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Original Research Article

# THERAPEUTIC EXPLORATION OF VANADIUM-ASPIRIN COORDINATION METAL COMPLEX AGAINST DIABETIC CATARACT EXACERBATED BY NICOTINE

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**Abstract:** Cataract is the leading cause of ocular blindness worldwide. It is one of the most secondary complications that occurs secondary to diabetes, the situation gets worse due to concurrent administration of nicotine. The current work had been done with the aim of evaluating the anti-cataract efficacy of Vanadium-Aspirin metal complex (VASCOM) against STZ induced diabetic cataract exacerbated by the nicotine. Metal complex had been synthesized using Aspirin and Vanadyl chloride. The compound had been characterized using IR studies, NMR studies, Magnetic moment studies. Sprague-Dawley albino rats (150-180 g) were assigned to groups each containing six animals. Animals were divided into six groups. Group 1 the control group, the group 2 the diabetic cataract group receiving Streptozotocin 35 mg/kg body weight, intraperitonially, the group 3 the diabetic cataract exacerbated by nicotine group receiving Streptozotocin 35 mg/kg body weight+ nicotine tartarate and the group 4, 5 and 6 receiving the Vanadium-Aspirin complex in a dose of 10,20mg and 30 mg/kg per day oral respectively. The study took 9 weeks. Blood glucose level, insulin and lenticular opacity were examined biweekly and pathophysiological parameters in eye lenses were evaluated after nine weeks of the experimental protocol.

After nine weeks administration of VASCOM (30mg/kg) concurrent with Streptozotocin + nicotine tartarate significantly controls the decrease in body weight, reduced the blood glucose level, elevated the insulin level and decrease in the percentage glycemic changes. Additionally, VASCOM (30mg/kg) treatment led to significant alleviation in lens antioxidants (CAT, SOD, GPx, and GSH), total protein, and $Ca^{2+}$ ATPase activity. Moreover, a significant reduction in lens MDA, polyol level and HbA1c was seen as compared to diabetic cataract exacerbated by nicotine group. The probable molecular mechanism has been evaluated using *in vivo* software like pkCSM, Molinspiration Cheminformatics and SwissADME. The result helps to conclude that VASCOM (30mg/kg) had plays a significant beneficial role in the management of diabetic cataractogenesis exacerbated by nicotine.

**Keywords:-** Diabetic cataract, Nicotine exacerbation, Oxidative stress,Polyol.

**Introduction*:*** Cataract is a multifactorial disease, characterized by cloudiness and opacification of the eye's lens mainly due to the formation of large protein aggregates in the lens. Cataract change the clarity of the natural lens inside the eye's that slowly degrades visual quality. [1,2] Cataract is one of the most common cause of visual disability and blindness all over the globe and the problem is more grim in the developing countries. In India there are 12 millions of cases of blindness out of which 81% of the subjects suffered from cataract [3-5]. The risk factors for the development of cataract include Diabetes mellitus, drugs, ultraviolet radiation, smoking, alcohol, nutrition and gender [6-8].

Chronic hyperglycemia is a major decisive factor in development of secondary ocular complications like diabetic cataract.[9-12] Concurrent consumption of nicotine leads to exacerbation of diabetic cataract. Bhattacharya *et al* (2015) had observed a positive correlation between exacerbation of diabetic cataract and concurrent use of nicotine.[13] In current scenario, the only treatments for cataract are surgery and intraocular lens implantation, which are associated with the significant cost. In addition to economical factors involved in these treatments, they may have various complications before, during and after the surgery.[14-16] Another problem associated with the cataract surgery in developing countries is the medical accidents that happen during the preoperative, operative and post-operative surgery.[17] To overcome the above mentioned shortcomings of the surgical approach, the pharmacotheruputical approach should be considered. In current study, we had taken Vanadyl chloride as the central ion and aspirin as the ligand for synthesis of Vanadium-Aspirin coordination metal complex and evaluate its efficacy as a potent anticataractogensis pharmacotheruputical agent. The rationale for selection of Vanadyl chloride is the insulinomimetic nature of vanadium which had been proved by various studies [18-21]. Aspirin had been one of the unexplored agents in pharmacotheruputic approach in the management of diabetic cataract. Aspirin had found to significantly reduce the level of tryptophan an important bio marker whose level is increased in case of cataract [22]. It was also observed that the aspirin reduced elevated aldose reductase level, advanced glycation end product and increase the level of GSH level asserting the role of VASCOM in diabetic cataract [23-26].

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## Materials and methods

**Chemicals and reagents:** Aspirin, $VOCl_2$ were purchased from Hi-media and other various chemicals and diagnostic kits were of analytical grade.

**Synthesis of metal complex:** Aspirin and $VOCl_2$ (50% aqueous solution) is mixed in a molar ratio of 2:1 in 96% ethanol stirred under nitrogen atmosphere (pH 3.5, 0-8$^0$C), green oil would be formed. Successive washings with bidistilled water produced a light green solid.

**Experimental animals:** Spraguee Dawley albino male rats (150 to 180 g) were used for this experimental study , they were housed under standard and optimum environmental condition (23 ± 20$^o$C, with 55 ± 5% humidity and 12 h light/dark cycle) according to the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Govt. of India. Animal were fed a standard pellet diet with water ad libitum under hygienic conditions. Animals were habituated to laboratory conditions for at least 48 to 72 h prior to the experimental protocol to reduce non-specific stress, if present any. The protocol was ethically approved by the Institutional Animal Ethics Committee (IAEC) of Institute of Pharmaceutical Science, Guru Ghasidas Vishwavidyalaya, Bilaspur (C.G), India (Reg. No.-994/GO/ Ere/S/06/CPCSEA), and the experiments were conducted according to the ethical principles and guidelines provided by

CPCSEA and the Association for Research in Vision and Ophthalmology (ARVO) for animals.

**Grouping of Animals:** Animals were divided into six groups. Group 1 the control group, the group 2 the diabetic cataract group, the group 3 the diabetic cataract exacerbated by nicotine group and the group 4, 5 and 6 receive the Vanadium-Aspirin complex in a dose of 10,20mg and 30 mg/kg per day oral respectively. In the experimental animals the diabetes were induced by STZ 35 mg/kg body weight, intraperitonially. The exacerbation of the diabetes was done by nicotine hydrogen tartrate, it was dissolved in phosphate buffer saline and administered subcutaneously at alternate sites to avoid accumulation of the drug with repeated injection. Three weeks after diabetes induction, of the nicotine treatment was started at the dose of 0.3mg/kg for 1 week. The dose was escalated to 0.9mg/kg for 3 days and then increased by 0.3mg/kg intervals every 3 days until a final dose of 2.1mg/kg was reached; this dose continued till the end of the study [27]. The time period required for induction of diabetic cataract and exacerbation by nicotine is 9 weeks

**Determination of lenticular opacity:** In experimental groups the lenticular opacity was determined using the photographic method based on the appearance of graph lines through the lens. The dissections of eye lens were done via a posterior approach. The dissected lenses were, put on graph paper immediately, and photographed by a digital camera (Sony Cybershot DSC-W810). The graph lines would appear clear in the transparent lens and cloudy or non visible in the cataractous lens. [28]

**Lens collection:** Animals were sacrificed after nine weeks and the eye balls were removed. Both lens were separated from eye balls and were rapidly, desiccated, washed with saline and dried over filer paper, weighted and placed in clean sterilized vials and kept at -20$^{O}$C. [29]

**Blood collection:** For biochemical analysis blood was collected from each group via cardiac puncture, and serum was separated and stored at 2-8$^{0}$C.

**Biochemical parameters:** The following biochemical parameters were analyzed:

**Enzymatic and non-enzymatic antioxidants in lens:** The activity of the Glutathione peroxidase was assayed by using the method proposed by Tappel, (1978) [30]. The CAT activity was monitored at 240 nm for 30 sec at 25ºC by using the method proposed by Aebi *et al* (1984). One unit of CAT could be defined as the amount of enzyme required to decompose 1.0 M of hydrogen peroxide into water per minute at pH 7.0 and 25ºC. [31]. The superoxide dismutase (SOD) activity was assayed based on photoreduction of nitro blue tetrazolium method [32]. Reduced glutathione (GSH) was measured using Ellman's reagent [33]

**Lipid peroxidation:** Malondialdehyde (MDA**)**, an end product of lipid peroxidation was measured by using the method of Ohkawa (1979). Tetra methoxy propane was used as a standard [34].

**Total protein content in lens:** The total protein content was estimated by using the method of Lowry *et al* (1951). The absorbance of the resultant coloured product was observed at 610 nm against blank. Bovine serum albumin was used as a standard used for establishing the calibration curve [35].

**Ionic contents ($Ca^{+2}$):** Ionic contents of the lens were evaluated using spectrophotometric method with the aid of diagnostic kits (Labcare Diagnostics Pvt. Ltd., India) [36].

**HbA1C Determination:** HbA1C were measured using HPLC method [37].

**Polyol pathway:** Lens polyol was determined by the method proposed by West and Rapoport (1949). Lenses were homogenized with 0.6 N perchloric acid and then centrifuged for 20 min at 5000 revolution per meter. The supernatant obtained in above step was neutralized with 2 N KOH and centrifuged again. The supernatant obtained was treated with 0.25 ml of periodic acid (0.03 M) for 10 minutes then freshly prepared 0.25 ml of stannous chloride (0.125 M) and 2.5 ml of chromotropic acid (0.2%) were added and the reaction mixture was heated on a boiling water bath for time period of 30 min. The

absorbance was measured at 570 nm using a UVvisible spectrophotometer dulcitol was used as standard [38].

**Statistical analysis:** The results were expressed in mean± standard deviation (SD) and mean ± standard error of mean (SEM). The significant variations between multiple groups were analyzed using one-way and two way analysis of variance (ANOVA). Statistical analysis was performed using Graph Pad Prism 5.0 software.

**Results**

**Characterization of the synthesized complex:** The structure had been characterized by using IR studies. Aspirin shows very strong band at 1694 (vs*)* cm-1 *(*carboxylic acid*)*. $VO^{+2}$/Aspirin complex showed peak at 1537 *(*s*)*, 1403 *(*vs*)* $cm^{-1}$ *(*nas COOy and ns COOy, respectively*)* and 988 *(*s*)* $cm^{-1}$ due to V-O stretching*)*. The difference between the antisymmetric and symmetric stretching modes of the carboxylate group is indicative of the formation of a binuclear complex with carboxylate bridges. The carbonyl *(*acetyl*)* stretching frequency at 1754 $cm^{-1}$remained unchanged after coordination. The strong and broad band at about 3500 $cm^{-1}$ *(*n OH*)* and the band at 1592 $cm^{-1}$ *(*d OH2*)* show the presence of water in the coordination sphere of the vanadium centres. In the NMR studies it was found that peak for –COOH that was present in aspirin but was absent in the Vanadium-Aspirin complex. Magnetic moment of the complex was found to be 1.43.

**Acute toxicity studies:** In the acute toxicity that was performed as per toxicity guidelines provided by the OECD it was found that VO-Aspirin showed no adverse effects or mortality were detected in the rats up to 300mg/kg, during the 24h observation period. In dose of 500 mg/kg the animal become lethargic before dying. In the dose of 1000 mg and 2000mg the animal were died, after the death necroscopic and histopathological studies of each organ had been performed. In the histopathological studies it was found that at this dose vanadium-aspirin can cause severe hepatotoxicity toxicity (Figure 1). In the hepatic tissues of the dose range 1000mg/kg vacoulation, fragmentation of the cells and congested central artery had been observed. The elevated hepatic enzyme level evidently proves the damage caused by the Vanadium-Aspirin complex. [**Figure 1]**

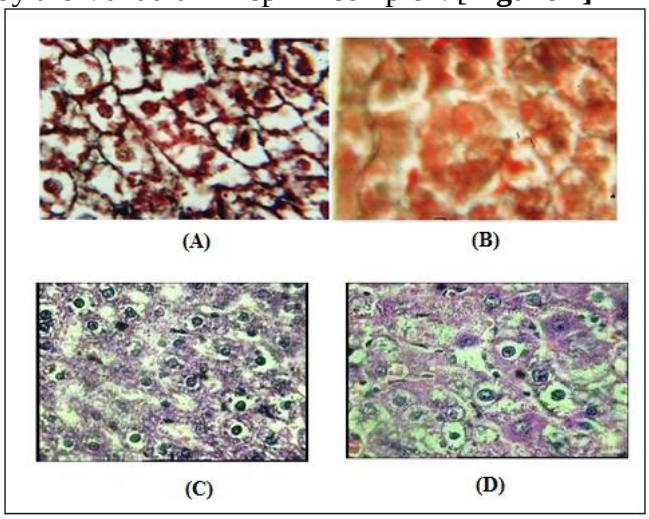



**Figure 1** Histopathology of the hepatocytes of rats receiving 1000 and 2000mg/kg Vanadium Aspirin complex. A) Normal group showing normal hepatocytes and collagen fibres at 1000 mg/kg B) 1000 mg/kg dose of Vanadium-Aspirin complex showing vacoulation, fragmented cells, coagulated central vein C) Normal hepatocytes at 2000 mg/kg D) 2000mg/kg Vanadium-Aspirin complex treated hepatocytes.

In the 2000mg/kg dose of Vanadium-Aspirin showed the damage of the liver cells .There are extensive areas of patchy and confluent hepatocyte necrosis and lobular inflammation, Sinusoidal spaces are flooded with inflammatory cells and RBC's.

It could be thus concluded as on the results obtained from this study, that the dose for all the pharmacological activities was fixed to be 30mg/kg of body weight (b.w.).

***In Vitro* studies:** All lenses in normal group remained transparent whilst all lenses in diabetic cataract group developed dense opacities indicating cataract. The opacity gradually increased towards the centre with complete opacification by 72 hours indicating complete cataractogenesis. Vanadium-Aspirin metal complex retarded the development of opacity compared to control group indicating the role of Vanadium-Aspirin in management of cataract.[ Figure 2]

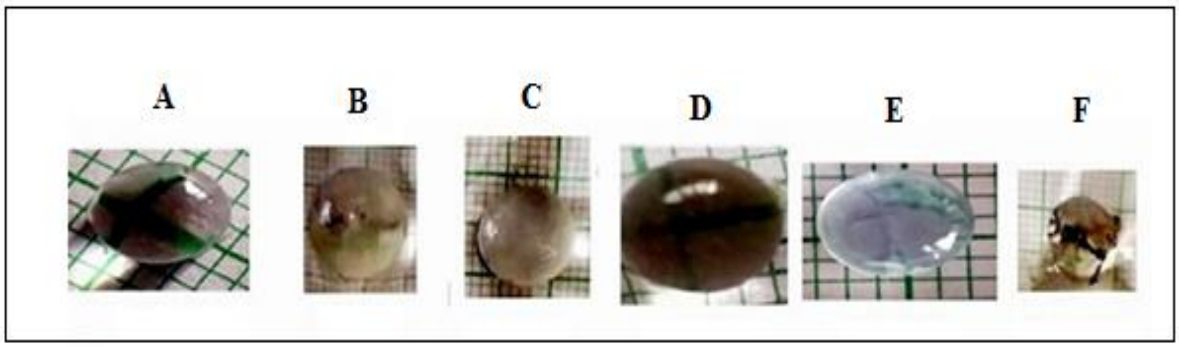
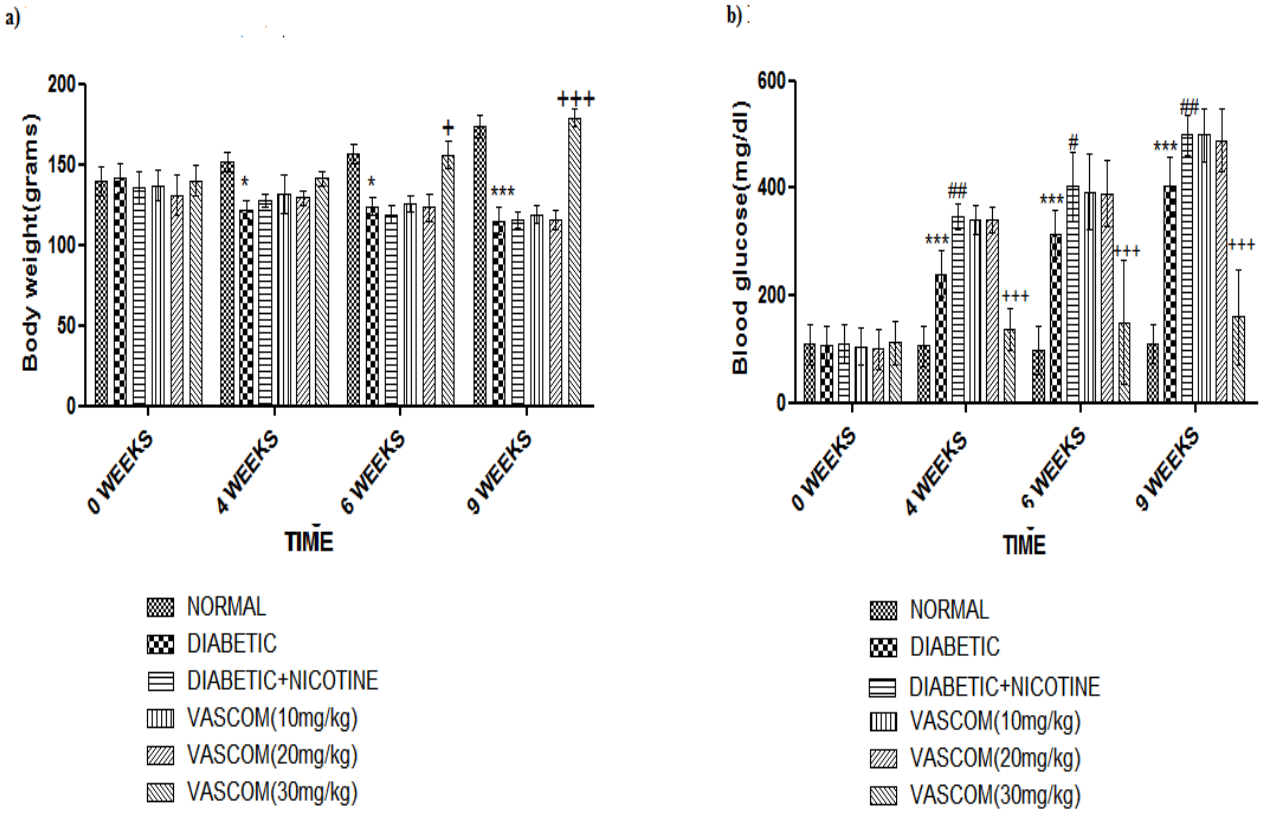



**Figure2** *In vitro* studies of various groups on the rat lens. A) Normal B) Diabetic C) Diabetic Nicotine D) VASCOM(100µg/ml) E) VASCOM(200µg/ml) F) VASCOM(300µg/ml)

**In *Vivo* studies:** In *vivo* studies VASCOM (30mg/kg) showed significant decrease in markers of diabetic cataract which had been exacerbated by nicotine. VASCOM (30mg/kg) had significantly elevated the body weight ($p<0.01$, $p<0.001$), decreased the blood glucose ($p<0.001$), elevated the plasma insulin level ($p<0.001$) and decreased the percentage of glycemic change as compared to the diabetic cataract exacerbated by nicotine. [Figure 4 (a) to (d)]



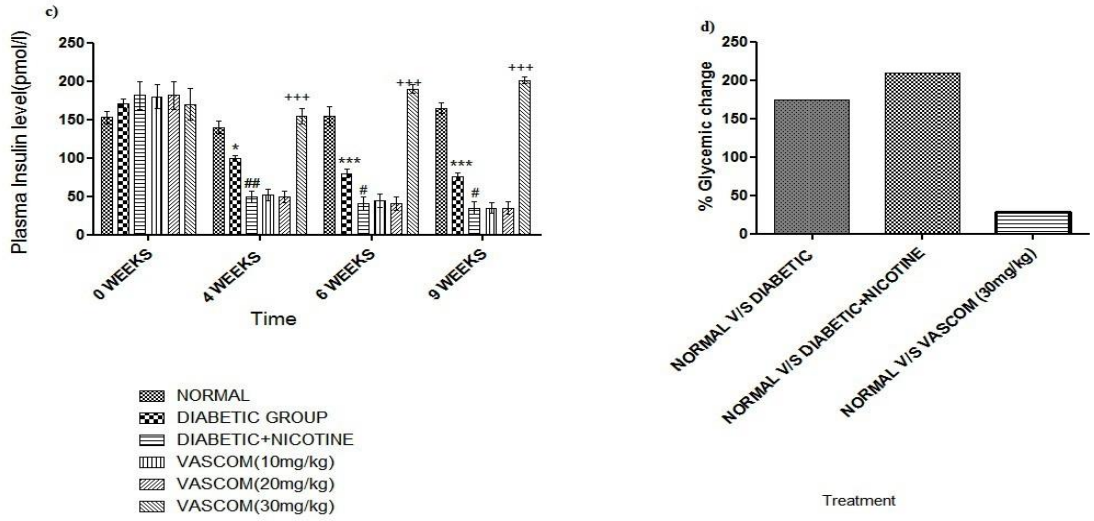



**Figure 3** a) Effect of VASCOM complex on body weight. Values are expressed as mean ± SD (n = 6) (Two-way ANOVA followed by Dunnet post hoc test). b) Effect of Aspirin and VASCOM complex on fasting blood glucose(Two-way ANOVA followed by Bonferoni post hoc test). c) Effect of VASCOM complex on insulin level. (Two-way ANOVA followed by Bonferoni post hoc test) d) Effect of VASCOM complex on % glycemic change. Values are expressed in %. Values are expressed as mean ± SEM (n = 6) *p<0.05 *** p<0.001 as compared to normal, # p<0.05,## p<0.01, ### p<0.001as compared to diabetic cataract + nicotine group + p<0.05 ++p<0.01 +++ p<0.001 aspirin and VASCOM(30mg/kg) as compared to diabetic cataract + nicotine group).* p<0.05 ** p<0.01 *** p<0.001 as compared to normal,## p<0.01, ### p<0.001as compared to diabetic cataract + nicotine group +++ p<0.001 aspirin and.* p<0.05 ** p<0.01 *** p<0.001 as compared to normal,## p<0.01, ### p<0.001as compared to diabetic cataract + nicotine group +++ p<0.001 aspirin and VASCOM(30mg/kg) as compared to diabetic cataract + nicotine group.

VASCOM (30mg/kg) had significantly elevated the antioxidant level of natural antioxidants like GPx (p<0.05), CAT (p<0.001) SOD (p<0.001) and GSH (p<0.001) as compare to diabetic group exacerbated by nicotine group.[Figure5 (a) to (d)]

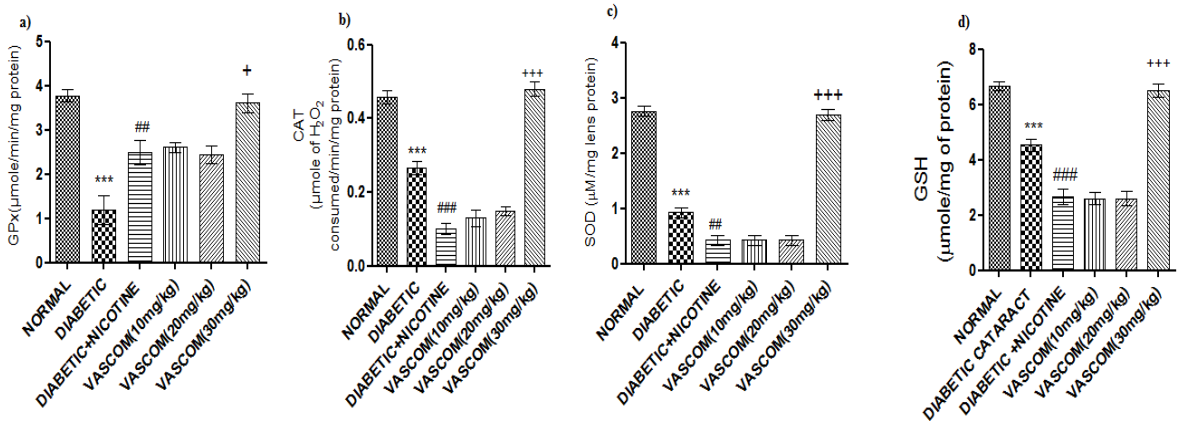



**Figure 4** Effect of VASCOM complex on antioxidant system. a) GPx b)CAT c) SOD d) GSH. Values are expressed as mean ± SEM (n = 6) (One way ANOVA followed by Bonferoni post hoc test).* p<0.05 *** p<0.001 as compared to normal, # p<0.05,## p<0.01, ### p<0.001 as compared to diabetic group+ p<0.05 ++p<0.01 +++ p<0.001. 001as compared to diabetic cataract + nicotine group

VASCOM (30mg/kg) had shown action against the lipid peroxidation evident by significant decrease in the MDA level (p<0.001). [Figure 5]

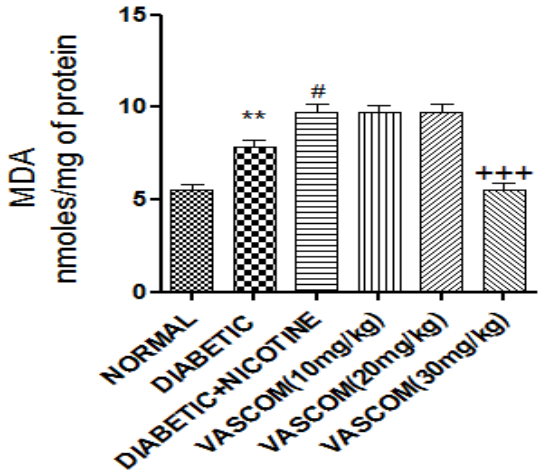



**Figure 5** Effect of VASCOM complex on MDA level. Values are expressed as mean ± SEM (n = 6) (One way ANOVA followed by Bonferoni post hoc test).* p<0.05 *** p<0.001 as compared to normal, # p<0.05,## p<0.01, ### p<0.001as compared to diabetic group + p<0.05 ++p<0.01 +++ p<0.001 001as compared to diabetic cataract + nicotine group

VASCOM (30mg/kg) had also increased significantly the level of Calcium ATPase (p<0.001) compared to the diabetic group exacerbated by nicotine group.[Figure 7]

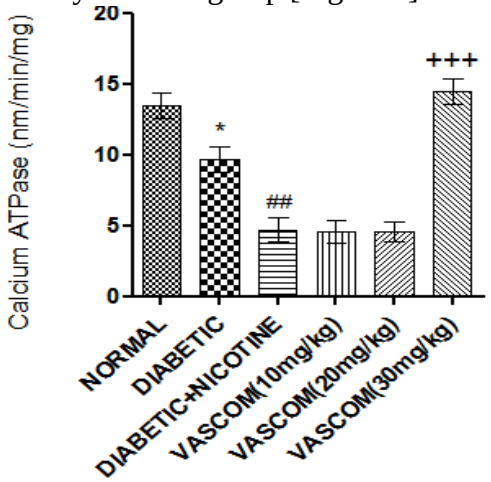



**Figure 6** . Values are expressed as mean ± SEM (n = 6) (One way ANOVA followed by Bonferoni post hoc test).* p<0.05 *** p<0.001 as compared to normal, # p<0.05,## p<0.01, ### p<0.001as compared to diabetic group + p<0.05 ++p<0.01 +++ p<0.001 001as compared to diabetic cataract + nicotine group

VASCOM (30mg/kg) had also increased significantly the level of total protein content (p<0.001) compared to the diabetic group exacerbated by nicotine group.[Figure 7]

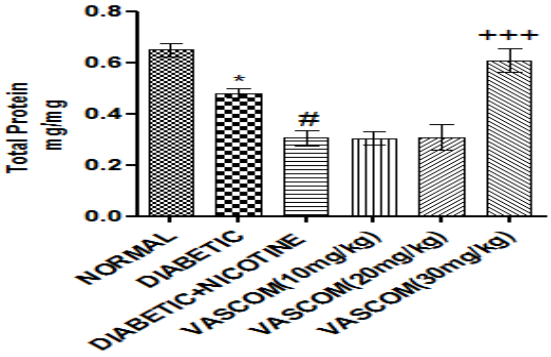



**Figure 7** Effect of VASCOM complex on Total protein content. Values are expressed as mean ± SEM (n = 6) (One way ANOVA followed by Bonferoni post hoc test).* p<0.05 *** p<0.001 as compared to normal, # p<0.05,## p<0.01, ### p<0.001as compared to diabetic group + p<0.05 ++p<0.01 +++ p<0.001 001as compared to diabetic cataract + nicotine group

VASCOM (30mg/kg) had also significantly decrease the level of HbA1c (p<0.001) (which had been the one the common marker that had been found to be elevated in the secondary complications arising due to diabetes) as compared to the nicotine exacerbated group. [Figure 8]

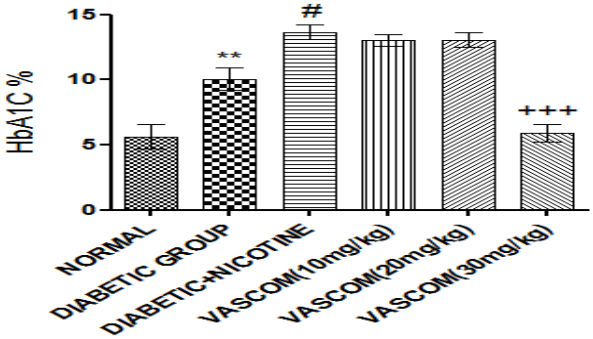



**Figure 8** Effect of VASCOM complex on HbA1c. Values are expressed as mean ± SEM (n = 6) (One way ANOVA followed by Bonferoni post hoc test).* p<0.05 *** p<0.001 as compared to normal, # p<0.05,## p<0.01, ### p<0.001as compared to diabetic group + p<0.05 ++p<0.01 +++ p<0.001 001as compared to diabetic cataract + nicotine group.

Polyol level ($p<0.001$) had been significantly decreased when compared to the diabetic group exacerbated by nicotine group.

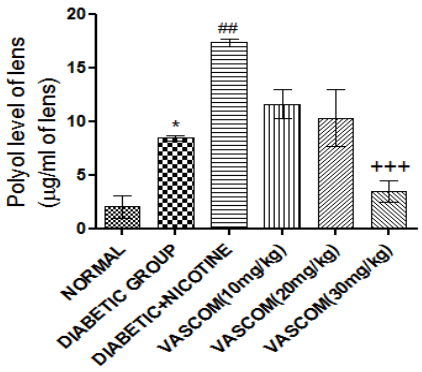



**Figure 9** Effect of VASCOM complex on polyol level. Values are expressed as mean ± SEM (n = 6) (One way ANOVA followed by Bonferoni post hoc test).* $p<0.05$ *** $p<0.001$ as compared to normal, # $p<0.05$,## $p<0.01$, ### $p<0.001$as

**Discussion:** Diabetic cataract is one of the most common ocular complications of the diabetes [28]. Concurrent consumption of nicotine by the subjects suffering from diabetic cataract exacerbated the condition [38]

The current work had been done with the objective of evaluating the role of Vanadium-Aspirin coordination complex against the diabetic cataract exacerbated by the nicotine. Structure of the synthesized VASCOM had been established using the IR, NMR and magnetic moment study. The probable structure is in accordance with the previously mentioned structure by Etcheverry *et al* [39].

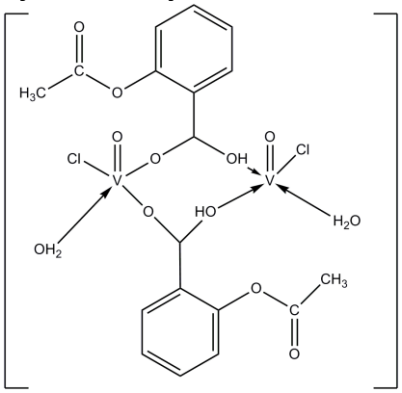



**Figure 10** The probable structure of VASCOM

There are four theories that could explain definite geometry, magnetic and optical properties of the complex.[40]. In metal-ligand bond of complex, ligands donates the electron to the $M^+$ (metal) ion which must possess vacant d orbital (transition metal) of ns,(n-1)d level.

In metal complex $d^2sp^3$, $sp^3$ $sp^2d$ and $sp^3d$ hybridizations commonly take place and they shows octahedral, tetrahedral, square planar and square pyramidal stereospecific geometry respectively. [41]

Crystal field theory describes effect of ligand as point charges arranged surrounding the M+ (metal) ion and due to the static electric field produced by a surrounding charge distribution (anion neighbours) causes the splitting of the degenerated d orbital into axial and equatorial regions. Splitting pattern depends upon the nature of crystal field location excreting its influence of central $M^+$ ion. Crystal field theory helps us to determine the nature of metal ion, metal oxidation state, arrangement of ligands around the metal ion, coordination number of the metal and nature of the ligands surrounding the metal ion.[42,43]

Vanadium-Aspirin complex has $d^2sp^3$ hybridization. Presence of chelate ring stabilizes the complex as well as oxo atom shows distorted octahedral geometry i.e. square pyramidal. VASCOM form bridged µ-ligand structure, two vanadium ions are joined through bridged aspirin molecule, ultimately enhancing the stability of complex.

The probable nomenclature of the complex would be µ µ'Aspirinato bis aquacholrido oxo Vanadium(IV) complex.

The *in vitro* activity of the VASCOM had been done with the aim of screening whether the VASCOM had any significant action against lenticular opacity or not. VASCOM (30mg/kg) showed that it had an action against the diabetic cataract by reducing the lenticular opacity in the rat lens which helps us to conclude that VASCOM (300µg/ml) had an anticataract action as it had reduced the lenticular opacity when compared to the nicotine exacerbated group.

To evaluate the *in vivo* cataract activity STZ induced diabetic cataract model had been used. Nicotine administration had shown to exacerbate the diabetic cataract. It has been observed in the study that diabetic cataract that had been exacerbated by the nicotine has caused significant increase in oxidative stress as compared to diabetic cataract, which is indicated by depletion of serum antioxidants and elevation of MDA level as well as markers like Polyol and HbA1c level as well as decrease in the Ca ATPase level.

VASCOM (30mg/kg) had shown to have a dual mechanism of action. It firstly reduces the elevated hyperglycemic condition, the main reason for generation of the cataract which is evident by normalization of the decrease in body weight ($p<0.01$), decrease in the elevated blood glucose level ($p<0.001$), increase in insulin level ($p<0.001$) and control of percentage glycemic change as compared to nicotine exacerbated diabetic cataract group. Secondly VASCOM (30mg/kg) shows an antioxidant effect against oxidative stress induced by chronic hyperglycemia. VASCOM (30mg/kg) had significantly improved the natural antioxidants level and decrease the MDA level ($p<0.001$) when compared to the nicotine exacerbated diabetic cataract group. VASCOM had significantly inhibits elevations of oxidative stress markers like Polyol ($p<0.001$) and HbA1c ($p<0.001$) as well as caused significant increase in the $Ca^{2+}$ATPase level ($p<0.001$) and total protein content ($p<0.001$) when compare to nicotine exacerbated diabetic group.

In pathophysiology of the diabetic cataract there are three pathways namely the oxidative stress pathway, AGE pathway and polyol pathway.[44] Oxidative stress pathway when activated leads to generation of the free radicals that cause increased in the oxidative stress, VASCOM (30mg/kg) had significantly increased the level of natural antioxidant counteracting this pathway. AGE pathway when activated by the diabetes cause production of advance glycation end product which causes detrimental effect on various tissues including the lens. HbA1c levels and AGE had shown to have a positive correlation. VASCOM (30mg/kg) had significantly decreased the level of HbA1c, establishing a negative correlation with AGE. Polyol pathway has been found to be an important pathway for the diabetic cataract, in the previous studies it had been demonstrated that elevated polyol level was positively correlated with the diabetic cataract. VASCOM (30mg/kg) had significantly decreased the level of polyols indicating its role in prevention of cataract. [Figure 10]

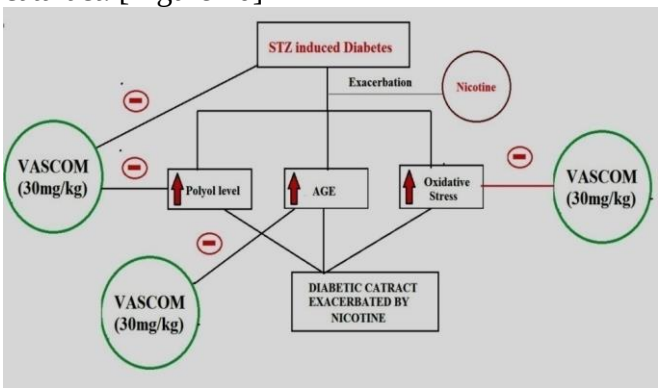



**Figure 10 Role of VASCOM on pathological pathways of Diabetic cataract exacerbated by nicotine**

It had been found in the previous study by Etcheverry *et al* [39] that Vanadium-Aspirin complex used to inhibit the PTPase enzyme in bone cell lines; PTPase enzyme had shown a negative correlation with insulin, it could be thus a potent site of action, but the effect Vanadium-Aspirin of PTPase enzyme in hyperglyecmic condition is yet to be evaluated. Another probable mechanism of action would be interaction of the VASCOM with the P-gp, as the pkCSM software predicts that VASCOM as P-gp substrate. P-gp plays a major role in formation of diabetic cataract it could be a probable site of action of VASCOM, but exact mechanism is yet to be explored as formation of cataract and role of P-gp is still controversial.[45-46]

**Conclusion:** The above results suggest that Vanadium Aspirin could be a probable candidate in treatment of Diabetic cataract which is exacerbated by nicotine. Development of this novel Vanadium-aspirin complex for management of one the most common ocular

complications caused secondary to diabetes open the new avenues for further researchers working in this field who could further works in corresponding areas like mechanism by which this Vanadium-aspirin complex works by effecting the PTPase enzyme as well as P-Gp , novel drug delivery system, and the toxicity profile of the complex ultimately leading to a system which had more benefits and minimum adverse effects to society.

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