IJFANS INTERNATIONAL JOURNAL OF FOOD AND NUTRITIONAL SCIENCES
ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, 2022

ANTIDYSLIPIDEMIC, ANTIHYPERLIPIDEMIC AND ANTIOXIDANT ACTIVITY OF AEGELINE ANALOGUES

Dr. Satinath Sarkar
Department of Chemistry, Netaji Mahavidyalaya, Arambagh, Hooghly, West Bengal, India.
satinath.cdri@gmail.com

Abstract: Aegeline (**V**) from the leaves of Aegle marmelos as a dual acting agent (antihyperlipidemic and antihyperglycemic). Alkaloidal amides [N-(2-hydroxy-2-p-tolylethyl)-amides and N-(2-oxo-2-p-tolylethyl)-amide derivatives] and N-acylated-1-amino-3-aryloxy-2-propanols related to Aegeline and evaluated for their in vivo antihyperlipidemic activity in Triton induced hyperlipidemia model. These compounds showed equipotent activity to the natural product, that is, Aegeline (V). These compounds also showed strong antioxidant activity, which support their antihyperlipidemic activity. Few Compounds showed better antihyperlipidemic and antioxidant profile than the natural product Aegeline.

Keywords: Aegeline**,** Antidyslipidemic activity**,** Antihyperlipidemic activity, Triton model**,** Aegle marmelos**,** Phenylethanolamine derivatives, N-acyl-β-amino alcohols, Anti-oxidant activity

1. Introduction:

Hyperlipidemia is an elevation of lipids in the bloodstream and these lipids include fats, fatty acids, cholesterol, cholesterol esters, phospholipids, and triglycerides. An increase in plasma lipids, particularly cholesterol, is a common feature of atherosclerosis, a condition involving arterial damage, which may lead to ischemic heart disease, myocardial infarction, and cerebrovascular accidents. These conditions are responsible for one-third of deaths in industrialized nations.[1] In 1984, it was demonstrated for the first time that there exists a link between serum cholesterol levels and risk to coronary heart disease (CHD).[2] CHD is caused by the narrowing of the artery that supplies nutrients and oxygen to the heart. A 1% drop in serum cholesterol reduces the risk for CHD by 2%.[3] In addition to this, cholesterol lowering drugs treatments can significantly reduce morbidity from CHD, thus providing a causal role for cholesterol in coronary events.

Similarly, when carbohydrates are in low supply or their breakdown is incomplete, fats become the preferred source of energy in diabetic patients. As a result, the fatty acids are mobilized into the general circulation leading to secondary triglyceridemia in which total serum lipids in particular triglycerides as well as the levels of cholesterol and phospholipids increase. This rise is proportional to the severity of the diabetes. Uncontrolled diabetes is manifested by a very high rise in triglycerides and fatty acid levels. An increase in plasma lipids, particularly cholesterol, is

a common feature of atherosclerosis, a condition involving arterial damage, which may lead to ischemic heart disease, myocardial infarction, and cerebrovascular accidents.

The discovery of new drugs from traditional medicine is a novel phenomenon (Fig. 1). Christophe et al.[4] discovered glucose induced insulin secretion in vitro and ex vivo of 4-hydroxyisoleucine. Furthermore, in type 2 diabetic rat model the compound was active and partly corrected hyperglycemia and glucose tolerance. The lipid lowering activity in phytoconstituents such as 4-hydroxyisoleucine,[5] amyrin derivatives,[6] lupeol derivatives,[7] calophyllic acid and isocalophyllic acid mixture, [8] canophyllic acid,[8] amentoflavone,[8] and furanoflavonoids[9] etc had reported earlier.
Metformin (**I**) is currently used as antidiabetic agent in the treatment of type 2 diabetes (Figure 1). Metformin (**I**) and its analogues[10] were synthesized on the basis of a natural product lead, that is, galegine (**II**).[11] The synthetic cholesterol lowering statins such as fluvastatin (**III**),[12] cerivastatin[13] were synthesized on the basis of natural product lead, that is, mevastatin (**IV**).[14] The plant derived saponin derivative, pamaqueside (CP-148623),[15] has been reported for cholesterol absorption up to 35–40% and the fish oils, which contain fatty acids such as eicosapentaenoic acid and docosahexenoic acids, have been reported for their lowering activity on triglycerides and cholesterol.[16] The plant Aegle marmelos is commonly known as 'bael' in India,[17] belongs to the family of Rutaceae, widely used in Indian Ayurvedic medicine for the treatment of diabetes mellitus. Chatterjee and Bose[18] isolated the Aegeline (V) for the first time in 1952 and its chemical structure and stereochemistry has been elucidated by synthesis.[19] Various methods for the synthesis of optically active Aegeline (V) have also been appeared in the literature.20 Aegeline is a naturally occurring N-acylated-β-amino alcohol.[21]

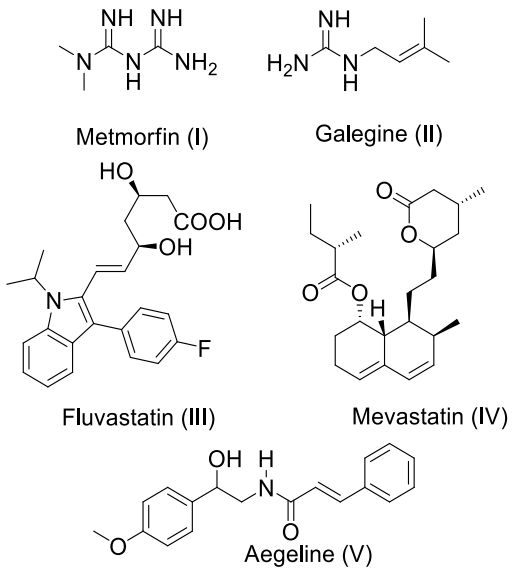


Figure 1. Naturally occurring and synthetic Antidiabetic and Antidyslipdemic agents

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, 2022

Aegeline is a naturally occurring N-acylated-1-amino-2-alcohol. This paper deals with comparative the study of N-acylated-1-amino-2-alcohols, and N-acylated-1-amino-3-aryloxy-2-propanols and their antihyperlipidemic and antioxidant activity.

2. Results and Discussion:

The synthesis of alkaloidal amide derivatives started with a reaction between p-methyl phenacyl bromide (**1**) and NaN_3 in MeOH to provide p-methylphenacylazide (**2**). The phenacyl azide (**2**) was reduced to give common synthon, p-methyl phenylacetamide (**3**) and the resultant p-methyl phenylacetamide was reacted with various acid/acid chlorides such as substituted cinnamic acids, substituted benzoic acid, phenylacetic acids and heterocyclic acids, provided the various amides **4–14** (Table 1) and subsequent reduction of ketone with $NaBH_4$ in MeOH at room temperature resulted in the synthesis of p-methyl phenyl ethanol amine derivatives **15–20** (Table 1). Male rats of Charles forest strain (100–150 g) were divided into four groups [control, triton-induced, triton+compound (**4–20**), and Gemfibrozil (100 mg/kg) treated] containing six rats in each group. In this experiment of 18 h, hyperlipidemia was developed by administration of triton WR-1339 (Sigma chemical company, St. Louis, MO, USA) at a dose of 400 mg/kg. b.w. intraperitoneally to animals of all the groups except the control. These derivatives were macerated with gum acacia (0.2% w/v), suspended in water and fed simultaneously with triton with a dose of 100 mg/kg po to the animals of treated group and the diet being withdrawn. Animals of control and triton group without treatment with compounds **4–20** were given same amount of gum acacia suspension (vehicle). After 18 h of treatment the animals were anaesthetized with thiopentone solution (50 mg/kg b.w.) prepared in normal saline and then 1.0 ml blood was withdrawn from retro-orbital sinus using glass capillary in EDTA coated Eppendorf tube (3.0 mg/ml blood).

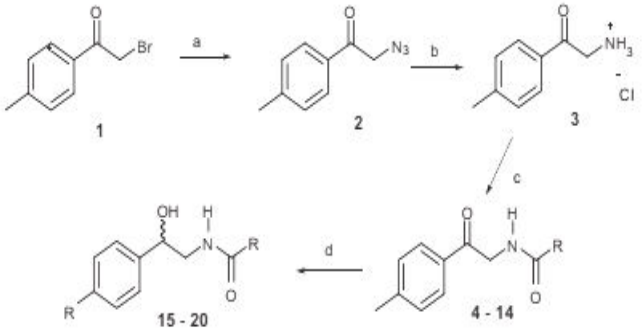


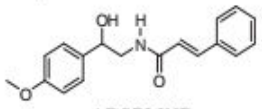
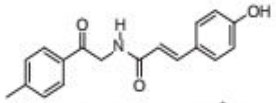
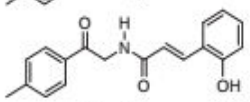
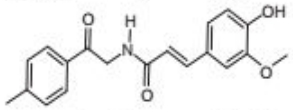
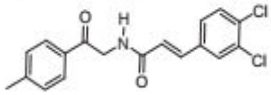
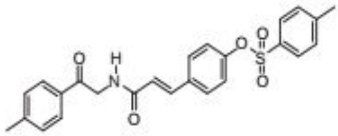
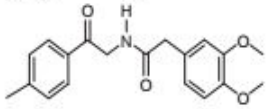
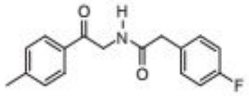
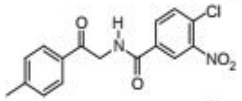
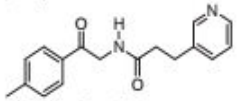
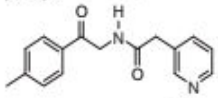
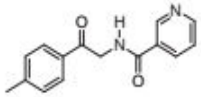
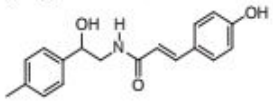
Figure 2. Synthesis of Aegeline analogues. Reagents: (a) NaN_3, MeOH and H_2O. (b) 10% Pd/C, concd HCl and dry MeOH. (c) acid, DEA, DIC, DCM and 0 °C to rt. (d) $NaBH_4$ and MeOH.

The blood was centrifuged at 4 C for 10 min and plasma was separated. Plasma was diluted with normal saline (ratio of 1:3) and used for analysis of total cholesterol (TC), triglycerides (TG) and phospholipids (PL) by standard enzymatic methods and post-heparin lipolytic activity (PHLA) were assayed using spectrophotometer and Beckmann auto-analyzer and standard kits purchased from Beckmann Coulter International, USA. The naturally occurring Aegeline (V) lowered the

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, 2022

TC by 24%, TG by 22% and PL by 23%, protein by 24% and also reactivated the postheparin lipolytic activity (PHLA) by 15% as compared to control at a dose of 100 mg/kg.12,20 All the synthesized compounds were also screened in the same model at a dose of 100 mg/kg.

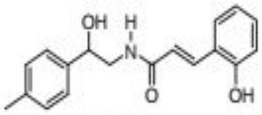
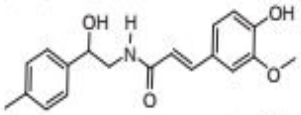
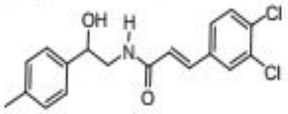
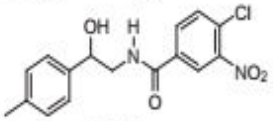
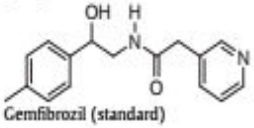
Table 1
Antihyperlipidemic activity of keto-amide (**4–14**) and amino-alcohol (**15–20**) series compounds in Triton induced hyperlipidemia model at a dose of 100 mg/kg

S. No	Compound	Total cholesterol[a]	Triglyceride[a]	Phospholipid[a]	Protein[b]	PHLA[c]
V	 AEGELINE	−24***	−22**	−23***	−24***	+14*
04		−22**	−21**	−23***	20**	+19*
05		−11*	−09	−10*	−08 NS	+10*
06		−05	−10*	−06	−10*	+13*
07		−12*	−12*	−12*	−13*	+06
08		−07	−04	−09	−06	+07
09		−10*	−12*	−14*	−14*	+12*
10		−14*	−11*	−15*	−19*	+06
11		−04	−09	−05	−09	+08
12		−24***	−22**	−24***	−21**	+20**
13		−07	−05	−07	−07	+08
14		−04	−02	−06	−04	+06
15		−07	−09	−09	−08	+07

.

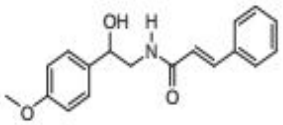
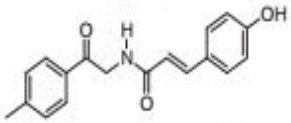
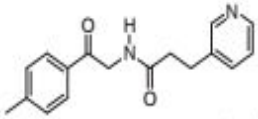
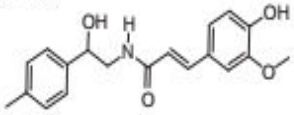
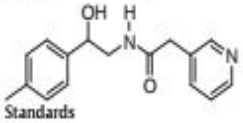
ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, 2022

Table 1 (continued)

S. No	Compound	Total cholesterol[a]	Triglyceride[a]	Phospholipid[a]	Protein[b]	PHLA[c]
16		−08	−09	−07	−08	+05
17		−24***	−23***	−22**	−21**	+21**
18		−16*	−14*	−13*	−15*	+14*
19		−05	−11*	−07	−11*	+08
20		−23***	−25***	−22**	−23***	+19*
	Gemfibrozil (standard)	−33***	−31***	−36***	−31***	+23***

Units of keto-amide series compounds: a: mg/dl; b: g/dl; c: n mol of free fatty acids formed/h/ml of plasma; d: Triton treated group compared with control and Triton plus drug treated group compared with Triton group: Values are mean ± SD of six rats, ***p <0.001; **p <0.01; *p <0.05; values without star = Non significant.

Table 2
Antioxidant activity of Aegeline and synthetic compounds

S. No	Compound	Dose (μg/ml)	Super oxide anions (O_2^-)[a]	Hydroxyl radicals (^-OH)[b]	Microsomal lipid peroxidation[b]
V		100 200	−19* −25***	−18* −22**	−12* −31***
	Aegeline				
4		100 200	−17* −31***	−17* −29***	−22** −29***
12		100 200	−24*** −31***	−19* −33***	−19* −29***
17		100 200	−21** −32***	−18* −27***	−19* −23***
20		100 200	−17* −31***	−17* −29***	−22** −29***
	Standards	200	−69*** (Allopurinol)	−45*** (Mannitol)	−63**,* (α-tocoferol)

Units: a: n mole formazone formed/minute. b: n mole MDA formed/h. Values are mean ± SD of six rats, ***p <0.001; **p <0.01; *p <0.05.

In the keto-amide series (**4–14**) compounds **4** and **12** showed good lipid lowering activity similar to the natural products. Compound **4** lowered the TC by 22%, TG by 21% PL by 23%, Protein by 20% and PHLA reactivation by 19%, where as **12** lowered the TC by 24%, TG by 22%, PL by 24%, Protein by 21% and reactivation of PHLA by 20%. In the hydroxyl amine series (**15–20**) compound **17** and **20** showed good lipid lowering activity. Compound **17** lowered the TC by 24%, TG by 23% and PL by 22%, Protein by 21% and PHLA reactivation by 21%. The amino-alcohol derivative with heterocyclic acid **20** lowered the TC by 23%, TG by 25% and PL by 22%, Protein by 23% and PHLA reactivation by 19%.

Recent studies have demonstrated that the generation of large quantities of reactive oxygen species can cause activation of lipid peroxidation, protein modification, which leads to cardiovascular diseases (CVD). Therefore, screened Aegeline (V) and synthetic compounds (**4–20**) for their antioxidant activity (Table 2). Superoxide anions were generated enzymatically by xanthine (160 mM), xanthine oxidase (0.04 U) and nitroblue tetrazolium (320 mM) in the absence or presence of compounds (100 mg/ml) in 100 mM phosphate buffer (pH 8.2). Fractions were sonicated well in phosphate buffer before use. The reaction mixtures were incubated at 37 °C and after 30 min the reaction was stopped by adding 0.5 ml glacial acetic acid. The amount of formazone formed was measured at 560 nm on a spectrophotometer. Percentage inhibition was calculated taking absorption coefficient of formazone as 7.2 103 M/cm. In another set of experiment, an effect of compounds on generation of hydroxyl radicals was also studied by non-enzymic reactants. Briefly hydroxyl radicals were generated in a nonenzymic system comprised of deoxyribose (2.8 mM), $FeSO4_7H_2O$ (2 mM), sodium ascorbate (2.0 mM) and H_2O_2 (2.8 mM) in 50 mM KH_2PO_4 buffer, pH 7.4 to a final volume of 2.5 ml. The above reaction mixtures in the absence or presence of compounds (100 mg/ml) were incubated at 37 °C for 90 min. Reference samples and reagent blanks were also run simultaneously. Malondialdehyde (MDA) content in both experimental and reference samples were estimated spectrophotometrically by Thio barbituric acid method as mentioned above. The natural products V exhibited moderate antioxidant activity at 200 lg/ml concentration. The compounds **4, 12, 17** and **20**, which are active in hyperlipidemia studies exhibited better antioxidant activity than the natural products at the same concentration (Table 2).

Similarly, the synthesis of N-acylated-β-amino alcohols (Fig. 3) via Ritter reaction, was started with the ring opening reaction of commercially available styrene oxide (**1)** in acetonitrile, in the presence of BF_3-OEt_2, which led to N-(2-hydroxy-2-phenylethyl) acetamide (**2**, Table 3) in good yield. Encouraged by this result similar reaction of styrene oxide (**1)** was performed with acrylnitrile and obtained respective N-(2-hydroxy-2-phenyl-ethyl) acrylamide (**3,** Table 3**)** in good yield. After the successful results with styrene oxide (**1**), oxiranes (**4-7**) were prepared in very good yields from 4-tert-butylphenol, 3-methoxyphenol, 4-chlorophenol and 3-methylphenol respectively by refluxing with epichlorohydrin in dry acetone in presence of potassium carbonate at 60ºC for 4h and employed in Ritter reaction in order to synthesize various new N-acyl-β-amino alcohols. The resultant oxiranes was treated with BF_3-OEt_2 in nitriles (acetonitrile,

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, 2022

acrylnitrile, benzonitrile and 4-methoxybenzonitrile) to provide N-acylated-β-amino alcohols (**8-21**, Table 3**)** in good yields.

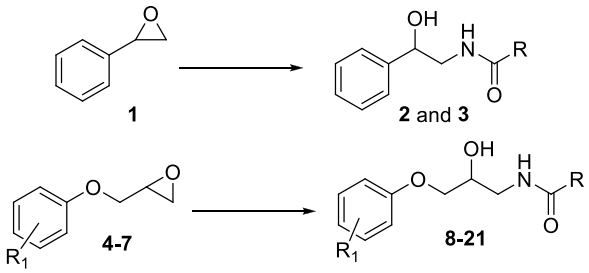


Figure 3. Reagents: BF_3-OEt_2, RCN, 80°C and H_2O

All the synthesized compounds (**8-21**) were screened in the in Triton-induced hyperlipidemic rats at dose of 100 mg/kg (Table 3). Compounds **3**, **11** and **13** showed good lipid lowering activity (Table 3). Compound **3** lowered the TC by 28%, TG by 28% PL by 26%, reactivation of PHLA by 17% and hepatic LPL by 36%, compound **11** lowered the TC by 26%, TG by 25% PL by 27%, reactivation of PHLA by 15% and hepatic LPL by 28%, compound **13** lowered the TC by 24%, TG by 23%, PL by 26%, reactivation of PHLA by 6% and hepatic LPL by 24% (Table 3 and Fig. 4). Standard drug Gemfibrozil (Gem) lowered the TC by 33%, TG by 31% PL by 35%, reactivation of PHLA by 18% and hepatic LPL by 42% (Table 3 and Fig. 4).

Comparison with keto amides, compound **4** lowered the TC by 22%, TG by 21% PL by 23%, Protein by 20% and PHLA reactivation by 19%, whereas **12** lowered the TC by 24%, TG by 22%, PL by 24%, Protein by 21% and reactivation of PHLA by 20%. In the hydroxyl amine series (**15–20**) compound **17** and **20** showed good lipid lowering activity. Compound **17** lowered the TC by 24%, TG by 23% and PL by 22%, Protein by 21% and PHLA reactivation by 21%. The amino-alcohol derivative with heterocyclic acid **20** lowered the TC by 23%, TG by 25% and PL by 22%, Protein by 23% and PHLA reactivation by 19%.

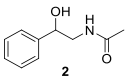
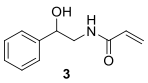
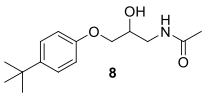
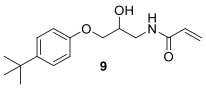
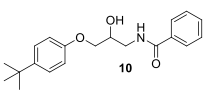
After the confirmation of most active compounds in the current series in primary screening, we further, evaluated the efficacy of compounds **3**, **11** and **13** in triton-induced hyperlipidemic rats at different doses in 50, 100 and 150 mg/kg body weight (Table 4). Compound **3** lowered the TC by 21% to 28%, PL by 22% to 27% and TG by 20% to 30% followed by increase in PHLA level by 12% to 18%. Compound **11** lowered the TC by 18% to 29%, PL by 16% to 28%, and TG by 18% to 27% followed by increase in PHLA level by 11% to 16% similarly compound **13** lowered the TC by 14% to 25%, PL by 17% to 28%, and TG by 16% to 26% followed by increase in PHLA level by 10% to 15% respectively. The results are shown in Table 4.

Further, the most active compounds **3**, **11** and **13** were tested for their effect on plasma lipoprotein lipids. As shown in Figure 4, the analysis of hyperlipidemic plasma of triton administered rats showed marked increase in the level of lipoprotein lipids and these effects were pronounced for VLDL and LDL followed by a decrease in HDL as compared to control rats.

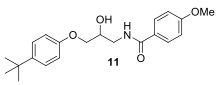
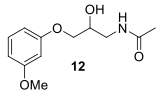
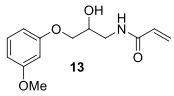
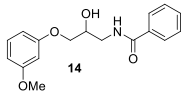
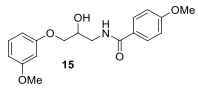
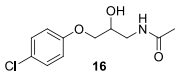
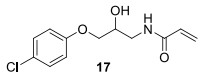
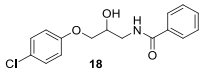
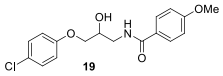
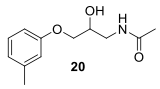
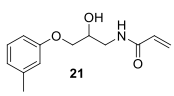
ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, 2022

Interestingly, the treatment with compounds **3**, **11** and **13**, significantly reversed the levels of VLDL, LDL and HDL, the complete lipid profile results are shown in Figure 4.
Further the compounds **3**, **11** and **14** was studied for hepatic-LPL activity in triton induced hyperlipidemic rats. Administration of triton in rats markedly decreased LPL activity in liver as shown in Figure 5. After treatment with compounds **3**, **11** and **14** significantly decreased the level of FFA followed by increase in LPL, complete activity results are shown in Figure 5. Compounds (**8-21**) were screened for their antioxidant activity (Table 4). The compounds **3**, **10**, **11** and **14** exhibited antioxidant activity (Table 4, Fig. 6), among them **3**, **11** and **14** are also active in hyperlipidemia studies.

Table 3. Percentage (%) change of plasma lipids with the treatment of compounds in Triton-induced hyperlipidemic rats at dose of 100 mg/kg body weight

Animal Groups	Lipids profile			PHLA (nmol of free fatty acids formed/h/ml of plasma)
	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	
Control	78.53±5.13	82.64±4.71	79.43±6.08	18.86±1.37
Triton	244.27±16.84 ^{C} (+3.110 Fold)	269.23±19.82 ^{C} (+3.257 Fold)	239.38±16.38 ^{C} (+3.013 Fold)	11.59±0.93 ^{C} (-38.54 Fold)
Triton+  2	195.41±12.33** (-20%)	212.69± 16.36** (-21%)	189.11± 14.28** (-21%)	12.98± 0.93* (+12%)
Triton+  3	175.87±10.56*** (-28%)	199.23±13.78*** (-26%)	172.35±11.99*** (-28%)	13.56±1.18* (+17%)
Triton+  8	219.84±17.26* (-10%)	239.61±13.67* (-11%)	208.26±18.61* (-13)	12.05±0.73 ^{NS} (+4%)
Triton+  9	217.40±14.83* (-11%)	242.30±15.48* (-10%)	210.65±12.96* (-12)	13.32±1.2 ^{NS} (+4%)
Triton+  10	202.74±15.91* (-17%)	226.15±14.26* (-16%)	203.47±18.21* (-15)	12.74±0.91* (+10%)

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, 2022

Triton+ 	180.75±13.49*** (-26%)	196.53±16.11*** (-27%)	179.53±13.73*** (-25)	11.93±0.52* (+15%)
Triton+ 	212.51±18.27* (-13%)	242.30±17.91* (-10%)	210.65±14.52* (-12)	12.28±0.88 NS (+6%)
Triton+ 	185.64±11.63*** (-24%)	199.23±16.19*** (-26%)	184.32±11.85*** (-23)	13.21±1.11* (+14%)
Triton+ 	217.40±16.62* (-11%)	242.30±21.68* (-10%)	215.44±17.33* (-10)	12.16±0.63 NS (+5%)
Triton+ 	222.28±29.35 NS (-9%)	247.69±15.82 NS (-8%)	217.83±13.29 NS (-9)	11.93±0.71 NS (+3%)
Triton+ 	224.72±18.69 NS (-8%)	253.07±19.47 NS (-6%)	220.22±18.46 NS (-8)	12.63±0.66 NS (+3%)
Triton+ 	214.95±17.32* (-12%)	242.30±17.83* (-10%)	213.04±17.83* (-11)	11.93±0.79 NS (+9%)
Triton+ 	227.17±12.87 NS (-7%)	255.76±22.31 NS (-5%)	220.22±15.39 NS (-8)	12.51±0.96 NS (+3%)
Triton+ 	210.07±14.63* (-14%)	231.53±18.72* (-14%)	208.26±16.26* (-13)	13.67±0.51 NS (+8%)
Triton+ 	205.18± 13.81* (-16%)	231.53±18.39* (-14%)	205.86± 17.38* (-14%)	12.28±0.82NS (+6%)
Triton+ 	214.95± 18.92* (-12%)	242.30±12.79* (-10%)	208.26± 18.34* (-13%)	12.05±0.77 NS (+4%)
Triton+	163.66±11.38***	185.76±11.66***	155.59±10.72***	13.67±0.51*

Gemfibrozil	(-33%)	(-31%)	(-35)	(+18%)

Each parameter represents pooled data from 6 rats/group and values are expressed as mean ± S.D. $^{c}P < 0.001$, Triton treated group compared with control group and $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ Triton plus compounds groups compared with Triton treated group only. NOTE: NS (non significant) and F (Fold change over control group).

Table 4. Percentage (%) change of plasma lipids with the treatment of compounds **3**, **11** and **13** in triton-induced hyperlipidemic rats at different doses

Animal Groups	Lipids profile			PHLA (nmol of free fatty acids formed/h/ml of plasma)
	TC (mg/dl)	PL (mg/dl)	TG (mg/dl)	
Control	83.26±5.82	80.19±6.31	79.68±4.83	20.03±1.61
Triton	263.33±20.08^{c}(+3.16 Fold)	251.69±16.59^{c}(+3.13Fold)	248.92±18.23^{c}(+3.12 Fold)	13.11±1.22^{c}(-34.54 Fold)
Triton+ 3 50mg/kg	208.03±13.36**(-21%)	196.31±11.83**(-22%)	199.13±13.61**(-20%)	14.68±1.08*(+12%)
100mg/kg	189.59±11.23***(-28%)	186.25±13.66***(-26%)	179.22±11.76***(-28%)	15.33±1.14*(+17%)
150mg/kg	189.03±15.44***,# (-28%)	183.73±15.73***,# (-27%)	174.24±14.59***,# (-30%)	15.46±1.12*,# (+18%)
Triton+ 11 50mg/kg	215.93±16.22*(-18%)	211.41±13.38*(-16%)	204.11±14.16*(-18%)	14.55±1.26*(+11%)
100mg/kg	194.86±14.31***(-26%)	183.73±12.49***(-27%)	186.69±12.27***(-25%)	15.05±1.20*(+15%)
150mg/kg	186.96±11.86***,# (-29%)	181.21±13.92***,# (-28%)	181.71±13.28***,# (-27%)	15.20±1.09*,# (+16%)
Triton+ 13 50mg/k	226.46±15.88*(-14%) 200.13±16.19***(-	208.90±15.64*(-17%) 186.25±14.38***(-	209.09±12.82*(-16%) 191.66±15.22***(-23%)	14.42±1.28*(+10%) 14.94±1.21*(+

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, 2022

g	24%)	26%)	184.20±14.46***, # (-	14%)
100mg/ kg	197.49±13.21***, # (-25%)	181.16±15.18***, # (-28%)	26%)	15.07±1.33*, # (+15%)
150mg/ kg				

Each parameter represents pooled data from 6 rats/group and values are expressed as mean ± S.D. $^{c}P < 0.001$, Triton treated group compared with control group and $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ Triton plus compounds groups compared with Triton treated group only. NOTE: # non significant between 100 and 150mg/kg doses in treated groups of compounds; F (Fold change over control group).

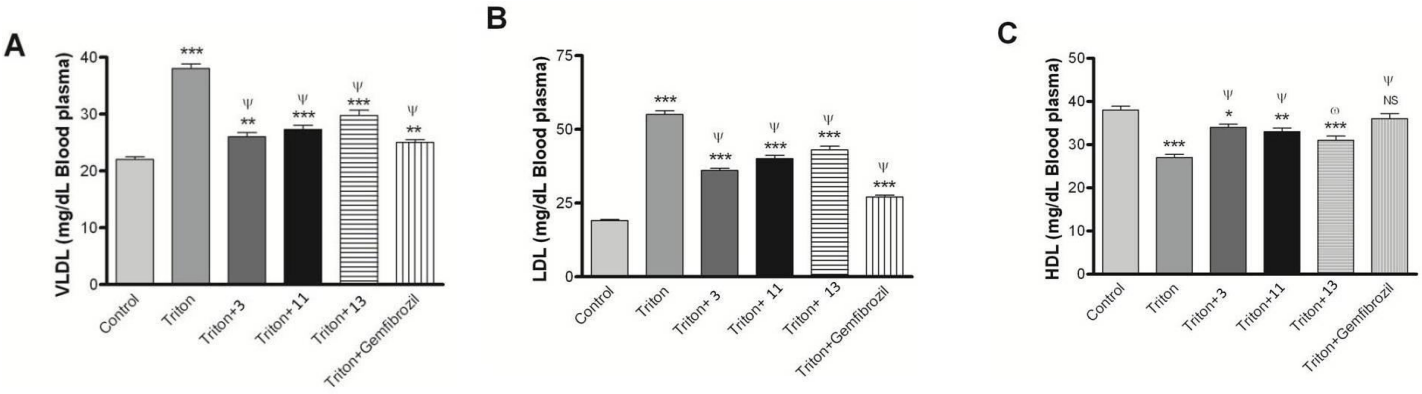


Figure 4: Effect of compounds **3**, **11** and **13** on lipoprotein metabolism in triton induced hyperlipidemic rats. Blood was drawn after 18 hours of hyperlipidemia was developed by administration of triton WR-1339 with and without compounds **3**, **11** and **13** and gemfibrozil (100 mg/kg). Compounds **3**, **11** and **13** and gemfibrozil (Gem) improve lipoprotein lipids profile level in triton induced hyperlipidemic rats. Values are expressed as the mean ± SD (n = 6). *P < 0.05; **P < 0.01; ***P < 0.001; NS (non significant) compared to triton treated only and $^{\omega}P < 0.01$; $^{\Psi}P < 0.001$ comparison triton and triton plus compound treated groups

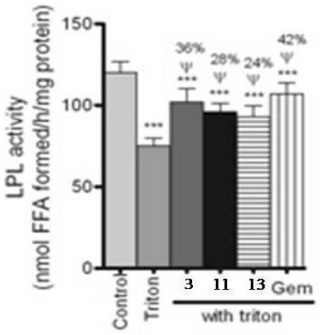


Figure 5: Compounds **3**, **11** and **13** at dose of 100mg/kg, re-activate hepatic LPL activity by 36%, 28% and 24% in triton induced hyperlipidemic rats. Each parameter represents pooled data from 6 rats/group and values are expressed as mean±S.D. $^{***}P < 0.001$ between control and

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, 2022

triton, triton plus compound treated rats groups gemfibrozil (100 mg/kg) taken as standard drug. ΨP < 0.001 between triton and triton plus compound treated rats groups gemfibrozil (Gem)

Table 4. Effect of compounds on generation of superoxide anions, hydroxyl radicals and lipid-peroxidation

Series of compounds	Dose (µg/ml	Superoxide anions (%) (n mol formazone formed/minute)	Hydroxyl radicals (%) (n mol MDA formed/h/mg protein)	Lipid-peroxidation (%) (n mol MDA formed/h/mg protein)
2	200	-17*	-14*	-18*
3	200	-26***	-23***	-25***
8	200	-11*	-13*	-14*
9	200	-14*	-12*	-13*
10	200	-27***	-29***	-26***
11	200	-33***	-35***	-34***
12	200	-17*	-15*	-19*
13	200	-25***	-23***	-23***
14	200	-14*	-17*	-15*

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, 2022

15	200	-17*	-19*	-19*
16	200	-11*	-10*	-12*
17	200	-21**	-20***	-21**
18	200	-16*	-18*	-15*
19	200	-20**	-20**	-22**
20	200	-13*	-10*	-15*
21	200	-16*	-12*	-17*
Standards	200	-43*** (Allopurinol)	-47*** (Manitol)	-50*** (α-tocopherol)

Each value is mean±SD of six values, $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ experimental values compared with control values NOTE: ^{NS} (non significant)

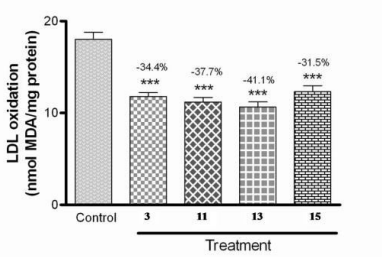


Figure 6: Compounds **3**, **11**, **13** and **15** reduced the LDL-oxidation at dose of 200µg/ml in normal donor blood sample. Data expressed as mean ± S.D. $^{***}P < 0.001$compared to treated values with Control

3. Conclusion:

Among alkaloidal amides (**4–20**) related to natural product Aegeline (V) having antihyperlipidemic and antioxidant activity. Some of the compounds of this series (**4, 17** and **20**) are equipotent to the natural product **V** in antihyperlipidemia studies and better antioxidants than the natural product **V**. Compound **12** showed better antihyperlipidemic and antioxidant profile than the natural product **V**. Other series of N-acyl-β-amino alcohols (**8-21**) were synthesized in one step via Ritter reaction on the basis of natural product lead i.e aegeline and evaluated their antihyperlipidemic and antioxidant activity. From this series compounds **3**, **11** and **14** are turned out to be active in antihyperlipidemic studies and also exhibited antioxidant activity. Comparison study revealed that N-acyl-β-amino alcohols are more potent that keto amides and amino alcohols.

4. References and notes

1. Eghdamian, E.; Ghose, K. Drugs of Today. **1998**. 34, 943.
2. McGill, H. C., Jr. Geographical Pathology of Atheroslclerosis; Williams and Wiken Co.: Baltimore, 1985.
3. http://www.americanheart.org/statistics. (American Heart Association: 2001 Heart and Stroke Statistical Update, Dallas Texas: American Heart Association, 2000).
4. Christophe, B.; Manteghetti, M.; Gross, R.; Baissac, Y.; Jacob, M.; Petit, P.; Sauvaire, Y.; Ribes, G. Eur. J. Pharma. **2000**, 390, 339.
5. Narender, T.; Anju, P.; Shweta; Khaliq, T.; Saxena, R.; Bhatia, G.; Chander, R. Bio-org. Med. Chem. Lett. **2006**, 16, 293.
6. Narender, T.; Khaliq. T.; Singh, A. B.; Joshi, M. D.; Mishra, P.; Chaturvedi, J. P.; Srivastava, A. K.; Maurya, R.; Agarwal, S. C. Eur. J. Med. Chem. **2009**, 44, 1215.
7. Reddy, K. P.; Singh, A. B.; Puri, A.; Srivastava, A. K.; Narender, T. Bio-org. Med. Chem. Lett. **2009**, 19, 4463.
8. Prasad, J.; Shrivastava, A.; Khanna, A. K.; Bhatia, G.; Awasthi, S. K.; Narender, T. Phytomedicine, **2012**, 19, 1245.
9. Narender, T.; Khaliq, T.; Anju, P.; Chander, R. Bio-org. Med. Chem. Lett. **2006**, 16, 3411.
10. Werner, E. A.; Bell, J. J. Chem. Soc. **1922**, 221, 1790; Shapiro, S. L.; Parrino, V. A.; Freedman, L. J. Am. Chem. Soc. **1959**, 81, 3728.
11. Bailey, C. T. Diabetic Care **1989**, 12, 553.
12. Deslypere, J. P. Curr. Ther. Res. **1995**, 56, 111.
13. McClellan, K. J. Drugs **1998**, 55, 415.

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 7, 2022

14. Yamamoto, A.; Yamamura, T.; Yokoyama, S.; Sudo, H.; Matsuzara, Y. Int. J. Clin. Pharmacol. Ther. Toxicol. **1984**, 22, 493.
15. McCarthy, P. A.; Deivinno, M. P.; Morchouse, L. A. J. Med. Chem. **1996**, 39, 1935.
16. Bang, H. O.; Dyerberg, J.; Nielsen, A. B. Lancet **1971**, 1, 1143; Bang, H. O.; Dyerberg, J. Acta Med. Scand. **1972**, 192, 85; Bang, H. O.; Dyerberg, J.; Hjorne, N. Acta Med. Scand. **1975**, 200, 69.
17. Kirtikar, B. D.; Basu, K. R. Indian medicinal plants Part I, **1993**.
18. 18. Chatterjee, A.; Bose, S. J. Ind. Chem. Soc. 1952, 29, 425.
19. Chatterjee, A.; Bose, S.; Srimay, S. K. J. Org. Chem. 1959, 24, 687.
20. Brown, R. F. C.; Jackson, W. R.; McCarthy, T. D. Tetrahedron: Asymmetry 1993, 4, 205; Yadav, J. S.; Reddy, P. T.; Nanda, S.; Rao, A. B. Tetrahedron: Asymmetry 2001, 24, 3381; Kamal, A.; Shaik, A. A.; Mahendra, S.; Malik, M. S. Tetrahedron: Asymmetry 2004, 15, 3939; Sadyandy, R.; Fernades, A. R.; Kumar, P. ARKIVOC
21. Narender, T.; Rajendar. K.; Sarkar, S; Singh, V. K.; Chaturvedi, U.; Khanna, A. K.; Bhatia, G. Bio-org. Med. Chem. Lett. **2011**, 21, 6393.