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INFLUENCE OF AGELESS LIQUID WITH OR WITHOUT PIPERINE ON SODIUM IODATE-INDUCED RETINAL DEGENERATION IN SPRAGUE-DAWLEY RATS

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ABSTRACT

To study the effect of ageless liquid on sodium iodate-induced retinal degeneration in Sprague-Dawley rats. Retinal degeneration was induced by single intraperitoneal injection sodium iodate to adult Sprague-Dawley rats weighing 100–250 g. Ageless liquid in three different doses were given for 45 days. On day 46, the rats were sacrificed and eyes were removed and processed for estimation of malondialdehyde (MDA), reduced glutathione (GSH), ATP and TGF-β content, activity of catalase (CAT) and superoxide dismutase (SOD). The sodium iodate treated rats showed a significant increase in MDA, and a significant decrease in GSH, SOD, catalase, TGF-1β and ATP level compared to control rats suggesting the retinal damage. Three different doses of ageless liquid with piperine and without piperine significantly reversed the retinal damage done by sodium iodate. The retinoprotective potential was found to be better for ageless liquid with piperine in comparison with ageless liquid without piperine and maximum therapeutic benefit was observed at 16 mg/kg of ageless liquid with piperine.

KEY WORDS: **Ageless liquid, piperine, macular degeneration, sodium selenite.**

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INTRODUCTION

Ageless liquid is an advanced formulation of high concentration of vitamins, minerals and resveratrol. Resveratrol is a potent polyphenolic antioxidant compound produced by grapes and other plants for protection against pathogens.[1] In humans, it exerts a broad range of physiological effects when ingested orally. Emerging evidence indicates that resveratrol may combat macular degeneration and promote eye health via several mechanisms. In an animal model, resveratrol was able to stave off diabetes-induced vascular lesions.[2] They also showed that resveratrol was able to dampen vascular endothelial growth factor (VEGF) signaling in mouse retinas, a key pathological feature of age related macular degeneration (AMD). Another study corroborated these results by showing that resveratrol inhibited angiogenesis and suppressed retinal neovascularization in mice prone to develop macular degeneration due to a genetic mutation.[3] There are reports that have suggested additional protective mechanisms of resveratrol in macular degeneration, including protecting retinal pigment epithelial cells from hydrogen peroxide-induced oxidative stress and light damage.[4,5] It is also reported that resveratrol produced endothelium-dependent and nitric oxide-mediated vasodilation in human internal mammary artery but partially in saphenous vein rings and improved their endothelial reactivity which may have a therapeutic potential in cardiovascular diseases.[6] However, one of the drawback of resveratrol is its poor oral bioavailability. Piperine is an alkaloid obtained from black pepper and has been reported to be a bioavailability enhancer.[7] Further, Johnson et al has reported that piperine significantly improves the in vivo bioavailability of resveratrol.[8] In view of these findings on resveratrol and macular degeneration, it is possible that individuals with AMD (especially the “wet” variety) may benefit from supplementation with resveratrol. In view of the piperine’s effect on bioavailability we planned to see the effect of resveratrol with or without piperine on macular degeneration, Hence, in the present study, we planned to investigate the effect of ageless liquid on sodium iodate induced retinal degeneration in Sprague-Dawley rats.

MATERIALS AND METHODS

Fifty four adult Sprague-Dawley rats weighing 100–250 g were divided into 9 groups of six rats each. They were housed in polypropylene cages, maintained under standard conditions with temperature (22–24°C), 12- h light/12-h dark cycle and relative air humidity 40–60%. Rats had continuous access to normocaloric standard rat pellet diet and to tap water. The animals were acclimatized to the laboratory conditions for one week before the start of the experiment. The experiment was conducted in accordance with CPCSEA guidelines and Institutional Animal Ethics Committee (Registration no. 94/1999/CPCSEA/KMC) approval was obtained before starting the experiment. All nine groups were treated over a period of 45 consecutive days as follow: group I (Normal control)- 2% gum acacia 1 ml/kg/day; orally + normal saline 1 ml/kg/day i.p. on 30th day; group II (Negative control)- 2% gum acacia 1 ml/kg/day; orally + single i.p. injection of 75 mg/kg Sodium iodate on 30th day; group III (Positive control)- Vitamin C 45 mg/kg/day; orally + single i.p. injection of 75 mg/kg Sodium iodate on 30th day; group IV (Test 1A)- Ageless liquid with pieprine 4 mg/kg/day; orally + single i.p. injection of 75 mg/kg Sodium iodate on 30th day; group V (Test 1B)- Ageless liquid with pieprine 8 mg/kg/day; orally + single i.p. injection of 75 mg/kg Sodium iodate on 30th day;Group VI (Test 1C)- Ageless liquid with pieprine 16 mg/kg/day; orally + single i.p. injection of 75 mg/kg Sodium iodate on 30th day; group VII (Test 2A) - Ageless liquid without pieprine 4 mg/kg/day; orally + single i.p. injection of 75 mg/kg Sodium iodate on 30th day;group VIII (Test 2B)- Ageless liquid without pieprine 8 mg/kg/day; orally + single i.p. injection of75 mg/kg Sodium iodate on 30th day and group IX (Test1 2C)- Ageless liquid without pieprine 16 mg/kg/day; orally + single i.p. injection of 75 mg/kg Sodium iodate on 30th day. On 46th day, all the rats were sacrificed by administering excess dose of urethane. The eyes were separated for further analysis.

BIOCHEMICAL ANALYSIS

Retina homogenate (10% w/v) was prepared in cold 50 mM potassium phosphate buffer (pH 7.4) using a Remi homogenizer. The unbroken cells and cell debris were removed by centrifugation at 10000 rpm for 30 minutes using a cooling centrifuge (Hettich, Germany). The resulting supernatant was stored at -20˚C for estimation of malondialdehyde (MDA), reduced glutathione (GSH), ATP and TGF-β content, activity of catalase (CAT) and superoxide dismutase (SOD).

Estimation of malondialdehyde

Lipid peroxidation as evidenced by the formation of TBARS and LH were measured by the method of Nichans and Samuelson.[9] About 0.1 ml of tissue homogenate was treated with 2 ml of 0.37% thiobarbituric acid (TBA) and 15% trichloroacetic acid (TCA) reagent and placed in a water bath for 15 min, cooled and centrifuged at room temperature for 10 min at 1000 rpm. The absorbance of the clear supernatant was measured against a reference blank at 535 nm. The values are expressed as µmoles of malondialdehyde (MDA) formed /min/mg protein.

Estimation of reduced glutathione (GSH)

The method was based on the reaction of reduced glutathione with 5, 5’-dithiobisnitrobenzoic acid (DTNB) to give a compound that absorbs at 412 nm. To the homogenate 0.1 ml of 10% TCA was added and centrifuged. About 0.1 ml of supernatant was treated with 0.5 ml of Ellman’s reagent (19.8 mg of DTNB in 100 ml of 0.1% sodium nitrate) and 3.0 ml of 0.2 M phosphate buffer (pH 8.0) and the absorbance was read at 412 nm. Activity was expressed as µmoles/min/mg protein.[10] ATP and TGF-1β level was analyzed in accordance with the standard protocols given along with the commercially available colorimetric and ELISA kits respectively. The activity of catalase and superoxide dismutase was measured as per the standard protocols given along with the commercially available colorimetric assay kits.

Estimation of superoxide dismutase (SOD)

SOD activity was determined by the inhibition of auto catalyzed adrenochrome formation in the presence of liver homogenate at 480 nm. The reaction mixture contained 150 µl of liver homogenate, 1.8 ml of carbonate buffer (30 mM, pH 10.2), and 0.7 ml of distilled water and 400 µl of epinephrine (45 mM). Auto oxidation of epinephrine to adrenochrome was performed in a control tube without the homogenate. Activity was expressed as µmoles/ min/mg protein.[11]

Estimation of catalase (CAT)

Catalase (CAT) activity was measured by the catalysis of H2O2toH2O in an incubation mixture adjusted to pH 7.0 was recorded at 254 nm. The reaction mixture contained 2.6 ml of 25 mM potassium phosphate buffer pH 7.0 and 0.1ml of tissue homogenate and was incubated at 37°C for 15 min and the reaction was started with the addition of 0.1 ml of 10 mM H2O2. The time required for the decrease in absorbance from 0.45 to 0.4 representing the linear portion of the curve was used for the calculation of enzyme activity. One unit of catalase activity was defined as the amount of enzyme causing the decomposition of µmol H2O2/mg protein/min. [12]

Estimation of TGF- β1

A monoclonal antibody specific for TGF-β1 has been coated onto the wells of the microtiter strips. Samples, including standards of known TGF-β1 content, control specimens, and extracted unknowns, are pipetted into the wells, followed by the addition of a biotinylated second antibody. During the first incubation, TGF-β1 antibody binds simultaneously to the immobilized (capture) antibody on one site, and to the solution phase biotinylated antibody on a second site. After removal of excess detection antibody, streptavidin-peroxidase (enzyme) is added. This binds to the biotinylated antibody to complete the four-member sandwich. After a second incubation and washing to remove all the unbound enzyme, a substrate solution is added, which is acted upon by the bound enzyme to produce color. The intensity of this colored product is directly proportional to the concentration of TGF-β1 present in the original specimen.[13]

STATISTICAL ANALYSIS

Using SPSS version 20.0, uniform data was expressed in terms of mean ± standard deviation and analyzed by one way analysis of variance followed by post hoc Tukey's test. P value less than 0.05 was considered as statistically significant.

RESULTS

The sodium iodate treated rats have shown a significant increase in MDA, and a significant decrease in GSH, SOD, catalase, TGF-1β and ATP level compared to control rats suggesting the retinal damage (Table 1-7). The different doses of ageless liquid with piperine and without piperine significantly reversed the retianl damage done by sodium iodate (Table 1-7). There was significant decrease in body weight in ageless liquid with/without piperine treated rats in comparison with sodium idoate intoxicated control rats. Further, the reversal of retinal damage was better with ageless liquid with piperine compared to ageless liquid without piperine and it was in dose dependent fashion.

Table 1

Effect on reduced glutathione in retinal homogenate (µmol/ml)

Groups	Dose	Mean±SD	P value	Significance
I	Normal saline 1 ml/kg/day + 2% gum acacia 1 ml/kg/day	49.54±2.13		
II	Sodium iodate 75 mg/kg + 2% gum acacia 1 ml/kg/day	5.43±0.86	<0.001[a]	**S**
III	Sodium iodate 75 mg/kg + Ascorbic acid 45 mg/kg/day	32.55±2.11	0.008[b]	**S**
IV	Sodium iodate 75 mg/kg + Ageless liquid with piperine 4 mg/kg/day	84.62±2.15	<0.001[b]	**S**
V	Sodium iodate 75 mg/kg + Ageless liquid with piperine 8 mg/kg/day	134.87±14.24	<0.001[b]	**S**
VI	Sodium iodate 75 mg/kg + Ageless liquid with piperine 16 mg/kg/day	509.36±133.81	<0.001[b-i]	**S**
VII	Sodium iodate 75 mg/kg + Ageless liquid without piperine 4 mg/kg/day	52.35±10.58	0.004[b]	**S**
VIII	Sodium iodate 75 mg/kg + Ageless liquid without piperine 8 mg/kg/day	68.52±14.33	0.002[b]	**S**
IX	Sodium iodate 75 mg/kg + Ageless liquid without piperine 16 mg/kg/day	265.48±60.73	<0.001[b-i]	**S**

[a]compared to normal control, [b]compared to sodium iodate treated control, [c]compared to Ascorbic acid 45 mg/kg, [d,e,f]compared to Ageless liquid with piperine 4, 8, 16 mg/kg respectively, [g,h,i]compared to Ageless liquid without piperine 4, 8, 16 mg/kgrespectively,S- Significant, NS- Not significant

Table 2
Effect on malondialdehyde in retinal homogenate (nmol of MDA formed/ml)

Groups	Dose		Mean±SD	P value	Significance
I	Normal saline 1 ml/kg/day + 2% gum acacia	1 ml/kg/day	42.94±1.31		
II	Sodium iodate 75 mg/kg + 2% gum acacia	1 ml/kg/day	61.53±11.72	<0.001[a]	**S**
III	Sodium iodate 75 mg/kg + Ascorbic acid	45 mg/kg/day	51.92±2.50	>0.05[b]	**NS**
IV	Sodium iodate 75 mg/kg + Ageless liquid with piperine 4 mg/kg/day		52.88±6.02	>0.05[b]	**NS**
V	Sodium iodate 75 mg/kg + Ageless liquid with piperine 8 mg/kg/day		45.83±1.98	0.001[b]	**S**
VI	Sodium iodate 75 mg/kg + Ageless liquid with piperine 16 mg/kg/day		41.66±6.04	<0.001[b] 0.049[d]	**S**
VII	Sodium iodate 75 mg/kg + Ageless liquid without piperine 4 mg/kg/day		45.83±3.47	0.001[b]	**S**
VIII	Sodium iodate 75 mg/kg + Ageless liquid without piperine 8 mg/kg/day		47.11±4.46	0.004[b]	**S**
IX	Sodium iodate 75 mg/kg + Ageless liquid without piperine 16 mg/kg/day		47.27±8.02	0.004[b]	**S**

[a]compared to normal control, [b]compared to sodium iodate intoxicated control, [c]compared to Ascorbic acid 45 mg/kg, [d,e,f]compared to Ageless liquid with piperine 4, 8, 16 mg/kg respectively, [g,h,i]compared to Ageless liquid without piperine 4, 8, 16 mg/kgrespectively,S- Significant, NS- Not significant

Table 3
Effect on superoxide dismutase in retinal homogenate (U/ml)

Groups	Dose		Mean±SD	P value	Significance
I	Normal saline 1 ml/kg/day + 2% gum acacia	1 ml/kg/day	47.55±5.82		
II	Sodium iodate 75 mg/kg + 2% gum acacia	1 ml/kg/day	14.11±2.31	0.002[a]	**S**
III	Sodium iodate 75 mg/kg + Ascorbic acid	45 mg/kg/day	22.17±15.10	>0.05[b]	**NS**
IV	Sodium iodate 75 mg/kg + Ageless liquid with piperine 4 mg/kg/day		52.90±27.96	0.004[b]	**S**
V	Sodium iodate 75 mg/kg + Ageless liquid with piperine 8 mg/kg/day		127.17±20.15	<0.001[b] 0.05[c]	**S**
VI	Sodium iodate 75 mg/kg + Ageless liquid with piperine 16 mg/kg/day		185.88±37.12	<0.001[b-i]	**S**
VII	Sodium iodate 75 mg/kg + Ageless liquid without piperine 4 mg/kg/day		24.83±2.38	0.03[b]	**S**
VIII	Sodium iodate 75 mg/kg + Ageless liquid without piperine 8 mg/kg/day		74.51±29.04	<0.001[b]	**S**
IX	Sodium iodate 75 mg/kg + Ageless liquid without piperine 16 mg/kg/day		116.90±38.67	<0.001[b-i]	**S**

[a]compared to normal control, [b]compared to sodium iodate intoxicated control, [c]compared to Ascorbic acid 45 mg/kg, [d,e,f]compared to Ageless liquid with piperine 4, 8, 16 mg/kg respectively, [g,h,i]compared to Ageless liquid without piperine 4, 8, 16 mg/kgrespectively,S- Significant, NS- Not significant

Table 4
Effect on catalase in retinal homogenate (nmol/min/ml)

Groups	Dose		Mean±SD	P value	Significance
I	Normal saline 1 ml/kg/day + 2% gum acacia ml/kg/day	1	4914.25±530.45		
II	Sodium iodate 75 mg/kg + 2% gum acacia ml/kg/day	1	2644.30±675.73	0.019[a]	**S**
III	Sodium iodate 75 mg/kg + Ascorbic acid mg/kg/day	45	5261.33±1111.16	0.004[b]	**S**
IV	Sodium iodate 75 mg/kg + Ageless liquid with piperine 4 mg/kg/day		6371.63±1597.16	<0.001[b]	**S**
V	Sodium iodate 75 mg/kg + Ageless liquid with piperine 8 mg/kg/day		5710.83±1348.31	<0.001[b]	**S**
VI	Sodium iodate 75 mg/kg + Ageless liquid with piperine 16 mg/kg/day		8154.23±1610.43	<0.001[b] 0.001[c] 0.009[e] <0.001[g,h]	**S**
VII	Sodium iodate 75 mg/kg + Ageless liquid without piperine 4 mg/kg/day		4937.87±540.15	0.017[b]	**S**
VIII	Sodium iodate 75 mg/kg + Ageless liquid without piperine 8 mg/kg/day		4760.99±946.12	0.037[b]	**S**
IX	Sodium iodate 75 mg/kg + Ageless liquid without piperine 16 mg/kg/day		6848.07±703.43	<0.001[b]	**S**

[a]compared to normal control, [b]compared to sodium iodate intoxicated control, [c]compared to Ascorbic acid 45 mg/kg, [d,e,f]compared to Ageless liquid with piperine 4, 8, 16 mg/kg respectively, [g,h,i]compared to Ageless liquid without piperine 4, 8, 16 mg/kgrespectively,S- Significant, NS- Not significant

Table 5
Effect on transforming growth factor-1β (TGF-1β) in retinal homogenate (pg/ml)

Groups	Dose		Mean±SD	P value	Significance
I	Normal saline 1 ml/kg/day + 2% gum acacia ml/kg/day	1	825.25±76.85		
II	Sodium iodate 75 mg/kg + 2% gum acacia ml/kg/day	1	164.32±25.61	<0.001[a]	**S**
III	Sodium iodate 75 mg/kg + Ascorbic acid mg/kg/day	45	222.92±53.14	>0.05[b]	**NS**
IV	Sodium iodate 75 mg/kg + Ageless liquid with piperine 4 mg/kg/day		323.52±80.55	<0.001[b]	**S**
V	Sodium iodate 75 mg/kg + Ageless liquid with piperine 8 mg/kg/day		346.72±13.74	<0.001[b] 0.016[c]	**S**
VI	Sodium iodate 75 mg/kg + Ageless liquid with piperine 16 mg/kg/day		457.12±93.42	<0.001[b] <0.001[c] 0.047[e] <0.001[g]	**S**

VII	Sodium iodate 75 mg/kg + Ageless liquid without piperine 4 mg/kg/day	254.85±72.86	>0.05[b]	**NS**
VIII	Sodium iodate 75 mg/kg + Ageless liquid without piperine 8 mg/kg/day	366.72±6.52	<0.001[b] 0.003[c]	**S**
IX	Sodium iodate 75 mg/kg + Ageless liquid without piperine 16 mg/kg/day	380.52±19.99	<0.001[b] 0.001[c]	**S**

[a]compared to normal control, [b]compared to sodium iodate intoxicated control, [c]compared to Ascorbic acid 45 mg/kg, [d,e,f]compared to Ageless liquid with piperine 4, 8, 16 mg/kg respectively, [g,h,i]compared to Ageless liquid without piperine 4, 8, 16 mg/kgrespectively,S-Significant, NS- Not significant

Table 6

Effect on Adenosine triphosphate retinal homogenate (mol/ml)

Groups	Dose		Mean±SD	P value	Significance
I	Normal saline 1 ml/kg/day + 2% gum acacia	1 ml/kg/day	0.60±0.06		
II	Sodium iodate 75 mg/kg + 2% gum acacia	1 ml/kg/day	0.10±0.02		
III	Sodium iodate 75 mg/kg + Ascorbic acid	45 mg/kg/day	0.25±0.03	<0.001[a]	S
IV	Sodium iodate 75 mg/kg + Ageless liquid with piperine 4 mg/kg/day		0.29±0.01	0.005[b]	S
V	Sodium iodate 75 mg/kg + Ageless liquid with piperine 8 mg/kg/day		0.50±0.01	0.003[b]	S
VI	Sodium iodate 75 mg/kg + Ageless liquid with piperine 16 mg/kg/day		1.20±0.01	<0.001[b]	S
VII	Sodium iodate 75 mg/kg + Ageless liquid without piperine 4 mg/kg/day		0.20±0.04	0.04[b]	S
VIII	Sodium iodate 75 mg/kg + Ageless liquid without piperine8 mg/kg/day		0.34±0.08	0.01[b]	S
IX	Sodium iodate 75 mg/kg + Ageless liquid without piperine 16 mg/kg/day		0.82±0.01	<0.001[b]	S

[a]compared to normal control, [b]compared to sodium iodate intoxicated control, [c]compared to Ascorbic acid 45 mg/kg, [d,e,f]compared to Ageless liquid with piperine 4, 8, 16 mg/kg respectively, [g,h,i]compared to Ageless liquid without piperine 4, 8, 16 mg/kgrespectively,S- Significant, NS- Not significant

Table 7

Effect on body weight (g)

Groups	Dose	Body weight (Mean±SD)		P value	Significance
		Basseline	Final		
I	Normal saline 1 ml/kg/day + 2% gum acacia 1 ml/kg/day	117.16±10.40	243.50±10.13		
II	Sodium iodate 75 mg/kg + 2% gum acacia 1 ml/kg/day	132.50±32.21	214.16±63.37	>0.05[a]	**NS**
III	Sodium iodate 75 mg/kg + Ascorbic acid 45 mg/kg/day	231.00±29.46	245.66±9.60	0.012[b]	**S**
IV	Sodium iodate 75 mg/kg + Ageless liquid with piperine 4 mg/kg/day	215.83±55.35	243.33±24.93	>0.05[b]	**NS**
V	Sodium iodate 75 mg/kg + Ageless liquid with piperine 8 mg/kg/day	240.50±15.01	251.16±13.74	0.006[b]	**S**
VI	Sodium iodate 75 mg/kg + Ageless liquid with piperine 16 mg/kg/day	233.33±10.32	227.16±7.70	<0.001[b]	**S**
VII	Sodium iodate 75 mg/kg + Ageless liquid without piperine 4 mg/kg/day	241.66±13.29	235.00±8.64	<0.001[b]	**S**
VIII	Sodium iodate 75 mg/kg + Ageless liquid without piperine 8 mg/kg/day	240.00±7.74	251.66±17.53	0.008[b]	**S**
IX	Sodium iodate 75 mg/kg + Ageless liquid without piperine 16 mg/kg/day	246.66±10.32	231.00±11.79	<0.001[b]	**S**

[a]compared to normal control, [b]compared to sodium iodate intoxicated control, [c]compared to Ascorbic acid 45 mg/kg, [d,e,f] compared to Ageless liquid with piperine 4, 8, 16 mg/kg respectively, [g,h,i]compared to Ageless liquid without piperine 4, 8, 16 mg/kgrespectively,S- Significant, NS- Not significant

DISCUSSION

Data generated shows that sodium iodate has caused retinal damage as evidenced by an increase in MDA and decrease in GSH, SOD, catalase, , TGF-1β and ATP level compared to control group. Similar results are reported by earlier workers.[14] the molecular mechanism of retinal damage that occurs after $NaIO_3$ administration is thought to be mediated through induction of oxidative stress. Recent studies have indicated a direct effect of $NaIO_3$ on the sensory retina. [15,16] The present study revealed that the ageless liquid with/wihout piperine can prevent the retinal degeneration induced by sodium iodate in Sprague-Dawley rats. The retinoprotective potential was found to be better for ageless liquid with piperine in comparison with ageless liquid without piperine and maximum therapeutic benefit was observed at 16 mg/kg of ageless liquid with piperine. This is due to the bioavailability enhancing property of piperine.[7,8] The mechanism by which piperine enhances the bioavailability is not fully known. But it has been found to inhibit human CYP3A4 and P-glycoprotein, enzymes important for the metabolism and transport of xenobiotics and metabolites.[17,18] In animal studies, piperine also inhibited other CYP 450 enzymes important for drug metabolism.[19,20] Though the observed effect on retinal degeneration is due to all the component of ageless liquid, we believe that it is mainly due to resveratrol. Further, the antioxidant property of resveratrol might have protected the oxidative damage caused by sodium iodate.[1]

CONCLUSION

The retinoprotective potential was found to be better for ageless liquid with piperine in comparison with ageless liquid without piperine and maximum therapeutic benefit was observed at 16 mg/kg of ageless liquid with piperine. As there is species variation in response drugs the effect seen in animal studies cannot always be entirely extrapolated to humans. Hence, clinical evaluation should be performed to precisely define the

role of ageless liquid with piperine in retinal degeneration subjects.

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CONFLICT OF INTEREST

None.

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