Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 4, 2014

Original Article

# ANTI-INFLAMMATORY ACTIVITY OF TELMISARTAN AND ROSUVASTATIN IN VARIOUS ANIMAL MODELS

**ANAND S[1], MUNIAPPAN M[1], SANGAVAI M[1], PARTHIBAN R[1].**

[1]Department of Pharmacology, Sree Balaji Medical College, Chrompet, Chennai

Email: sananddr@gmail.com

*Received: 24 Jan 2014 Revised and Accepted: 09 Feb 2014*

**ABSTRACT**

**Objective:** To study the anti-inflammatory activity of telmisartan and rosuvastatin in various animal models.

**Methods:** Anti-inflammatory activity of telmisartan and rosuvastatin alone and in combination is assessed in carrageenan induced paw enema in rats; formalin induced arthritis in rats, in all these tests the comparator is aspirin.

**Results**: In carrageenan induced paw oedema, rosuvastatin and telmisartan showed anti-inflammatroy activity, while the combination group had a significant activity comparable to aspirin. In formalin induced arthritis, all groups showed more than 60% of inhibition of inflammation, while the combination group and aspirin showed more than 80% inhibitions.

**Conclusion:** These results show that rosuvastatin had more anti-inflammatory effect than telmisartan, but the combination of these drugs proved to have significant activity comparable to aspirin. So these drugs have potential as adjuvants or standalone drugs in coexisting inflammatory disorders and dyslipidaemia, hypertension.

**Keywords**: Anti-inflammatory effect, Telmisartan, Rosuvastatin, Pleiotropic effects.

## INTRODUCTION

Many drugs like non-steroidal anti-inflammatory drugs and corticosteroids are being used in modern medical practice to supress pain and inflammation. The drawback of these drugs is they provide symptomatic relief and long-term use of these drugs is associated with serious adverse effects. Hence, the search for a new, safe analgesic and anti-inflammatory drug is on-going.

Vascular wall inflammation plays a key role in the pathogenesis and progression of atherosclerosis, cardiovascular disease and hypertension. Usually hypertension accentuates the progression of atherosclerosis that has an inflammatory component which also plays an integral role in its pathogenesis[**1**], and which is also present in other conditions associated with cardiovascular events, such as metabolic syndrome[**2**] and diabetes mellitus[**3**]. Indeed, inflammation is now recognized as a central mechanism contributing to progression of cardiovascular disease in general, and may be involved in the triggering of myocardial ischemia and infarction[**4**]. Isolated systolic hypertension results from age associated vascular stiffening and reduced compliance[**5**]. Arterial stiffness increases with advancing age and in the presence of other cardiovascular risk factors, including hypertension, the metabolic syndrome, diabetes, obesity, hypercholesterolemia, and elevated levels of C-reactive protein.

It is also suggested that many chronic inflammatory pathologies is usually found to be coexisting in people who are obese. Obesity is found to be associated with modest risk of developing rheumatoid arthritis. Given the rapidly increasing prevalence of obesity, this has had a significant impact on rheumatoid arthritis incidence and may account for much of the recent increase in the incidence of rheumatoid arthritis[**6**]. Also there are many recent studies that allow us to better understand the relationships between osteoarthritis and obesity. Although it is evident that mechanical components contribute to joint destruction in overweight people, osteoarthritis is considered not only a disease of articular cartilage but also a systemic disorder in which circulating factors linked to altered lipid and glucose metabolism may explain the diversity of pathophysiological changes found in generalised osteoarthritis[**7**].

Treatment of arthritis in modern medicine is currently limited to drugs that provide only symptomatic relief, and these drugs are associated with serious adverse effects. Hence, research for finding a better and safe drug for osteoarthritis has been a continuous process.

The elderly people almost have one or more other major disease conditions, even life-threatening conditions which may be of inflammatory in origin. Also they have senescent changes in all organ systems, whether the heart is normal or diseased. If at all understanding the pathogenesis of the symptoms and signs to establish a diagnosis and prognosis is difficult, it becomes even more challenging for managing them with drugs with their geriatric changes like age related reduction in hepatic blood flow and hepatocyte mass and primary aging changes in hepatic sinusoidal endothelium. This has an effect on drug transfer and oxygen delivery and causes reduction of hepatic drug clearance. Age related changes in renal clearance is evident, although renal clearance reduction in older people is predominantly disease-related and is poorly estimated by standard methods. The geriatric dosing axiom, "start low and go slow" is based on pharmacokinetic considerations and concern for adverse drug reactions since there is lack of clinical trial data[**8**].

If a single drug can be given to a patient for more than one indication with such coexisting comorbid conditions, it can potentially reduce their drug load and minimize the drug toxicity. This may also prove to be a cost effective method of treatment.

Statins have been shown to decrease the secretion of pro-inflammatory cytokines IL-6 (interleukin-6) and IL-8 (interleukin-8) from macrophages, and inhibit the release of the chemokine CCL2/MCP-1 (macrophage chemotactic protein-1) from these cells. The molecular mechanisms sub serving such anti-inflammatory and/or immunomodulatory activities are unclear [**9**][**10**]. Angiotensin II increases adhesion molecules, cytokines and chemokines and exerts a proinflammatory effect on leucocytes, endothelial cells and vascular smooth muscle cells. Telmisartan is a highly selective AT1-receptor antagonist act as a partial agonist on the nuclear peroxisome proliferator-activated receptor-γ (PPAR- γ)

that has been reported to exert anti-oxidative and anti-inflammatory effects[**11**]. Peroxisome proliferator-activated receptor γ (PPAR- γ) partial agonist activity regulates metabolic and inflammatory pathways, and improves left ventricular functions[**11**][**12**]. Rosuvastatin a lipid lowering drug and Telmisartan an anti-hypertensive drug if found to be having anti-inflammatory property, then it would be a great boon to geriatric patients who are suffering with number of comorbidities. Hence, this study was planned to evaluate and compare the anti-inflammatory actions of rosuvastatin and telmisartan in different animal models of inflammation.

## MATERIALS AND METHODS

### Experimental Animals

Adult Wistar albino rats (*Rattus norvegicus*) weighing between 200 to 240 gram and Swiss Mice (*Mus musculus*) of either sex weighing 25 – 30 gram were purchased from King Institute of Preventive Medicine, Guindy, Chennai and maintained in the Central Animal House, Sree Balaji Medical College and Hospital, Chennai, India for acclimatization. All experiment was performed with Institutional Animal Ethics Committee approvalnumbered 001/01/IAEC/2013 and under CPCSEA guidelines.

### Experimental Drugs

Rosuvastatin (from Micro Labs Ltd), Telmisartan (from Micro Labs Ltd) and Aspirin (from Zydus Cadila Healthcare Ltd) were obtained by pure powdered form and given in dosage of Rosuvastatin 5 mg/kg[**13**][**14**][**15**], Telmisartan 2 mg/kg[**16**][**17**][**18**][**19**]and aspirin dose of 100 mg/kg[**20**][**21**][**22**] orally by gavage feeding tube. For all the oral drugs carboxymethyl cellulose is used as a solvent and 1% Carrageenan via intra-dermal route and 2% Formalin via subcutaneous route as inflammatory agents. In this study, dosages used for evaluation of both analgesic and anti-inflammatory activities were in accordance with their respective indication provided in previous published studies[**23**][**24**][**25**][**26**][**27**].

### Acute anti-inflammatory action

### Carragennean induced paw oedema.

To assess acute inflammatory action, carrageenan induced paw oedema is used[**28**]. The experimental drugs were given by oral gavage one hour before the start of experiment. With the help of 27 gauge ½-inch needle 0.1 ml of 1% carrageenan is intra-dermally administered into the plantar surface of the right hind paw of rats. The acute phase of inflammatory reaction, i.e., oedema volume of right hind paw was determined using a plethysmometer modified by Harayal Singh and Ghosh[**29**] at time points prior to (basal) and 30 min, 60 min and 120 min after carrageenan injection.

$$P\ \% = \frac{Pc - Pt}{Pc} \times 100$$

Where,

P%, Percentage inhibition at given time interval

$P_c$, Paw volume in control group

$P_t$, Paw volume in test group

### Chronic anti-inflammatory activity

### Formalin induced arthritis

To quantify chronic inflammatory action, formalin induced arthritis method is used. The experimental drugs were given by oral gavage continuously daily for ten days with exactly 24 hours dosing interval for subsequent doses. With the help of 27 gauge ½-inch needle 0.1 ml of 2 % formalin is administered subcutaneously under the plantar aponeurosis of right hind paw of rats on day 01 and day 03 of the experiment. The chronic phase of inflammatory reaction of paw thickness is measured by linear cross section (LCS) with Vernier calliper on day 01 during treatment and at end of day 10.

$$L\ \% = \frac{Lc - Lt}{Lc} \times 100$$

Where,

L%, Percentage anti-inflammatory effect

$L_c$, Mean difference in linear cross section in control group

$L_t$, Mean difference in linear cross section in test group

### Statistical Analysis

Results are expressed as mean ± Standard Error of Mean (SEM). Data was analysed using IBM SPSS Version 20. Comparison between different groups was done by One-Way Analysis of Variance (ANOVA) followed by a post hoc test Tukey's. P value less than 0.05 was considered statistically significant.

## RESULTS

The Table1 shows the mean paw volume at all-time points for all groups. At time point 30 minutes the mean paw volume of rosuvastatin, telmisartan and combination group showed no difference from control, but aspirin had significant difference from control in reducing the paw oedema with P value <0.001. At time points 60 minutes and 120 minutes aspirin, rosuvastatin,, telmisartan and combination groups when compared to control showed a P value of <0.001.

But at 120 minute when the groups were compared with aspirin, control showed greater difference in mean paw volume with significance with P <0.001 followed by Rosuvastatin and Telmisaratan with P value <0.05. Also at the same time point there were no statistically significant difference between aspirin and the combination group, this signifies combined effect of study drugs is similar to aspirin, even though the mean paw volume was greater in combination group.

**Table 1: Table showing mean volume of paw oedema in ml in carrageenan induced paw oedema.**

| Groups | Basal | 30 Min | 60 Min | 120 Min |
|---|---|---|---|---|
| Group I: Control | 0.417 ±0.031 | 0.750 ±0.034 | 0.950 ±0.067 | 0.900 ±0.037 ^ |
| Group II: Aspirin (standard) | 0.400 ±0.026 | 0.517 ±0.031 * | 0.467 ±0.021 * | 0.383 ±0.04 * |
| Group III: Rosuvastatin | 0.417 ±0.031 | 0.700 ±0.026 | 0.567 ±0.021 * | 0.517 ±0.031 *^ |
| Group IV: Telmisartan | 0.417 ±0.031 | 0.733 ±0.033 | 0.600 ±0.026 * | 0.550 ±0.022 *^ |
| Group V: Rosuvastatin + Telmisartan | 0.400 ±0.026 | 0.650 ±0.022 | 0.533 ±0.042 * | 0.450 ±0.022 * |

*P < 0.001 when compared to control of same time point., ^P <0.05 when compared to aspirin of same time point.

Table 2 shows the percentage of inhibition of paw oedema for all study dugs. Percentage inhibition of acute inflammation was greater in aspirin group when compared to rosuvastatin, telmisartan and combination group at all-time intervals. Similarly, the percentage inhibition at 120 minutes of combination group (50.00%) is greater than that of Rosuvastatin (42.59%) and Telmisartan (38.89%). It can also be seen at the same time point that the percentage inhibition of combination group (50.00%) is closer to aspirin (57.41%).

**Table 2: Table representing the percentage inhibition of paw oedema**

| Groups | % Inhibition at 30 Min | % Inhibition at 60 Min | % Inhibition at 120 Min |
|---|---|---|---|
| Aspirin | 31.11% | 50.88% | 57.41% |
| Rosuvastatin | 6.67% | 40.35% | 42.59% |
| Telmisartan | 2.22% | 36.84% | 38.89% |
| Rosuvastatin + Telmisartan | 13.33% | 43.86% | 50.00% |

Table 3 shows the mean of Day 01 and Day 10 linear cross sections. The mean difference between linear cross section on tenth day and first day was calculated for each group.

The mean differences in linear cross section of all the drug treated groups were statistically significantly when compared to control (P <0.001). There is a significant difference in linear cross section of Rosuvastatin and Telmisartan to that of aspirin group (P<0.001). But there is no significant difference between combination group and aspirin which shows that combined action of rosuvastatin and telmisartan is as effective as aspirin. The least difference in mean linear cross section was found in the aspirin group followed by combination group.Also the percentage of anti-inflammatory effect of aspirin was greater with 90.37% followed by combination group with 83.05% which is followed by rosuvastatin and telmisartan with 70.71% and 65.89% respectively.

**Table 3: Table showing mean Linear Cross Section (LCS) in mm. Also showing percentage of anti-inflammatory effect in formalin induced arthritis.**

| Group | Initial LCS | Day 10 LCS | Difference in LCS | % anti-inflammatory effect |
|---|---|---|---|---|
| Control | 3.960 ±0.066 | 7.283 ±0.157 | 3.323 ±0.168 ^ | Not Applicable |
| Aspirin (standard) | 3.883 ±0.076 | 4.203 ±0.017 | 0.320 ±0.069 * | 90.37% |
| Rosuvastatin | 3.877 ±0.060 | 4.850 ±0.29 | 0.973 ±0.075 *^ | 70.71% |
| Telmisartan | 3.897 ±0.056 | 5.030 ±0.021 | 1.133 ±0.041*^ | 65.89% |
| Rosuvastatin + Telmisartan | 3.890 ± 0.064 | 4.453 ±0.056 | 0.563 ±0.074 * | 83.05% |

*p < 0.001 when compared to control, ^ p<0.001 when compared to aspirin

**DISCUSSION**

Many inflammatory conditions are associated with disorders of cardiovascular system. Cardiovascular disorders like dyslipidaemia, hypertension etc. is usually known to occur together due to sedentary modern life style. These conditions with other chronic inflammatory conditions like arthritis and also the inevitable aging can cause function restricting pain. Statins have been widely used in the treatment of dyslipidaemia since long. More recently there has been an interest in the analgesic and anti-inflammatory activities of statins following reports about their ability to relieve pain and inflammation[**30**][**31**]. Also angiotensin receptor blocker is used in hypertension which is a usual comorbid condition and it is also suggested to have anti -inflammatory actions.

Carrageenan is a mucopolysaccharide extract, discovered by the British pharmacist Stanford in 1862[**32**]. Carrageenan is the phlogistic agent of choice for testing anti-inflammatory drugs as it is not known to be antigenic and is devoid of apparent systemic effects. Hence the inflammatory response induced by carrageenan is acute and nonimmune. Carrageenan-induced hind paw oedema has become standard experimental model of acute inflammation. This model exhibits a high degree of reproducibility and has significant predictive value for clinically useful anti-inflammatory drugs[**33**]. Carrageenan-induced oedema is a biphasic response. The first phase for the first 2 hours is mediated through the release of histamine, serotonin and kinins, whereas the second phase is due to the release of prostaglandin and slow reacting substances which starts only after 3 to 4 hours.[**34**]. Inhibition of carrageenan induced oedema by rosuvastatin and telmisartan can therefore be attributed to their ability to inhibit release of histamine, serotonin and kinins. This inflammation is usually quantified by increase in paw size using a plethesmometer[**29**]. It is clearly evident that rosuvastatin, telmisartan and their combinations have a good anti-inflammatory activity when compared to the control. Also the percentage of inhibition of inflammation was very low at 30 minutes but it has increased many folds with in next 30 minutes and the increase was gradual for the next hour. However, at 120 minutes the combination group fared better in respect to inhibiting acute inflammation just below aspirin. The synergistic action of the two drugs is also obvious from the observations.

Formalin a potent inflammatory agent is used by Brownlee in 1950 to induce arthritis in animals. When the formalin is reinforced subsequently it would produce inflammation which would resemble chronic inflammation mimicking arthritis[**35**]. The nociceptive effect of formalin is biphasic, an early neurogenic component followed by a later tissue mediated response [**36**]. Thus formalin induced arthritis is a model used for the evaluation of an agent with probable anti-proliferative activity. This experiment is associated with the proliferative phase of inflammation[**37**]. All group of drugs showed a significant inhibition of chronic inflammation with maximum effect obviously for aspirin and comparable to that of combination group. There is a significant inhibition of chronic inflammatory action for the combination group, working synergistically when compared to rosuvastatin and telmisartan given alone. Also percentage inhibition of inflammation is more than 80% for aspirin and combination group. Inflammation protective action is present in both drugs and it is also seen to be working synergistically. Chronic inflammation protective effect is more compared to the inhibition of acute inflammation. The important finding will be that with the combined action of drugs there is no significant difference in protection of chronic inflammation from aspirin. In other words these both drugs together can be compared with an anti-inflammatory drug.

Many investigations are on-going to explore the mechanisms underlying the anti-inflammatory activity of statins and angiotensin receptor blockers. Rosuvastatin therapy significantly decreased high-sensitivity C-reactive protein (a bio-marker of inflammation) levels in patients of systemic sclerosis[**38**].

It is also demonstrated for the first time, in a clinical trial, the anti-inflammatory and antioxidant properties of telmisartan, previously observed only in pre-clinical models[**39**]. Moreover, the beneficial

effect shown by telmisartan may be explained by its multiple therapeutic characteristics. Indeed, telmisartan is a unique ARB with selective PPAR-γ-modulating activity which affects nitric oxide bioavailability thus leading to its anti-inflammatory, antioxidant and anti-proliferative effects on vascular wall cells[**40**]. Telmisartan was also shown to be able to increase the number of regenerative endothelial progenitor cells and improve endothelial function independently of its blood pressure lowering action[**41**]. Additionally, it has also been shown to play a role in lipid and glucose metabolism[**42**].Hence, it appears that rosuvastatin and telmisartan can effectively suppress both acute as well as chronic inflammation by inhibiting the release of various mediators of inflammation.

Further investigations for all drugs in both statin group and angiotensin receptor blocker group for their pleiotropic effect must be undertaken so that new indications of these drugs can come to light.

**CONFLICT OF INTEREST:** None

**REFERENCES**

1. Libby P, Ridker PM. Inflammation and atherosclerosis. Circulation. 2002; 105:1135–1143.
2. Chae CU, Lee RT. Blood pressure and inflammation in apparently healthy men. Hypertension 2001; 38:399–403.
3. Festa A, D'Agostino RJ. Chronic subclinical inflammation as part of the insulin resistance syndrome: IRAS.. Circulation 2000; 102:42–47.
4. P.Libby. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 2001; 104:365–372.
5. O'Rourke MF, Staessen JA, Vlachopoulos C, et al. Clinical applications of arterial stiffness definitions and reference values. Am J Hypertens 2002; 15:426–444.
6. Crowson CS, Matteson EL. Contribution of obesity to the rise in incidence of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2013 Jan;65(1):71-7.
7. P Pottie et al. Obesity and osteoarthritis: more complex than predicted! Ann Rheum Dis 2006;65:1403-1405.
8. McLean AJ, Le Couteur DG. Aging biology and geriatric clinical pharmacology. Pharmacol Rev. 2004 Jun;56(2):163-84.
9. McKay A, Leung BP, McInnes IB, Thompson NC, Liew FY. A novel anti-inflammatory role of simvastatin in a murine model of allergic asthma. J Immunol 2004;172:2903-8.
10. Youssef S, Stüve O, Patarroyo JC, Rulz PJ, Radosevich JL, Hur EM, et al. HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverse paralysis in central nervous system autoimmune disease.. Nature 2002;420:78-84.
11. Benson, S.C., Pershadsingh, H.A., Ho, C.I., Chittiboyina, A., et al., Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARc-modulating activity. 2004 Hypertension 43, 993–1002.
12. Schupp, M., Janke, J., Clasen, R., Unger, T., Kintscher, U. Angiotensin type 1 receptor blockers induce peroxisome proliferator activated receptor-gamma activity. 2004 Circulation 109, 2054–2057.
13. Xinying Hu, MD et al., Rosuvastatin Changes Cytokine Expressions in Ischemic Territory and Preserves Heart Function after Acute Myocardial Infarction in Rats. J CARDIOVASC PHARMACOL THER March 2013 vol. 18 no. 2 162-176.
14. Ma YX, Li WH, Xie Q. Rosuvastatin inhibits TGF-beta1 expression and alleviates myocardial fibrosis in diabetic rats. Pharmazie. 2013 May;68(5):355-8.
15. Wingard CJ, Moukdar F, Prasad RY, Cathey BL, Wilkinson L. Reversal of voltage-dependent erectile responses in the Zucker obese-diabetic rat by rosuvastatin-altered RhoA/Rho-kinase signaling. J Sex Med. 2009 Mar;6 Suppl 3:269-78.
16. Wienen W, Richard S, Champeroux P, Audeval-Gerard C. Comparative antihypertensive and renoprotective effects of telmisartan and lisinopril after long-term treatment in hypertensive diabetic rats. J Renin Angiotensin Aldosterone Syst. 2001 Mar;2(1):31-6.
17. Kishi T, Hirooka Y, Sunagawa K. Telmisartan Reduces Mortality and Left Ventricular Hypertrophy with Sympathoinhibition in Rats with Hypertension and Heart Failure. Am J Hypertens (2013) October 5, 2013
18. DeMarco VG, Johnson MS, Habibi J, Pulakat L, Gul R, Hayden MR, Tilmon RD, Dellsperger KC, Winer N, Whaley-Connell AT, Sowers JR. Comparative analysis of telmisartan and olmesartan on cardiac function in the transgenic (mRen2)27 rat. Am J Physiol Heart Circ Physiol. 2011 Jan;300(1):H181-90.
19. van Meel JC, Redemann N, Haigh RM. Hypotensive effects of the angiotensin II antagonist telmisartan in conscious chronically-instrumented transgenic rats. Arzneimittelforschung. 1996 Aug;46(8):755-9.
20. Dejana E, Cerletti C, de Castellarnau C, Livio M, Galletti F, Latini R, de Gaetano G. Salicylate-aspirin interaction in the rat. Evidence that salicylate accumulating during aspirin administration may protect vascular prostacyclin from aspirin-induced inhibition. J Clin Invest. 1981 Oct;68(4):1108-12.
21. Jablonski P, Howden BO. Oral buprenorphine and aspirin analgesia in rats undergoing liver transplantation. Lab Anim. 2002 Apr;36(2):134-43.
22. Christian Doutremepuich, Omar Aguejouf,Vanessa Desplat, and Francisco X. Eizayaga. Paradoxical Effect of Aspirin. Thrombosis Volume 2012 (2012), Article ID 676237, 4 pages.
23. Haim Shirin, Efrat Sharvit, Hussein Aeed, Dov Gavish, Rafael Bruck. Atorvastatin and rosuvastatin do not prevent thioacetamide. World J Gastroenterol 2013 January 14; 19(2): 241-248.
24. Die J, Wang K, Fan L, Jiang Y, Shi Z. Rosuvastatin preconditioning provides neuroprotection against spinal cord ischemia in rats through modulating nitric oxide synthase expressions. Brain Res. 2010 Jul 30;1346:251-61.
25. Nandi U, Karmakar S, Das AK, Ghosh B, Padman A, Chatterjee N, Pal TK. Pharmacokinetics, pharmacodynamics and toxicity of a combination of metoprolol succinate and telmisartan in Wistar albino rats: safety profiling. Regul Toxicol Pharmacol. 2013 Feb;65(1):68-78.
26. Al-Hejjaj WK, Numan IT, Al-Sa'ad RZ, Hussain SA. Anti-inflammatory activity of telmisartan in rat models of experimentally-induced chronic inflammation: Comparative study with dexamethasone. Saudi Pharm J. 2011 Jan;19(1):29-34.
27. Hadi N, Yousif NG, Al-amran FG, Huntei NK, Mohammad BI, Ali SJ. Vitamin E and telmisartan attenuates doxorubicin induced cardiac injury in rat through down regulation of inflammatory response. BMC Cardiovasc Disord. 2012 Aug 6;12:63..
28. Winter CA, Riely EA, Nuss GW. Carragenan induced oedema in hind paw of the rat as assay for anti-inflammatory drugs. Proc Soc Exp Biol Med 1962;111:544-7..
29. Ghosh MN, Singh H. Modifi ed plethysmometer for measuring foot volume of unanaesthtized rats. J Pharm Pharmacol 1968;20:316-7.
30. Nakagami H, Jensen KS, Liao JK. A novel pleiotropic effect of statins: prevention of cardiac hypertrophy by cholesterol independent mechanisms. Ann Med 2003;35:398-403.
31. Y.Levy. Beyond cholesterol lowering: effect of statins on markers of cardiovascular disease. Isr Med Assoc J 2004;6:490-1.
32. Carole A. Lembi, J. Robert Waaland. Algae and Human Affairs. 1988 p 219.
33. D'Amour FE, Smith DN. A method for determining loss of pain sensation. J Pharmacol Exp Ther 1941;72:74-9.
34. Vinegar R, Schreiber W, Hugo R. Biphasic development of carrageenan oedema in rats. J Pharmacol Exp Ther 1969;166:96-103.
35. G.Brownlee. Effect of deoxycortone and ascorbic acid on formaldehyde induced arthritis in normal and adrenalectomised rats. The Lancet 1950;28:157-9.
36. Wheeler-Aceto H, Cowan A. Neurogenic and tissue mediated components of formalin induced oedema. 1991 Agents Actions;34:264-9.
37. Banerjee S, Kumar Sur T, Mandal S, Chandra Das, P, Sikdar S. Assessment of the anti-inflammatory effects of Swertia chirata

in acute and chronic experimental models in male albino rats. 2000 Indian Journal of Pharmacol 32: 21-24.

38. Timar O, Szekanecz Z, Kerekes G, Vegh J, Olah AV, Nagy G, Csiki Z, Danko K, Szamosi S, Nemeth A, Soltesz P, Szucs G. Rosuvastatin improves impaired endothelial function, lowers high sensitivity C-reactive protein, complement and immuncomplex production in patients with systemic sclerosis: a prospective case-series study. Arthritis Res Ther. 2013 Sep 4;15(5):R105.
39. Cianchetti S, Del Fiorentino A, Colognato R, Di Stefano R, Franzoni F, Pedrinelli R. Anti-inflammatory and anti-oxidant properties of telmisartan in cultured human umbilical vein endothelial cells. Atherosclerosis. 2008 May;198(1):22-8.
40. Yamagishi S, et al. Angiotensin II augments advanced glycation end product-induced pericyte apoptosis through RAGE overexpression. FEBS Lett. 2005 Aug 15;579(20):4265-70.
41. Pelliccia F, Pasceri V, Cianfrocca C, Vitale C, Speciale G, Gaudio C, Rosano GM, Mercuro G. Angiotensin II receptor antagonism with telmisartan increases number of endothelial progenitor cells in normotensive patients with coronary artery disease: a randomized, double-blind, placebo-controlled study. Atherosclerosis. 2010 Jun;210(2):510-5.
42. ML.Tuck. Angiotensin-receptor blocking agents and the peroxisome proliferator-activated receptor-gamma system. Curr Hypertens Rep. 2005 Aug;7(4):240-3.
43. Jonhson BA, Iacono AT, Zeevi A, McCurry KR, Duncan SR. Statin is associated with improved function and survival of lung allografts. Am J Crit Care Med2003;167:1271-8.
44. McCarey DW, McInnes IB, Madhok R, Hampson R, Sherbakova O, Ford I, et al. Trial of atorvastatin in rheumatoid arthritis (TARA): Double-blind, randomised placebo-controlled trial. Lancet 2004;363:2015-21.