P. dactylifera*) hence decrease in plasma LDL, cholesterol, and TGs in all groups by *Aseel* date fruit might be due to the flavonoid content in date fruit. It can be said that the combined effects of Vitamin C, folate, flavonoids and polyphenolic antioxidants in the date fruit may be responsible for marked biological activity including hypocholesterolemia (Alsaif *et al.*, 2007 and *Rock et al.,* 2009).

This study however lacks in that inflammatory changes taking place in terms of raised hepatic enzyme levels were not correlated with histo-pathological changes in liver for all groups. Moreover dose response relationship of oral date fruit suspension was not clearly understood as the antihyperlipidemic and hepatoprotective effects produced at 300mg/kg were not observed at 600mg/kg.

CONCLUSION

In conclusion, we can say that despite high consumption of fat and sugar *Aseel* fruit suspension had prevented hyperlipidemia and fatty changes in liver of rats especially at 300mg/kg. This considerable anti-hyperlipidemic activity of *Aseel* fruit suspension may be due to presence of flavonoids and poly phenols presence in dates. These findings are in accordance with previous studies supporting the benefits of date fruit extract in prevention and treatment of related disorders (Kamada *et al.,* 2005; Dhingra and Bansal 2006; Kaur and Bansal 2009, Hafeman and Hoekstra 1977; Domitrović *et al.,* 2008).

Aseel fruit suspension appears to have an edge over the Statins, in reducing the chances of atherogenesis and development of fatty liver since decreases the serum lipoprotein levels without stressing liver and also manage serum glucose levels within normal limits however more studies are required to assess its effect on human subjects.

REFERENCES

Al-Farsi MA and Lee CY (2008). Nutritional and functional properties of dates: A review. *Crit. Rev. Food Sci. Nutr.,* **48**: 877-887.

Al-Farsi M, Alasalvar C, Morris A, Baron M and Shahidi F (2005). Comparison of antioxidant activity, anthocyanins, carotenoids and phenolics of three native fresh and sun-dried date (Phoenix dactylifera L.) varieties grown in Oman. *J. Agric. Food Chem.,* **53**: 7592-7599.

Ali-Mohamed AY and Khamis AS (2004). Mineral ion content of the seeds of six cultivars of Bahraini date palm (Phoenix dactylifera). *J. Agric. Food Chem.,* **52**: 6522-6525.

Alsaif MA, Khan LK, Alhamdan AA, Alorf SM, Harfi SH, Al-Othman AM and Arif Z (2007). Effect of dates and gahwa (Arabian Coffee) supplementation on lipids in hypercholesterolemic hamsters. *Int. J. Pharm*., **3**: 123-129.

Bellosta S and Corsini A (2012). Statin drug interactions and related adverse reactions. *Expert. Opin. Drug Saf*., **11**: 933-946.

Byington RP, Jukema JW, Salonen JT, Pitt B, Bruschke AV, Hoen H and Mancini GJ (1995). Reduction in cardiovascular events during pravastatin therapy pooled analysis of clinical events of the pravastatin atherosclerosis intervention program. *Circulation,* **92**: 2419-2425.

Carlson RV, Boyd KM and Webb DJ (2004). The revision of the Declaration of Helsinki: Past, present and future. *Br. J. Clin. Pharmacol.,* **57**: 695-713.

Chun MR, Lee YJ, Kim KH, Kim YW, Park SY, Lee KM and Park YK (2010). Differential effects of high-carbohydrate and high-fat diet composition on muscle insulin resistance in rats. *J. Korean Med. Sci.,* **25**: 1053-1059.

Dhingra S and Bansal MP (2006). Modulation of hypercholesterolemia-induced alterations in apolipoprotein B and HMG-CoA reductase expression by selenium supplementation. *Chem. Biol. Interac.*, **161**: 49-56.

Domitrovic R, Jakovac H, Grebic D, Milin C and Radošević-Stašić B (2008). Dose-and time-dependent effects of luteolin on liver metallothioneins and metals in carbon tetrachloride-induced hepatotoxicity in mice. *Biol. Trace Elem. Res.,* **126**: 176-185.

Hafeman DG and Hoekstra WG (1977). Protection against carbon tetrachloride-induced lipid per oxidation in the rat by dietary vitamin E, selenium and methionine as measured by ethane evolution. *J. Nutr.,* **107**: 656-665.

Jamil MS, Nadeem R, Hanif MA, Ali MA and Akhtar K (2010). Proximate composition and mineral profile of eight different unstudied date (Phoenix dactylifera L.) varieties from Pakistan. *Afr. J. Biotechnol.,* **9**: 3252-3259.

Jung UJ, Lee MK, Park YB, Jeon SM and Choi MS (2006). Antihyperglycemic and antioxidant properties of caffeic acid in db/db mice. *J. Pharmacol. Exp. Ther.,* **318**: 476-483.

Kamada C, Da Silva EL, Ohnishi-Kameyama M, Moon JH and Terao J (2005). Attenuation of lipid per oxidation and hyperlipidemia by quercetin glucoside in the aorta of high cholesterol-fed rabbit. *Free Radic. Res.,* **39**: 185-194.

Kaur HD and Bansal MP (2009). Studies on HDL associated enzymes under experimental hypercholesterolemia: Possible modulation on selenium supplementation. *Lipids Health Dis.,* **8**: 55-65.

Khare CP (2007). Indian medicinal plants: An illustrated dictionary. Springer Science & Business Media. Springer-Verlag Berlin/Heidelberg

Kohli R, Kirby M, Xanthakos SA, Softic S, Feldstein AE, Saxena V and Woods SC (2010). High□fructose, medium chain trans-fat diet induces liver fibrosis and elevates plasma coenzyme Q9 in a novel murine model of obesity and nonalcoholic steatohepatitis. *Hepatol.,* **52**: 934-944.

Khushk MK, Qureshi MA and Memon MS (2004). General features and properties of date palm fruit of Khairpur. *Sci. Sindh.,* **11**: 67-75.

Markhand GS, Abul-Soad AA, Mirbahar AA, Kanhar NA. Fruit characterization of Pakistani dates. *Pak. J. Bot.,* **42**: 3715-3722.

Massiera F, Barbry P, Guesnet P, Joly A, Luquet S, Moreilhon-Brest C and Ailhaud G (2010). A Western-like fat diet is sufficient to induce a gradual enhancement in fat mass over generations. *J. Lipid Res.,* **51**: 2352-2361.

Mastroianni CM, Lichtner M, Mascia C, Zuccala P and Vullo V (2014). Molecular mechanisms of liver fibrosis in HIV/HCV co-infection. *Int. J. Mol. Sci.,* **15**: 9184-9208.

Mendis S, Puska P and Norrving B (2011). Global atlas on cardiovascular disease prevention and control. World Health Organization.

Munshi RP, Joshi SG and Rane BN (2014). Development of an experimental diet model in rats to study hyperlipidemia and insulin resistance, markers for coronary heart disease. *Indian J. Pharmacol.,* **46**: 270-276.

Naci H, Brugts J and Ades T (2013). Comparative tolerability and harms of individual statins a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. *Circ. Cardiovasc. Qual. Outcomes*, **6**: 390-399.

Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M and Aziz MIA (2015). Global, regional and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet,* **385**: 117-171.

Nielsen LB, Stender S and Kjeldsen K (1993). Effect of lovastatin on cholesterol absorption in cholesterol□fed rabbits. *Pharmacol. Toxicol.,* **72**: 148-151.

Panchal SK and Brown L (2011). Rodent models for metabolic syndrome research. *J. Bio Med. Biotechnol.,* Published online Dec 2010 doi: 10.1155/2011/351982

Rahmani AH, Aly SM, Ali H, Babiker AY, Srikar S and Khan AA (2014). Therapeutic effects of date fruits (Phoenix dactylifera) in the prevention of diseases via modulation of anti-inflammatory, anti-oxidant and anti-tumour activity. *Int. J. Clin. Exp. Med.,* **7**: 483-491.

Rock W, Rosenblat M, Borochov-Neori H, Volkova N, Judeinstein S, Elias M and Aviram M (2009). Effects of date (Phoenix dactylifera L., Medjool or Hallawi Variety) consumption by healthy subjects on serum glucose and lipid levels and on serum oxidative status: A pilot study. *J. Agri. Food Chem.,* **57**: 8010-8017.

Selvam ABD (2008). Inventory of vegetable crude drug samples housed in Botanical Survey of India, Howrah. *Pharmacogn. Rev.,* **2**: 61-94.

Shin YW, Bok SH, Jeong TS, Bae KH, Jeoung NH, Choi MS and Park YB (1999). Hypocholesterolemic effect of naringin associated with hepatic cholesterol regulating enzyme changes in rats. *Int. J. Vit. Nutr. Res.,* **69:** 341-347.

Tahraoui A, El-Hilaly J, Israili ZH and Lyoussi B (2007). Ethno pharmacological survey of plants used in the traditional treatment of hypertension and diabetes in south-eastern Morocco (Errachidia province). *J. Ethnopharmacol.,* **110**: 105-117.

Verlecar XN, Jena KB and Chainy GBN (2007). Biochemical markers of oxidative stress in Perna viridis exposed to mercury and temperature. *Chem. Biol. Interact,* **167**: 219-226.

Wilcox LJ, Borradaile NM and Huff MW (1999). Antiatherogenic properties of naringenin, a citrus flavonoid. *Cardiovasc. Drug Rev.,* **17**: 160-178.

Wong ND (2014). Epidemiological studies of CHD and the evolution of preventive cardiology. *Nature Rev. Cardiol.,* **11**: 276-289.

Zaid A and De Wet PF (1999). Chapter I botanical and systematic description of date palm. FAO plant production and protection papers, pp.1-28.