

# Antihypercholesterolemic and antiatherosclerotic potencies of *Pandanus tectorius* fruits via increasing scavenger receptor-B1 genes expression and inhibition of 3-hydroxy-3-methylglutaryl coenzyme a reductase activity

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## ABSTRACT

Atherosclerosis is a leading cause of death worldwide. The adverse side effects of currently available drugs urge to find more effective and safe remedial agents. Alternative candidates from natural resources are of great consequence in the emerging of new drugs. *Pandanus tectorius* (*Pandanaceae*) was traditionally used in Ayurvedic medicine to cure certain diseases. Thus, the current study conducted to elucidate the potency of *P. tectorius* fruit as antiatherosclerosis and antihypercholesterolemia agents through the regulation of high density lipoprotein (HDL) receptor (scavenger receptor [SR]-B1) gene expression and 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) *in vitro*, respectively. The *P. tectorius* fruit was noncytotoxic against the HepG2 cell line confirmed by 3-(4,5-dimethylthiazol-2-yl) 2,5-diphenyl tetrazolium bromide assay. The *P. tectorius* fruit successfully upregulates the SR-B1 gene expression and downregulate the HMGCR. Moreover, an *in vivo* study showed that *P. tectorius* has good activity on the upregulation of HDL and subsequently downregulation of total cholesterol level. Moreover, *P. tectorius* fruit did not show any increase in toxicity biomarkers serum glutamic oxaloacetic transaminase and serum glutamate pyruvate transaminase *in vivo*. These results found that *P. tectorius* fruits have potency as the preventive agent for hypercholesterolemia and atherosclerosis via SR-B1 and HMGCR mechanisms of action.

**Key words:** 3-hydroxy-3-methylglutaryl coenzyme A reductase, antiatherosclerosis, antihypercholesterolemia, *Pandanus tectorius*, scavenger receptor-B1

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## INTRODUCTION

Cardiovascular diseases (CVDs) as myocardial infarction, acute coronary syndrome, and stroke occur due to the formation of plaques in the arteries.<sup>[1,2]</sup> Hypercholesterolemia, a crucial significant factor for the development of CVDs

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along with atherosclerosis and heart stroke.<sup>[3,4]</sup> Various genetic factors such as hypertension, insulin resistance, obesity, and environmental factors as smoking, fat-enriched diet, poor lifestyle, lack exercise considered primary risk factors involved in the expansion of atherosclerosis.<sup>[5,6]</sup>

Scavenger receptor BI (SR-B1) is a multiligand receptor glycoprotein. SR-B1 receptor mediates uptake of HDL-derived cholesteryl esters into cells and surrounding tissue.<sup>[7-9]</sup> Statins widely used in the prevention of cardiovascular disease and lowering of LDL (low-density lipoproteins). The main aim of the drug is to regulate cholesterol levels via inhibiting -hydroxy-3-methylglutaryl coenzyme A reductase reductase (HMGCR) activity (as a competitive inhibitor). HMGCR considers having a vital role in the rate-limiting step involved in the biosynthesis of cholesterol.<sup>[7]</sup> However, it involves organ damage (liver injury) and muscle toxicity.<sup>[10-12]</sup> Over the past few decades, herbal medicines have captivated much attention for atherosclerosis due to their potential of multiple targeting steps involved in disease pathogenesis with reduce side effects. Previous studies have reported the *Pandanus tectorius* to possess cholesterol-reducing activity,<sup>[13]</sup> and hypolipidemic activity.<sup>[14]</sup> The caffeoylquinic acid isolated from *P. tectorius* possessed an antiglycemic and antilipidemic effect.<sup>[15,16]</sup> Therefore, the current study focus on the *P. tectorius* fruit as an anti-atherosclerosis agent via regulating the SR-B1 gene expression and HMGCR activity.

## MATERIALS AND METHODS

The HepG2 cells obtained from the American Type Culture Collection (Rockville, MD, USA). The plasmid midi kit purchased from Qiagen 100 protocol, cat no (Valencia, CA, USA) all the reagents purchased from Sigma Aldrich. While, the rats (male *Sprague Dawley*) purchased from Takrif Bistari Enterprise, Kuala Lumpur, Malaysia.

### Sampling location

The *P. tectorius* (fruit) collected from Batu Rakit, Kuala Terengganu, Malaysia (TER0618002). The sample deposited at the Institute of Marine Biotechnology, Universiti Malaysia Terengganu.

### Extraction and solvent fractionation of *Pandanus tectorius* fruits

The *P. tectorius* (fruit) extraction done by using cold maceration method using methanol to yield methanol extract first (PMK). Then, the PMK was used to produce the PHK (Hexane) and PEK (Ethyl acetate) extract by solvent-solvent partitioning method.

### In vitro study

#### Cytotoxicity study

Cytotoxicity performed by 3-(4,5-dimethylthiazol-2-yl) 2,5-diphenyl tetrazolium bromide (MTT) assay.<sup>[17,18]</sup> The

HepG2 cells seeded at a concentration of  $2 \times 10^4$  cells/well on 96-well plates. After the treatment, 20  $\mu$ L fresh MTT solution was added, and the plate incubated at 37°C, 5% CO<sub>2</sub>. The plate read by ELISA reader at a wavelength of 570 nm.

### The effect of extracts on the transcriptional activity of scavenger receptor-B1

#### Extraction of the reporter plasmid DNA and Lipofectin™ transfection and luciferase activity

Two recombinant plasmids pGL-3 SR-B1 and Mammalian co-reporter vector of Renilla luciferase purified by using plasmid midi kit, Qiagen 100 protocol, cat no 12145 (Valencia, CA, USA). Transient transfection carried out using Lipofectin™ (Invitrogen), and luciferase activity were measured using the Dual-Luciferase™ (Promega).<sup>[19]</sup>

### Inhibitory effect of *Pandanus tectorius* fruit on 3-hydroxy-3-methylglutaryl coenzyme A reductase reductase enzyme

The inhibition study of HMGCR enzyme performed according to the method provided (Sigma Aldrich, CS1090, St. Louis, USA).

### In vivo study

#### Ethics statement

The Research Ethics approved the experimental design protocol and guidelines in this study.

The Research Ethics includes experimental design, protocol and guidelines in this study approved by Committee (JKEP), Universiti Malaysia Terengganu, with the reference number UMT/JKEPHT/2018/18. 31.

### Animal and treatments

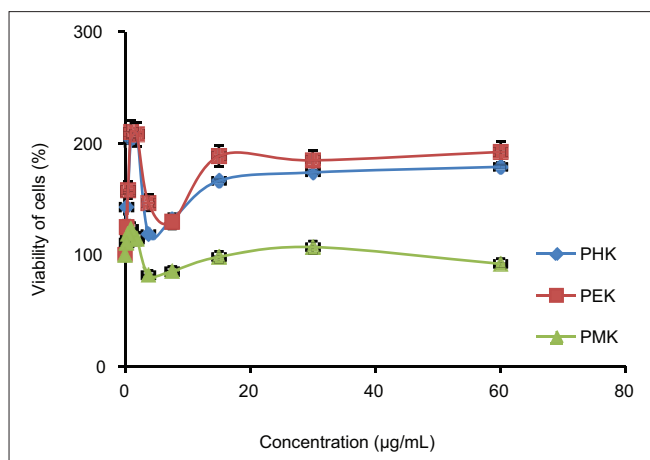
A forty male of *Sprague dawley* rats, healthy with regular activity. The 6–8 weeks old with approximately body weight 160–200 g. All of the Rats divided into four groups (Group A, B, C, and D) randomly, where there are ten rats in each group. Group A: As a negative control (feed by standard food only); Group B: As a positive control (feed by high cholesterol diet food); Whereas Group C and D are treatment groups that were feed by high cholesterol diet food and actives fraction of *P. tectorius* fruit PEK/PMK (500 g/kg BW), respectively. After the treatment periods, the rats conducted for recovery periods for more than 2 weeks. The blood sample of rats withdrawn to analysis their HDL, total cholesterol, serum glutamic oxaloacetic transaminase (SGOT), and serum glutamine-pyruvate transaminase (SGPT) levels. Cholesterol diet food in this current study made by 2% of cholesterol, 0.1% of propylthiouracil (PTU), 10% of cooking oil, and then mixed with the standard food until 100%.<sup>[19]</sup>

### Measuring total cholesterol level and enzymes activity

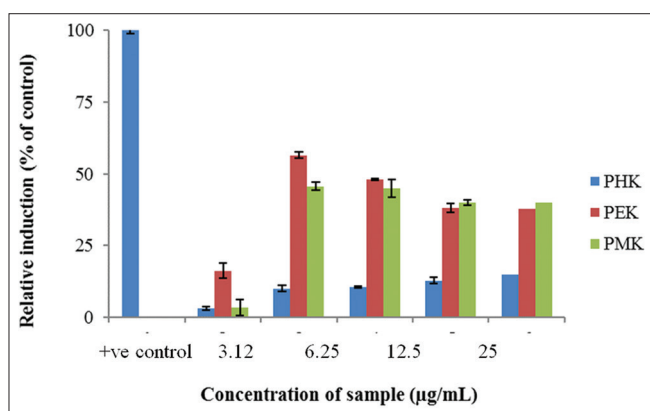
The total cholesterol levels analyzed by cholesterol oxidase phenol 4-aminoantipyrene peroxidase (CHOD-PAP) Method. The HDL levels were analyzed using manufacturer

precipitant method of HDL cholesterol (Randox, Crumlin Co., Antrim, UK). The enzyme activity measured

by using SGPT and SGOT reagents (1000  $\mu$ L). The activities read by spectrophotometer at 365 nm wavelength.



**Figure 1:** Cytotoxicity property PHK, PEK and PMK of *Pandanus tectorius* fruit against HepG2 cell lines. PHK (Pandanus Hexane Extract), PEK (Pandanus Ethyl acetate Extract) and PMK (Pandanus Mathanol Extract)



**Figure 2:** The activity value of scavenger receptor-B1 promoter that given PHK, PEK, PMK and positive control (rosiglitazone)

### Statistical analysis

The experiment conducted in triplicates (mean  $\pm$  standard deviation). The analysis of variance was applied, followed by the Tukey test using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). The significant results considered as  $P \leq 0.05$  among groups.

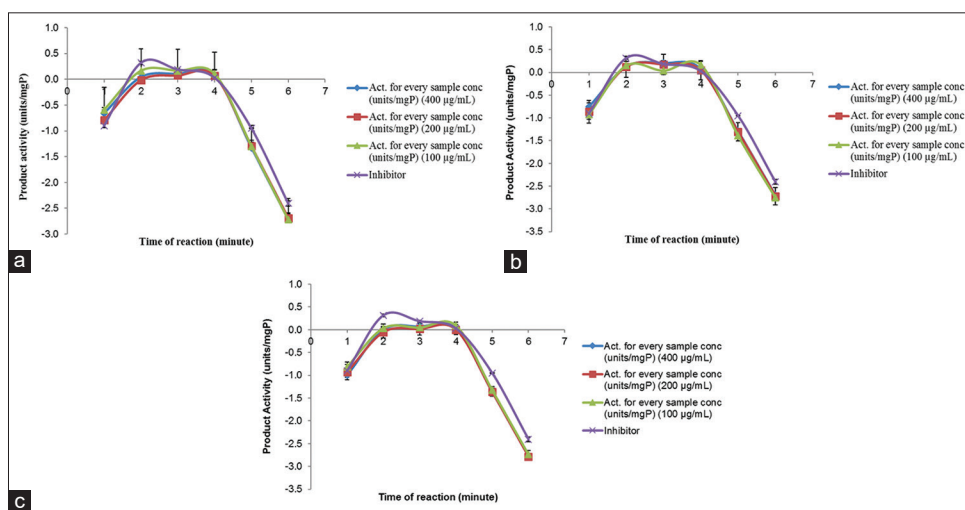
## RESULTS AND DISCUSSION

### Cytotoxicity study and scavenger receptor-B1 gene expression assay

The cytotoxicity analysis shows that PHK, PEK, [Figure 1] and PMK of *P. tectorius* fruits extract noncytotoxic (half maximal inhibitory concentration [ $IC_{50}$ ]  $<30 \mu\text{g/mL}$ ). As a criterion, the  $IC_{50}$  value below  $30 \mu\text{g/mL}$  considers as cytotoxic.<sup>[17]</sup> Moreover, the role of *P. tectorius* fruit in the regulation of the regulator of receptor protein SR-B1 also determine. The PEK and PMK exhibited a maximum increase at the concentration of  $6.25 \mu\text{g/mL}$ ; however, PHK produced the dose-dependent increase in SR-B1 gene expression, where the maximum exhibition noticed at  $50 \mu\text{g/mL}$  [Figure 2]. Furthermore, PEK produced a higher level of expression (56.56%) comparable to PMK (45.70%). According to Zanoni *et al.*<sup>[20]</sup>, SR-B1 as an HDL receptor can protect against atherosclerosis and CDV diseases. SR-B1 plays a significant part in cholesterol homeostasis, lipoprotein metabolism, and particularly atherosclerosis.<sup>[21,22]</sup> SR-B1 is a factor responsible for regulating cholesterol via reverse cholesterol transport.<sup>[20,23]</sup>

### A reductase 3-hydroxy-3-methylglutaryl coenzyme inhibition activity

To further investigate the cholesterol regulatory effects of *P. tectorius* fruit, HMGCR activity assay performed.



**Figure 3:** (a-c) The effect of PHK on 3-hydroxy-3-methylglutaryl coenzyme A reductase reductase activity at concentration of 400, 200, and 100  $\mu\text{g/mL}$  compare to the inhibitor (Pravastatin)

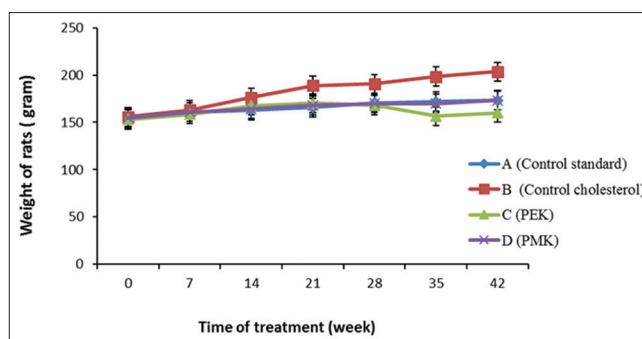
Figure 3a-c shows that extracts (PHK, PEK, and PMK) inhibited the HMGCR enzyme activity at 400, 200, and 100 mg/mL. PEK achieved the highest activity (0.21 units/mgP or 65.63% activity) comparable to the Pravastatin (+ve control), followed by PHK and PMK. The activity of *P. tectorius* extracts (PHK, PEK, and PMK) correlated to our previous study, which showed the presence of the phenolic and flavonoids constituents in extracts.<sup>[17]</sup>

### In vivo study

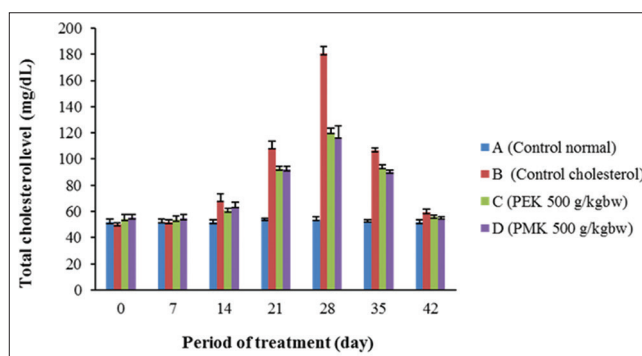
#### Bodyweight and cholesterol levels

The high cholesterol diet food intake de-regulate the HMGCR contributes to fat stored and weight gain of rats.<sup>[24,25]</sup> The decrease in the total cholesterol level in Groups C and D are seen after 2 weeks of treatment of the *P. tectorius* fruits, with 67% and 65% compared to the cholesterol Group (B), respectively (significantly different at  $P < 0.05$ ) [Figures 4 and 5]. The reduction in total cholesterol levels in Groups B, C, D was comparative to Group A which shows that PEK and PMK might consider as preventive agents for hypercholesterolemia and atherosclerosis. Similarly, the increase in HDL level [Figure 6] might be due to the presence of secondary metabolites in *P. tectorius* fruit. The  $\beta$ -carotene presence represented by the deep orange-red color of the fully ripe fruit. The previous studies showed that the *P. tectorius* (fruit) contains secondary metabolites such as (vanillin, chrysin, trans-ethyl caffeate, naringenin, caffeoylquinic acid, and tangeretin).<sup>[14,26]</sup> The HDL particles lower cholesterol levels and reducing the risk of atherosclerosis by it binding to hepatic SR-B1.<sup>[27,28]</sup> The sterol regulatory element-binding proteins (SREBPs) belong to a class of transcription factors (membrane-bound) that play a fundamental role in the regulation of cholesterol and fatty acids biosynthesis.<sup>[29]</sup> Li Y *et al.*, 2013 studied that the activation of SREBPs and the lipogenic process may trigger lipid accumulation and deposition in an atherosclerotic aorta.<sup>[30]</sup> Thus, the sample, which has an increasing the SR-B1 gene expression, could also have a capability in inhibiting HMGCR activity. These two mechanisms of action could be correlated to the capability of *P. tectorius* fruits to reduce total cholesterol levels and prevent atherosclerosis.

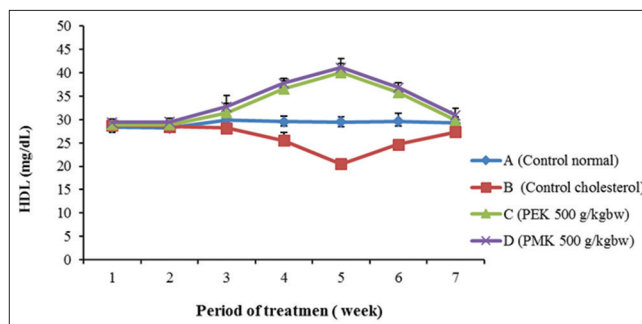
Furthermore, the SGOT and SGPT levels were determined to measure the toxicity of *P. tectorius* fruit on the liver. The influence of *P. tectorius* (PEK and PMK) in Group C and D exhibited SGOT activities ranging from 132.303 to 134.653 U/l (Unit per liter) and from 134.140 to 135.380 U/l, respectively comparable to toxic value  $242.10 \pm 36.40$  U/l (Jeong *et al.*, 2005).<sup>[31]</sup> Similarly, Groups C and D exhibited SGPT activity is less with range 64.872–66.462 U/l as compare to previous reported toxic ranges  $232.65 \pm 17.38$  U/l– $283,30 \pm 30.10$  U/l range [Table 1].<sup>[32]</sup> Hence, the administration of PEK and PMK of *P. tectorius* fruits at a dose of 500 mg/kg BW can be categorized as nontoxic and selected as a safe therapeutic dose [Table 2].



**Figure 4:** Rats body weight during 42 days of treatment that taken each week



**Figure 5:** The reduction of total cholesterol levels during treatment on groups of standard food (A); control cholesterol food (B); PEK 500 g/kg BW (C); and PMK 500 g/kg BW (D)



**Figure 6:** The HDL cholesterol level during 42-day treatment

## CONCLUSIONS

All samples from *P. tectorius* fruits extracts showed good activity on increasing of SR-B1 gene expression and inhibiting HMGCR activity in the *in vitro* study, and also reducing total cholesterol levels in the *in vivo* study. Besides, the cytotoxicity assay has shown that *P. tectorius* fruit was proven to have noncytotoxic activity on HepG2 cells. The SGOT and SGPT levels remained constant after treatment with PEK, and PMK reflected the nontoxic activity of *P. tectorius* fruits. Thus, the study proved that *P. tectorius* (fruits) as an excellent alternative source of natural phytochemicals for anti-hypercholesterolemia and anti-atherosclerosis potential agents via a regulatory effect on SR-B1 and HMGCR activities.

**Table 1: The serum glutamic oxaloacetic transaminase activities of rat plasma during treatment on each group**

Group	Activity of SGOT (U/I) for every 7 days during treatment						
	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
A	134.23±1.04	134.51±1.28	134.25±1.41	134.19±0.95	134.25±0.86	134.19±0.888	134.02±1.15
B	134.32±1.14	137.14±0.93*	137.35±1.19*	138.53±1.41*	137.93±1.22*	137.78±1.22*	137.91±1.17*
C	134.65±0.68	133.59±0.96	132.30±1.55	132.32±1.13	132.42±1.99	132.54±2.07	132.70±1.07
D	134.63±0.58	134.14±0.75	134.40±0.84	134.93±0.62	135.13±0.77	135.38±0.41	135.29±0.87

Group A as control of standard food, Group B as control of cholesterol food, Group C as PEK (Pandanus Ethyl acetate Extract), and Group D as PMK (Pandanus Methanol Extract). \* $P < 0.05$  significantly different in comparison among normal, cholesterol, and treatment group; each value is presented as mean±SD ( $n = 10$ ). SGOT: Serum glutamic oxaloacetic transaminase, SD: Standard deviation

**Table 2: The serum glutamate pyruvate transaminase activities of rat plasma during treatment on each group**

Group	Activity of SGPT (U/I) for every 7 days during treatment						
	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42
A	64.46±1.20	63.95±1.61	64.73±1.23	64.96±1.18	64.85±1.12	65.15±0.94	64.34±0.57
B	64.66±0.68	67.32±1.66*	66.95±2.98*	71.83±0.41*	70.99±4.13*	71.17±1.78*	71.39±2.47*
C	64.87±0.86	65.98±0.76	66.46±0.94	64.95±1.31	65.04±1.28	64.87±0.89	64.87±0.96
D	65.21±0.69	65.70±0.97	65.74±0.94	65.83±0.95	65.52±0.90	65.10±0.83	65.69±1.19

Group A as control of standard food, Group B as control of cholesterol food, Group C as PEK, and Group D as PMK. \* $P < 0.05$  significantly different in comparison among normal, cholesterol, and treatment group; each value is presented as mean±SD ( $n = 10$ ). SGPT: Serum glutamate pyruvate transaminase, SD: Standard deviation

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### Conflicts of interest

There are no conflicts of interest.

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