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ISOTINE, AN HERBAL EYEDROPS, IMPROVES CATARACT-INDUCED BLINDNESS: A RETROSPECTIVE OBSERVATIONAL STUDY

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Cataract, Blindness, Herbal-eyedrops, Isotine, Ayurveda, Visual impairment

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ABSTRACT: Gradual vision loss is linked to degenerative changes and cataract. The Isotine-herbal eyedrop has been clinically used for 36 years with a claim to reverse the cataract-induced visual impairment. This retrospective observational study on 308 cataract patients, registered between 2017 to 2019 at Basu Eye hospital, Bareli, UP, India, having 3 months of treatment, shows the significant therapeutic response in uncorrected distance visual acuity (UDVA) based on logMAR mean before and after treatment (P<.001). The improvement has been observed in patients having UDVA 0.1 to 1.7 and in UNVA from N-6.1 to N-36and above. Patients of partial vision impairment, having logMAR up to 0.99, significantly attained either normal vision or below 6/18 (logMAR- 0.47). In 103 patients of severe vision impairment (logMAR mean 1.0 to 1.77, considered as Blind by WHO), only 40 patients did not respond, but the remaining 63 patients attained a logMAR mean below logMAR-0.8. In the case of UNVA, 169 patients had vision between N-12 to N35, but after treatment, either they got normal vision of N-6 or lower than N-12. In patients with severely impaired visions (N36 or more), 39 patients got visions below N-12 and 62 below N-20. Only 27 patients were left in range, but about 60% of them further improved their vision by using external eyeglasses. Thus, it could be concluded that Isotine probably improved cataract-linked impaired vision for distance and near vision through its antioxidant, anti-inflammatory, and protease activities, reducing lens-opaqueness, strengthening the ciliary muscle, lens-growth/nutrition supply, and improved retinal sensitivity.

INTRODUCTION: Vision impairment has a personal, social and economic impact on an individual, affecting the overall development of a Nation.

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Vision loss with aging is a progressive disease, primarily attributed to degenerative changes so that it can be delayed by lifestyle changes, diet, and therapeutic interventions.

As per the WHO report, about 2.2 billion people have vision impairment, and 50% of them are preventable, linked to refractive error, cataract, glaucoma, corneal opacities, diabetic retinopathy, and trachoma and presbyopia. A recent report indicates about 30% population aging 65 years

have a cataract-linked visual impairment, and only 10% of them adopt cataract surgery. The remaining patients prefer to live with bad life quality due to financial issues, non-awareness, or fear of post-operative adverse effects/poor prognosis. Another report indicates that in surgical intervention, greater improvements have been found in uncorrected distance visual acuity (UDVA) compared to uncorrected near visual acuity (UNVA), which is also a drawback. Since, presbyopia and cataracts are progressive stages of lens aging after 40 years, but are associated with different pathophysiological reasons, a new term, "Dysfunctional lens syndrome" has been introduced (DLS). It defines three clinical stages of the patient, based on changes in the lens crystalline.

In stage 1, there is a significant symptom of presbyopia, with loss of accommodation power but no light-scattering. In the 2nd and 3rd stages, significant ocular scattering appears, indicating combined symptoms of presbyopia and cataract. It is attributed to the failure of the microcirculation system in the lens cortex, bad regulation of cell volume, poor delivery of nutrients and antioxidants, and cataract formation in the lens. Thus, DLS is attributed to more than one pathogenic factor-like lens opaqueness, lens hardening, reduction of α-crystallin protein in the lens, and weakness in the ciliary muscle, so all these factors need to be corrected simultaneously [1]. Unfortunately, no Pharmacological drug is available to prevent or reverse DLS-related pathologies related to DLS. When one talks about blindness, cataract-linked blindness contributes to about 51% of worldwide blindness.

This can be prevented in case of age-related, as it belongs to degenerative disease, linked to cloudiness in the eye lens, alteration in protein crosslinking, exposure of hydrophobic surfaces, protein aggregation, and poor nutrition to the lens, changed refractive properties of the lens and poor retinal sensitivity. The etiological factors like a deficiency in Lanosterol, a reduced reserve of antioxidants, molecular chaperone, α-crystallin decrease, lens swelling due to polyol accumulation, abnormal function of Na^+-K^+ pump, disturbed pump-leak equilibrium, and high concentration of Cl^- and Na^+, in the lens are attributed to this pathology. In the case of diabetes, cataract formation is more common, so strict glycaemic control is recommended [2]. Since cataract formation is multi-etiological, multi-targeted therapies would be more promising and polyherbal formulations with many bioactive phytochemicals would be effective. Though surgical intervention is the main line of treatment, due to economic factors and fear of poor prognosis, patients avoid this option and explore the possibility of using medical treatments, which are not in a very developed stage due to the lack of significant therapeutic claims. Some earlier reports show claims like eye drops, liquid crystalline (LC) gels, Chitosan-poly(acrylic acid) (CS-PAA) nanoparticles as drug carriers, intravenous (IV) nutrition, oxidative therapy, micro-current stimulation, syntonic light therapy, *etc*.

They include (1) use of aldose-reductase-inhibitor "Kinostat" [3], (2) lanosterol and 25-hydroxycholesterol (acting through its binding to αB-crystallin chaperone protein for dissolving the lenticular opacities) [4], (3) compounds responsible for regulation of *Pax6* and *Bmi1* for activation of the lens epithelial stem/progenitor cells (LECs) [5], (4) regulation of intraocular-microbiome [6], (5) use of N-Acetyl carnosine (reducing glycation of crystallin crosslinking), (6) use of an US patentto normalize phase separation temperature and inhibition of formation of aggregates in eye lenses, (7) use of antioxidant like Vitamin C, E, A; pyruvate, LPA, carotenoids, etc and ARIs like M-79175, imirestat (AL-1576), epalrestat, zenarestat (FR-74366) to prevent glycation, (8) use of aspirin to promote acetylation of lysine, indicating the use of anti-inflammatory agents [7] and (9) transcriptional regulation of HS genes by the heat shock factor 1 (HSF1), reported to inhibit oxidation, post-translational modifications and misfolding of crystalline lens-proteins [8].

However, no multi-centric big clinical trial has been done in this respect. These approaches may delay the progress of cataracts and improve visual acuity. Still, these efforts are not enough to make the "blindness free society, so novel efforts are needed. In India, Isotine, an herbal eyedrop, has been in clinical use for more than 36 years, and its inventor has claimed it a "drug to reverse the formation of cataract and associated blindness" (www.drbasueyehospital.com**,** www. jagatpharma.

com). Though it has a long clinical success story, no scientific data is available. For the 1st time, here we have made a retrospective statistical analysis of clinical data collected from the records of Basu Eye Hospital, Bareli, UP, India.

METHODS: Ethical clearance: Ethical clearance for the progressive clinical trial of Isotine has been given by the ethical committee of the Institute of Medical Sciences (dean/2021/EC/2408, dated 15th February 2021), but here we have made a retrospective study on the clinical data, already preserved in the Basu eye hospital, to understand its clinical claim. We have not done any intervention here, but only statistical analysis has been carried out. As per guidelines of CTRI portal, Govt of India, only prospective studies are registered, so this study has not been registered. Since it was a study on old data, so ethical guidelines and principles of Helsinki- declaration could not be followed for taking pre-informed consent from the patients.

Data Collection: The patients registered in its OPD from 2017 to 2019 were considered for this study. Out of 750 registered patients, the 308 patients were diagnosed as cataract with inclusion criteria of poor-vision acuity, with cloudiness in the lens as evaluated by an ophthalmologist.

Recorded Parameters: At the time of patient's registration, uncorrected distance visual acuity (UDVA) and uncorrected near visual acuity (UNVA) in each patient's eyes, and treatment protocol on the registration card was recorded. All patients had been prescribed to use Isotine eye drop, 3 times a day.

After this treatment, the responses in both the eyes were recorded at the time of the 2nd visit of the patient to the hospital, which varied between 1-3 months. However, we have considered all the patients as "3-months treatment" for our study protocol. After treatment, again UDVA and UNVA were recorded the same way as before treatment to avoid a minimum manual error. The primary outcome of this study was to measure the change in visual acuity (VA) for distance and near vision, without eyeglass, in both the eyes (right and left eye) after treatment. The secondary outcomes included changes in the improvement in glare, halo, dryness, and problems with night vision.

Statistical Analysis: The UDVA, recorded by Snellen chart, was converted to logMAR value (log of the minimum angle of resolution). For distance vision, normal visual acuity was considered as logMAR 0.0 (equivalent to 6/6 meter). For near vision, the Jaeger scale was used for reading at 40 cm distance, and normal vision was considered N6[9]. Change in visual acuity was calculated directly by subtracting LogMAR data of UDVA and N value of UNVA [10]. Based on UDVA, in the right eye, all patients were divided into 4 groups (Group-1) normal vision (6/6), (Group-2)6/8 to 6/18 (logMAR 0.1 to 0.47, (Group-3) 6/24 to 6/60 (0.5 to 1.00) and (Group-4) 4/60- 1/60 (1.17 to 1.77). Those patients with visual acuity below 3/60 or only having the capability of finger counting or torch light perception were assumed to have vision of 3/60, because there is no scale to major the VA for these patients on the Snellen chart **Table 1**.

TABLE 1: THE SNELLEN CHART USED FOR THIS STUDY ALONG WITH CORRESPONDING LogMAR VALUE

Meter	Distance vision (LogMAR)	Near Vision (Jaeger scale)
Torch light perception		
1/60 (Finger count)	1.77	
2/60 (Finger count)	1.47	
3/60 (Finger count)	1.30	
4/60	1.17	
6/60	1.00	
6/36	0.77	
6/24	0.60	36
6/18	0.47	24
6/12	0.30	18
6/9	0.17	12
6/8	0.12	9
6/6	0.00	6

Note: We have assumed a cutoff of 3/60 for the calculation of vision of those patients who are only capable of finger count or light perception

As per WHO guidelines, these patients were considered blind. In these patients, the UNVA was also determined, and the patients were further grouped as (Group-1) normal vision (N6), (Group-2) N9 to N12, (Group-3) N12.1 to N35.9, and (Group-4) N36 and above. The results have been defined in two objective parameters, i.e. (1) in terms of change in the number of patients, who moved from one group to another, showing improvement, and (2) the change in the mean value of VA in before and after treatment, in terms of paired t-test, using SPSS program. All the data

have been reported as Mean ± SD, with C.I. 95% (Confidence Intervals) limits and results have been reported graphically through different figures.

Standardization of the Isotine: The Isotine, eye drop is a licensed ayurvedic medicine under the drug and cosmetics act 1940, Govt of India. Govt of Uttar Pradesh, India, gave the manufacturing and marketing license. It consists of the root of palash (*Butea monosperma* – 0.3% W/V), apamarg (*Achyranthus aspera* - 0.3% W/V) and punarnava (*Boerrhavin diffusa* - 0.3% W/V); the herbo-mineral preparations (Bhasma) – Yashad Bhashm - 0.6% W/V, Shudh Tankan Bhashm - 2.0% W/V, Shudh Fitkari Bhashm - 0.4% W/V and Shudh Tutth Bhashm - 0.04% W/V, (all prepared as per Ayurvedic formulary India), with the essence of Pudina (*Mentha pipreta* - 0.015% W/V) and Benzalkonium chloride - 0.01% W/V (preservative). Finally, the steam-distillate of this preparation is used as an eyedrop. The chemical standardization of Isotine eye drop was carried out by analyzing high-resolution liquid chromato-graphy mass spectroscopy (HRLCMS) by using TOF/Q-TOF Mass Spectrometer (Model-G6550A), FTIR spectroscopy by outsourcing to SAIF/CRNTS, IIT, Bombay (central instrumentation facility).

RESULTS:

Results Related to Standardization Parameters of Isotine:

FTIR Spectroscopy: Peak in the range of 3550-3200 nm, indicating the presence of O-H (Alcohol) group; peak 3000-2840 for C-H (Alkane and aldehydes; 1600-1700 indicating C=O (conjugated ketone, secondary amide, tertiary amide, C=C (Alkenes) and peak ranging 1440-1395, indicating O-H (bending) carboxylic acid **Fig. 1.**

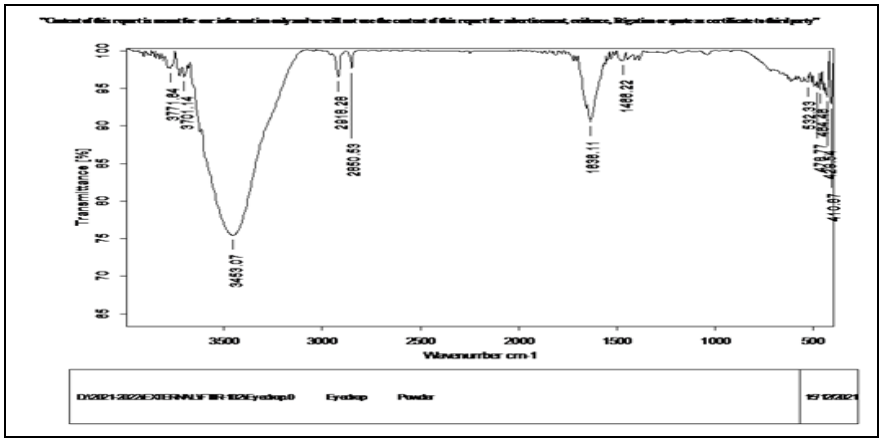

FIG. 1: CHROMATOGRAM OF FTIR OF ISOTINE

HRLCMS Spectroscopy: It showed the presence of 80 phytochemicals with a high abundance of compounds like 1,3-Dipropyl-8- cyclopentyl-xanthine [DPCPX], 2-Hexadecanone, N-Acetyl-leu-leu-tyr, edetate, quinic acid, shikimic acid, Indoleacrylic acid, 2-Carboxy-5,7- dimethyl-4-octanolide, Fibrin, and Nε-Acetyl-L-lysine **Fig. 2**. Major compounds of isotine, as per HRLCMS chromatogram, based on abundance of +ve charge, are shown in **Table 2.**

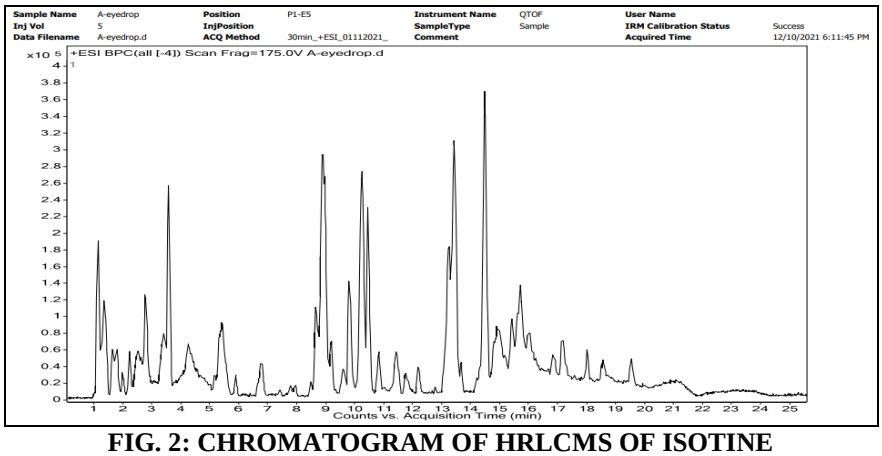

FIG. 2: CHROMATOGRAM OF HRLCMS OF ISOTINE

TABLE 2: MAJOR COMPOUNDS OF ISOTINE, AS PER HRLCMS CHROMATOGRAM, BASED ON ABUNDANCE OF +VE CHARGE

Sample Name	A-eyedrop	**Position**	P1-E5	**Instrument Name**	QTOF	**User Name**	
Inj Vol	5	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	A-eyedrop.d	**ACQ Method**	30min_+ESI_01112021_	**Comment**		**Acquired Time**	12/10/2021 6:11:45 PM

S. no.	Cpd	Name	m/z	RT	Abundance
1	38	1,3-Dipropyl-8-cyclopentylxanthine [DPCPX]	327.1763	10.352	140043
2	1	Edetate	293.0962	1.119	125022
3	8	N-Acetyl-leu-leu-tyr	472.2487	1.682	60417
4	18	Quinic acid	215.0514	3.574	46904
5	6	Fibrin	146.0916	1.415	35588
6	10	N6-Hydroxy-L-lysine	185.0911	1.892	35367
7	12	Quinic acid	215.0513	2.424	33429
8	4	Nε-Acetyl-L-lysine	189.1223	1.282	28684
9	26	2-Carboxy-5,7-dimethyl-4-octanolide	215.124	5.22	28661
10	19	Indoleacrylic acid	188.0696	4.041	26837
11	75	Monomenthyl succinate	279.1578	17.204	24791
12	23	2-Methylbenzaldehyde	121.0643	4.391	19698
13	5	(±)-2-(2-Methylpropylthiazolidine	146.0986	1.282	19395
14	71	CE(14:1(9Z))	298.2729	16.694	19091
15	22	cis-1,2-Diphenylcyclobutane	231.1187	4.367	18019
16	11	(2R,4S)-2,4-Diaminopentanoate	155.0809	2.215	17479
17	69	17beta-Hydroxy-4, 17-dimethyl-4-azaandrost-5-en-3-one	318.2386	15.885	16388
18	66	Fesoterodine	434.2725	15.431	16251
19	50	Sulfometuron	351.0779	12.146	15670
20	74	Cassine	298.2722	16.988	14972
21	24	2-Methylbenzaldehyde	121.0644	4.683	14231
22	46	Sulfadimidine	279.0921	11.353	14156
23	61	Taraxacolide 1-O-b-D-glucopyranoside	451.1919	14.659	12721
24	25	Maculosin	261.1221	4.885	12323
25	20	2-Descarboxy-cyclo-dopa	152.0698	4.145	11274
26	27	Pentobarbital	227.1375	5.276	11002
27	32	Chrysin	255.0641	8.603	10371

Effect of Isotine Treatment on the Uncorrected Near Visual Acuity (UNVA) of Right and Left Eye: Further, we analyzed the improvement in uncorrected near visual acuity (UNVA) in terms (1) change in (1) number of patients, attaining better UNVA, and (2) difference in the mean value of UNVA, before versus after treatment **Table 3**. The number of patients was high in Group-1 (having normal UNVA-N6). Before treatment, the number of patients was only 20, but this number rose to 87 after the Isotine-treatment. In Group-2 (N6.1 to N12) also, there were only 62 patients before treatment, but this number rose to 132 after treatment. On the contrary, in Group-3 (UNVA-N12.1 to N35.9), which is considered partial vision loss, the number of patients significantly reduced after treatment. It was 107 before treatment but reduced to 62 only in the after-treatment group. More interestingly, in patients with "severely visual impairment" (Group-4 having UNVAN-36 and above), the number of patients was 119, but it reduced to 27, after treatment in the right eye. These data clearly show the rise in a number of patient's Group-1 and 2 and the fall in group-3 and 4, indicating visual improvement in patients of all the stages of cataract with a significant change in the mean value of UNVA **Table 3.**

TABLE 3: THE CHANGE IN THE NUMBER OF PATIENTS WITH THEIR MEAN VALUE OF UNVA (UNCORRECTED DISTANCE VISUAL ACUITY) OF RIGHT AND LEFT EYES IN PATIENTS OF BEFORE AND AFTER TREATMENT

UNVA (uncorrected near visual acuity) (mean with 95% confidence interval [CI]:				
Right Eye (Jaeger scale)				
Category based on UNVA	Before Treatment		After Treatment	
	N	Mean ± SD	N	Mean ± SD
Group 1 (6)	20	6 ± 0	87	6 ± 0

Group 2 (6.1 – 12)	62	11.17 ± 1.34 (10.83, 11.52)	132	10.45 ± 1.50 (10.19, 10.71)
Group 3 (12.1 – 35.9)	107	21.02 ± 3.01 (20.45, 21.60)	62	20.51 ± 2.98 (19.75, 21.27)
Group 4 (36 and above)	119	36.0 ± 0.00	27	36.0 ± 0.00
Left Eye (Jaeger scale)				
Group 1 (6)	22	6 ± 0	84	6 ± 0
Group 2 (6.1 – 12)	69	11.04 ± 1.40 (10.70, 11.38)	132	10.15 ± 1.46 (9.90, 10.41)
Group 3 (12.1 – 35.9)	97	20.84 ± 3.01 (20.23, 21.45)	61	20.26 ± 2.93 (19.51, 21.01)
Group 4 (36 and above)	120	36.00± 0.00	31	36.00 ± 0.00

Statistical Analysis of Near Vision: While analyzing the pattern of movement of patients from groups of poorer vision to better- vision, based on the vision scale and cross-tabulation **Table 4** in SPSS software **Table 4**, we found that out of 62 patients of Group-2 (mean-N11), the 38 patients attained normal (N6) vision and only 24 patients were left in that group only, but with better UNVA (mean-N9). Similarly, in Group-3, before treatment, the 107 patients had had a mean value of N21±3.01, 95% confidence interval [CI]: 20.45, 21.60), but after treatment, the 18 patients attained the normal UNVA, 80 patients got UNVA below N-12 (10.65±1.50, 95% confidence interval [CI]: 10.31, 10.98) and only 9 patients were left in the Group-3, but with better UNVA (mean-19.33±2.64, 95% confidence interval [CI]:17.29, 21.36). This data also indicated improvement in all cases of cataracts. More interestingly, in the patients of Group-4 (n-119 in the right eye) who were categorized as "severely impaired vision" (considered as Blind, as per WHO), the 11 patients attained the normal vision (N6), 28 attained UNVA 11.14± 1.38, 95% confidence interval [CI]: 10.60, 11.67) and 53 patients attained UNVA of 20.71±3.01, 95% confidence interval [CI]: 19.88, 21.54). Only 27 patients showed no improvement in their VA and remained in the same Group-4.

TABLE 4: PAIRED T-TEST OF MEAN VALUE OF NEAR VISION (UNVA) OF RIGHT AND LEFT EYE, BEFORE TREATMENT (BT) AND AFTER TREATMENT (AT), IN CATARACT PATIENTS OF DIFFERENT GROUPS BASED ON TABLE-3A, AND CROSS-TABULATION, SHOWING THE MOVEMENT OF PATIENTS FROM POOR TO BETTER VISION

UNVA (uncorrected near visual acuity) Right Eye					
Category	**N**	**Before Treatment Mean ± SD**	**After Treatment Mean ± SD**	**T**	**P**
BT: Group 2 (6.1 – 12)	62				
AT: Became Normal	38	10.73 ± 1.50 (10.24, 11.23)	6 ± 0	19.453	0.000
AT: Unchanged	24	11.87 ± 0.61 (11.61, 12.13)	9 ± 0	23.000	0.000
BT: Group 3 (12.1 – 35.9)	107				
AT: Became Normal	18	20.66 ± 3.06 (19.14, 22.19)	0 ± 0	20.283	0.000
AT: Improved	80	20.77 ± 3.01 (20.10, 21.44)	10.65 ± 1.50 (10.31, 10.98)	29.145	0.000
AT: Unchanged	9	24 ± 0	19.33 ± 2.64 (17.29, 21.36)	5.292	0.001
BT: Group 4 (36 and above)	119				
AT: Became Normal	11	36 ± 0	6 ± 0		
AT: Improved	28	36 ± 0	11.14 ± 1.38 (10.60, 11.67)	95.304	0.000
AT: Improved – 2	53	36 ± 0	20.71 ± 3.01 (19.88, 21.54)	36.900	0.000
AT: Unchanged	27	36 ± 0	36 ± 0		
UNVA (uncorrected near visual acuity) Left Eye					
BT: Group 2 (6.1 – 12)	69				
AT: Became Normal	34	10.32 ± 1.51 (9.79, 10.85)	6 ± 0	16.674	0.000
AT: Unchanged	34	11.82 ± 0.71 (11.57, 12.07)	9.08 ± 0.51 (8.90, 9.26)	18.466	0.000
AT: Deteriorated	1	9 ± 0	36 ± 0		
BT: Group 3 (12.1 – 35.9)	97				
AT: Became Normal	20	20.10 ± 2.93 (18.72, 21.47)	6 ± 0	21.476	0.000
AT: Improved	66	20.72 ± 3.01 (19.98, 21.46)	10.31 ± 1.50 (9.94, 10.68)	30.801	0.000
AT: Unchanged	11	22.90 ± 2.42 (21.27, 24.53)	18.54 ± 1.80 (17.33, 19.76)	5.164	0.000
BT: Group 4 (36 and above)	120				
AT: Became Normal	9	36 ± 0	6 ± 0		
AT: Improved	31	36 ± 0	11.03 ± 1.42 (10.50, 11.55)	97.515	0.000
AT: Improved – 2	50	36 ± 0	20.64 ± 3.00 (19.78, 21.49)	36.101	0.000
AT: Unchanged	30	36 ± 0	36 ± 0		

This number was about 9% of total number of 308 patients. This data indicated that the improvement was better in UNVA (9% left unaffected) as compared to UDVA (12% left unaffected).

Effect of Isotine Treatment on the Uncorrected Distance Visual Acuity (UDVA) of Right and Left Eye: In the distance vision also, a significant improvement was recorded in both the eyes after Isotine treatment. Similar to the change in near vision, described above, the results have been described in terms of (1) the number of patients shifting to groups of better visual acuity **Table 5**. At the time of registration, there were only 5 patients in Group 1, 63 in Group 2, 137 in Group 3, and 103 in Group-4 (Group's description is given in the method section). This data indicates a higher number of cataract patients with poor or severely poor UDVA (78% of total patients). Interestingly, after treatment, 88% of the 308 registered patients showed significant improvement in their UDVA, and 12% did not change. The number of patients rose to 60 in Group 1 (normal vision) and 120 in Group 2. On the contrary, the number of patients was reduced to 88 in Group-3, 137 before treatment. Similarly, in Group-4 also, there were 103 patients earlier before treatment but reduced to only 40 after treatment **Fig. 3.**

TABLE 5: THE NUMBER OF PATIENTS AND THEIR MEAN VALUE OF UDVA (UNCORRECTED DISTANCE VISUAL ACUITY) OF RIGHT AND LEFT EYES IN GROUPS OF PATIENTS IN BEFORE AND AFTER TREATMENT

UDVA (uncorrected distance visual acuity (logMAR mean with 95% confidence interval [CI]:				
Right Eye				
Category	**Before Treatment**		**After Treatment**	
	N	**Mean ± SD**	**N**	**Mean ± SD**
Group 1 (0)	5	0 ± 0	60	0 ± 0
Group 2 (0.1 – 0.49)	63	0.38 ± 0.11 (0.35, 0.41)	120	0.32 ± 0.13 (0.29, 0.34)
Group 3 (0.50 – 1.00)	137	0.85 ± 0.15 (0.82, 0.87)	88	0.80 ± 0.16 (0.77, 0.84)
Group 4 (1.01 – 1.9)	103	1.33 ± 0.12 (1.31, 1.36)	40	1.30 ± 0.03 (1.29, 1.31)
Left Eye				
Group 1 (0)	3	0 ± 0	55	0 ± 0
Group 2 (0.1 – 0.49)	62	0.36 ± 0.11 (0.33, 0.39)	126	0.30 ± 0.11 (0.28, 0.33)
Group 3 (0.50 – 1.00)	137	0.85 ± 0.16 (0.82, 0.87)	87	0.82 ± 0.15 (0.78, 0.85)
Group 4 (1.01 – 1.9)	106	1.33 ± 0.12 (1.31, 1.35)	40	1.30 ± 0.04 (1.29, 1.32)

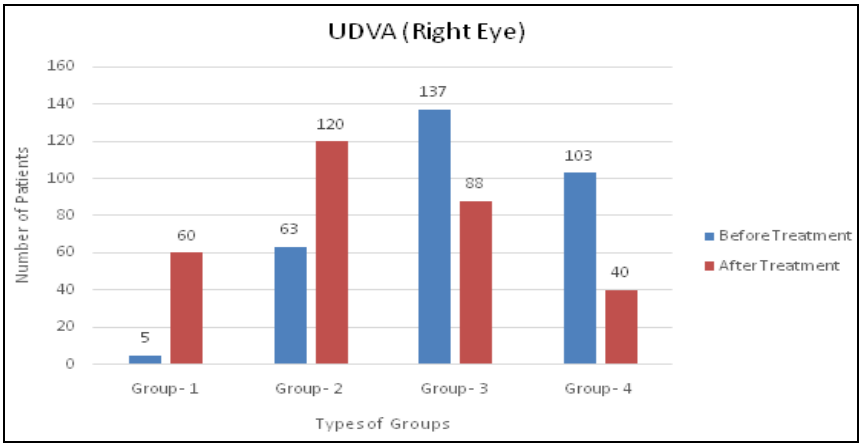

FIG. 3: EFFECT OF ISOTINE ON UDVA IN RIGHT EYE, IN TERMS OF NUMBER OF PATIENTS, BEFORE VERSUS AFTER TREATMENT. GROUPS- (1) NORMAL VISION (6/6), (2) 6/8 TO 6/18 (LOGMAR 0.1 TO 0.47, (3) 6/24 TO 6/60 (0.5 TO 1.00) AND (4) 4/60- 1/60 (1.17 TO 1.77)

Based on the analysis of cross tabulation **Table 5**, we have shown the movement of patients from one group to another, in terms of their number. Before treatment there were 63 patients in group-2, but after treatment, 36 patients attained normal value (Group-1), and only 27 patients remained in that Group-2. Similarly, In Group-3, there were 137 patients before treatment, but after treatment, 19 patients attained normal vision (Group-1), 86 patients moved to Group-2, and only 32 patients

remained in Group-3. Further in Group-4, before treatment, there were 103 patients having log MAR 1 and above. After treatment, no patient attained normal vision (Group 1), but 7 patients moved to Group 2 and 56 patients moved to Group 3, and only 40 patients remained in Group 4 **Fig. 4.**

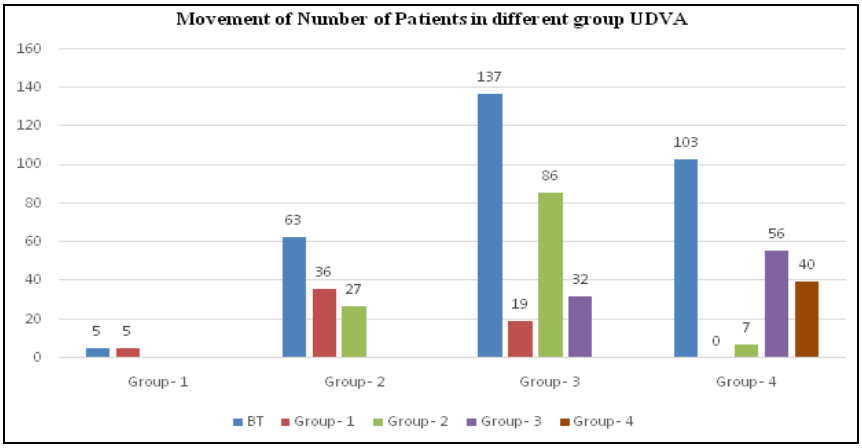

FIG. 4: EFFECT OF ISOTINE ON MOVEMENT OF NUMBER PATIENTS FROM GROUPS OF POOR VISION TO BETTER VISION BASED ON UDVA IN RIGHT EYE (FIGURE SHOWING THE MOVEMENT OF PATIENTS FROM BEFORE TREATMENT TO AFTER TREATMENT IN DIFFERENT GROUPS OF PATIENTS BASED ON THEIR UDVA. THE BLUE BAR INDICATES THE NUMBER OF PATIENTS BEFORE TREATMENT, AND THE OTHER BARS INDICATE THE NUMBER OF PATIENTS IN GROUP – 1 (6/6), GROUP -2 (6/8 – 6/18), AND GROUP – 3 (6/24 – 6/60), AND GROUP – 4 MORETHAN 6/60).

Statistical Analysis of UDVA: On further analysis of the logMAR mean of patients, **Table 6**, who moved to different groups with better UDVA, it was found that in all such cases, the logMAR mean significantly lower after treatment when compared with the logMAR mean of the same patient, before treatment.

The mean values were also significantly changed in all the groups (P< .001).In the Group-2, initially, there were 63 patients logMAR mean of 0.38 ± 0.11 (95% confidence interval [CI]:0.35, 0.41, n-63). Still, after treatment, 36 patients attained the normal vision (6/6), and the remaining 27 attained lower logMARmean (0.20±0.06), though they were left in the same Group-2.

Similarly, out of 137 patients in 3rd group, the logMAR mean before treatment was 0.85±0.16), but after treatment, 19 patients attained normal vision (6/6), 86 patients attained UDVA below 6/18 (logMAR 0.35), and only 32 patients remained in Group-3, but with lower logMAR mean (0.67± 0.1). More interestingly, when we analyzed the data of patients in the "severely vision impaired" state, who had logMARmean between 1.17 to 1.77 (4/60-1/60), almost considered to blind, as per WHO classification, out of 103 registered patients, before treatment, (Group-4), the calculated logMAR mean of that group was1.33 ± 0.12 (95% confidence interval [CI]: 1.31, 1.36), but after treatment the 7 patients attained UDVA below 6/18 (logMAR mean-0.32±0.15), 56 patients attained VA below 6/48 (logMAR mean- 0.88±0.15), and only 40 patients did not show any improvement, which was about 12% of total 308 patients.

Thus, it can be concluded that Isotine brought visual improvement in 88% of patients after 3 months treatment. It also brought vision to patients of severely visual impaired category. Further, in the paired "t" test analysis of the mean values of respective groups of before and after treatment of those208 patients, who showed improvement in their UDVA **Table 6**, significant improvement (P<0.001) was observed in all the cases.

It is interesting to note that among the 137 patients of group 3 (partial vision loss), who were previously having log MAR mean 0.85± 0.15 (95% confidence interval [CI]:0.82, 0.87, n-137) before treatment, about 73% of patients attained logMAR mean below 0.35 (VA-6/18).

Thus, based on cross-tabulation, it can be summarized that patients with partial vision loss (logMAR below 0.47) showed a better therapeutic response, as most either attained normal vision or near-normal vision. However, the patients severely visual impaired (logMAR 1.0 and above), also

attained significant improvement as 61% of patients got UDVA logMAR below 1.0, making a case of "reversal of cataract induced blindness".

From the specific analysis of visual improvement in those patients, who were left in the same group, we made a quantitative analysis of the betterment of their vision by making a paired t-test analysis.

We noticed that all the patients significantly reduced their logMAR mean value. In case of 27 patients of Group-2, who remained in that group, after treatment, showed lower logMAR mean of 0.20± 0.06 (95% confidence interval [CI]: 0.18, 0.23, as compared to their logMAR mean of 0.43± 0.08 (95% confidence interval [CI]:0.40, 0.47), before treatment (P<.001).

Similarly, inGroup-3, the 32 patients who remained in that group after treatment, got logMAR mean of 0.67± 0.10 (95% confidence interval [CI]: 0.63, 0.71, which was 0.95 ± 0.08 (95% confidence interval [CI]: 0.92, 0.99), before treatment, showing better VA (P<.001) (Table-4B).

TABLE 6: PAIRED T-TEST OF MEAN VALUE OF DISTANCE VISION (UDVA) OF RIGHT AND LEFT EYE, BEFORE TREATMENT (BT) AND AFTER TREATMENT (AT), IN CATARACT PATIENTS OF DIFFERENT GROUPS AND CROSS-TABULATION, SHOWING THE MOVEMENT OF PATIENTS FROM POOR TO BETTER VISION

Category	N	Before Treatment Mean ± SD	After Treatment Mean ± SD	T	P
UDVA (uncorrected distance visual acuity) Right Eye					
BT: Group 2 (0.1 – 0.49)	63				
AT: Became Normal	36	0.35 ± 0.12 (0.31, 0.39)	0 ± 0	16.669	0.000
AT: Unchanged	27	0.43 ± 0.08 (0.40, 0.47)	0.20 ± 0.06 (0.18, 0.23)	11.907	0.000
BT: Group 3 (0.50 – 1.00)	137				
AT: Became Normal	19	0.72 ± 0.12 (0.66, 0.78)	0 ± 0	24.422	0.000
AT: Improved	86	0.84 ± 0.14 (0.80. 0.87)	0.35 ± 0.12 (0.33, 0.38)	26.219	0.000
AT: Unchanged	32	0.95 ± 0.08 (0.92, 0.99)	0.67 ± 0.10 (0.63, 0.71)	12.218	0.000
BT: Group 4 (1.01 – 1.9)	103				
AT: Improved	7	1.27 ± 0.10 (1.17, 1.37)	0.32 ± 0.15 (0.18, 0.46)	16.029	0.000
AT: Improved – 2	56	1.36 ± 0.16 (1.32, 1.41)	0.88 ± 0.15 (0.84, 0.92)	17.190	0.000
AT: Unchanged	40	1.30 ± 0	1.30 ± 0.03 (1.29, 1.31)	-0.274	0.785
UDVA (uncorrected distance visual acuity) Left Eye					
BT: Group 2 (0.1 – 0.49)	62				
AT: Became Normal	33	0.31 ± 0.11 (0.27, 0.36)	0 ± 0	15.293	0.000
AT: Unchanged	29	0.41 ± 0.09 (0.37, 0.45)	0.21 ± 0.08 (0.18, 0.24)	9.440	0.000
BT: Group 3 (0.50 – 1.00)	137				
AT: Became Normal	19	0.72 ± 0.16 (0.64, 0.80)	0 ± 0	19.149	0.000
AT: Improved	87	0.83 ± 0.15 (0.80. 0.87)	0.34 ± 0.11 (0.31, 0.36)	28.319	0.000
AT: Unchanged	31	0.97 ± 0.07 (0.94, 0.99)	0.69 ± 0.13 (0.64, 0.74)	10.105	0.000
BT: Group 4 (1.01 – 1.9)	106				
AT: Improved	10	1.30 ± 0.07 (1.25, 1.35)	0.31 ± 0.10 (0.23, 0.38)	34.378	0.000
AT: Improved – 2	56	1.34 ± 0.14 (1.31, 1.38)	0.88 ± 0.13 (0.85, 0.92)	20.344	0.000
AT: Unchanged	40	1.32 ± 0.10 (1.29, 1.35)	1.30 ± 0.04 (1.29, 1.32)	1.038	0.306

DISCUSSION: Thus, based on the evaluation of overall response Isotine treatment, in terms of % improvement in several patients, it can be safely summarized that Isotine brought significant improvement in both distance and near vision in both the eyes of cataract patients; we divided the patients in 4 groups (1) logMAR 0 and below, (2) logMAR 0.1-0.47, (3) logMAR 0.48-0.99, (4) logMAR 1 and above and we found that out of 308 registered patients of cataract, the 19% patients attained normal UDVA (Group-1), 39% attained UDVA below logMAR 0.47 (Group-2), 28% attained logMAR mean below 0.99 (Group-3) and about 13% patients did not show any change and they remain in the range of 1 and above (Group-4) **Fig. 5.**

Similarly, in the case of UNVA, 28% of patients attained normal near vision, 62% of patients attained UNVA in the range of 6.1 to 35.9, and among them, 43% had UNVA in the range of N-6.1 to N 12 (improved -1) and 20% (Improved-2) were

having UNVA in range of N-12.1 to N 35.9. Only 9% of patients did not show any change **Fig. 6**. Further 1 patient (0.32%) deteriorated for distance vision in the right eye and 2 patients deteriorated (0.64%) in case of near vision in the left eye.

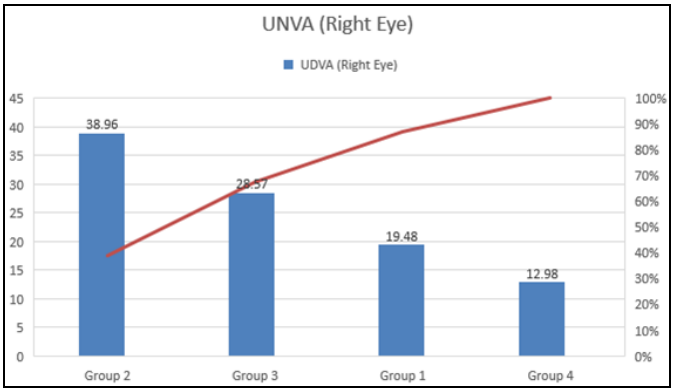

FIG. 5: HISTOGRAM SHOWING THE OVERALL IMPROVEMENT IN UDVA IN RIGHT EYE AFTER TREATMENT WITH ISOTINE

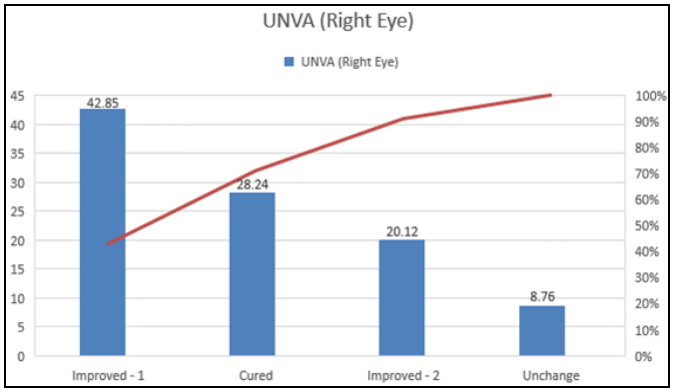

FIG. 6: HISTOGRAM SHOWING THE EFFECT OF ISOTINE IMPROVEMENT IN UNVA IN RIGHT EYE

Since, visual acuity is dependent on the optical and neural elements, like (1) retinal sensitivity, (2) lens capability to make a sharp image on the retina, and (3) neural system/optical nerve sending a message to the brain for interpretation, so for achieving the visual improvement, all these factors need to be corrected. In cataracts, because of the opaqueness of lens, refractive errors are most important for visual impairments, as they affect the way and intensity of light on the retina.

Recently, strategies to enhance the regeneration of the lens are the most effective path for treating cataracts, as it restores the accommodative vision. The stem cell therapy has shown promising results in in vitro experiments; there could be a possibility to activate the natural pluripotent stem cells already found in the eye. The lens growth continues throughout life, resulting in volumetric growth, which maintains the lens's capability to coordinate with other tissues involved in the optical system. Lens arises from the ectoderm situated next to the optic vesicles.

The progenitor cell population is located at its surface, and differentiated cells are confined to the interior. Epithelial cells proliferate and shift below the lens equator to differentiate into new fibers progressively added to the fiber mass. The posterior cells in lens vesicle, elongate to form the primary fibers, and the anterior cells differentiate into epithelial cells. FGFs (required to initiate fiber differentiation), BMPs, Wnt, and Shh are required to induce lens differentiation from ectoderm, and the Wnt signaling is involved), finally giving distinctive polarity. The changes in this continuous growth process, with aging and environmental insults, are linked to presbyopia and cataract. Volumetric growth results from the continuous proliferation of lens epithelial cells (LECs), which is also modulated by a mechanical strain. It increases the magnitude of static stretching and the stretching frequency in cyclic stretching [11].

The lens-cell regeneration occurs either from the pigmented epithelium of the dorsal iris or the corneal epithelium. Lens regeneration from the cornea requires suppression of Wnt/β-catenin signaling [12]. In humans, the lens growth is biphasic i.e (1) prenatal, having rapid growth showing sigmoidal pattern and (2) second growth phase, throughout the life is slow and linear (wet weight). It has been hypothesized that the lens nucleus, contains the rapidly growing fiber cells and the diffusion barrier contains cells, involved in linear slow growth [13].

Cataract(s) linked lens-opacity and light scattering is attributed to aggregation of high molecular weight proteins and disruption of the lens microarchitecture itself, which involves abnormalities in (1) lens crystallins, (2) connexins, (3) membrane proteins, (4) components, (5) intermediate filament proteins *etc*. These factors are regulated through activities of different (1) chaperone (2) protein degradation components, (3)

transcription factors, (4) growth factors, (5) channels for lens circulation, and (6) collagen and extracellular matrix etc. So, any intervention, normalizing these factors would help reverse the cataract pathology. In age-related cataracts, the environmental insults destabilize these factors by epigenetic mode of action resulting in raised susceptibility of lens-proteins, resulting in the formation of high molecular weight (HMW) aggregates and denatured crystallins, bound by α-crystallin [14]. Cataract-linked lens-opacity and light scattering, is attributed to aggregation of high molecular weight proteins and disruption of the lens microarchitecture itself, which involves abnormalities in (1) lens crystallins, (2) connexins, (3) membrane proteins, (4) components, (5) intermediate filament proteins, *etc*. These factors are regulated through activities of different (1) chaperone (2) protein degradation components, (3) transcription factors, (4) growth factors, (5) channels for lens circulation, and (6) collagen and extracellular matrix, *etc*. So, any intervention, normalizing these factors would help reverse the cataract pathology. In age-related cataracts, the environmental insults destabilize these factors by epigenetic mode of action resulting in raised susceptibility of lens-proteins, resulting in the formation of high molecular weight (HMW) aggregates, denatured crystallins, bound by α-crystallin [14].

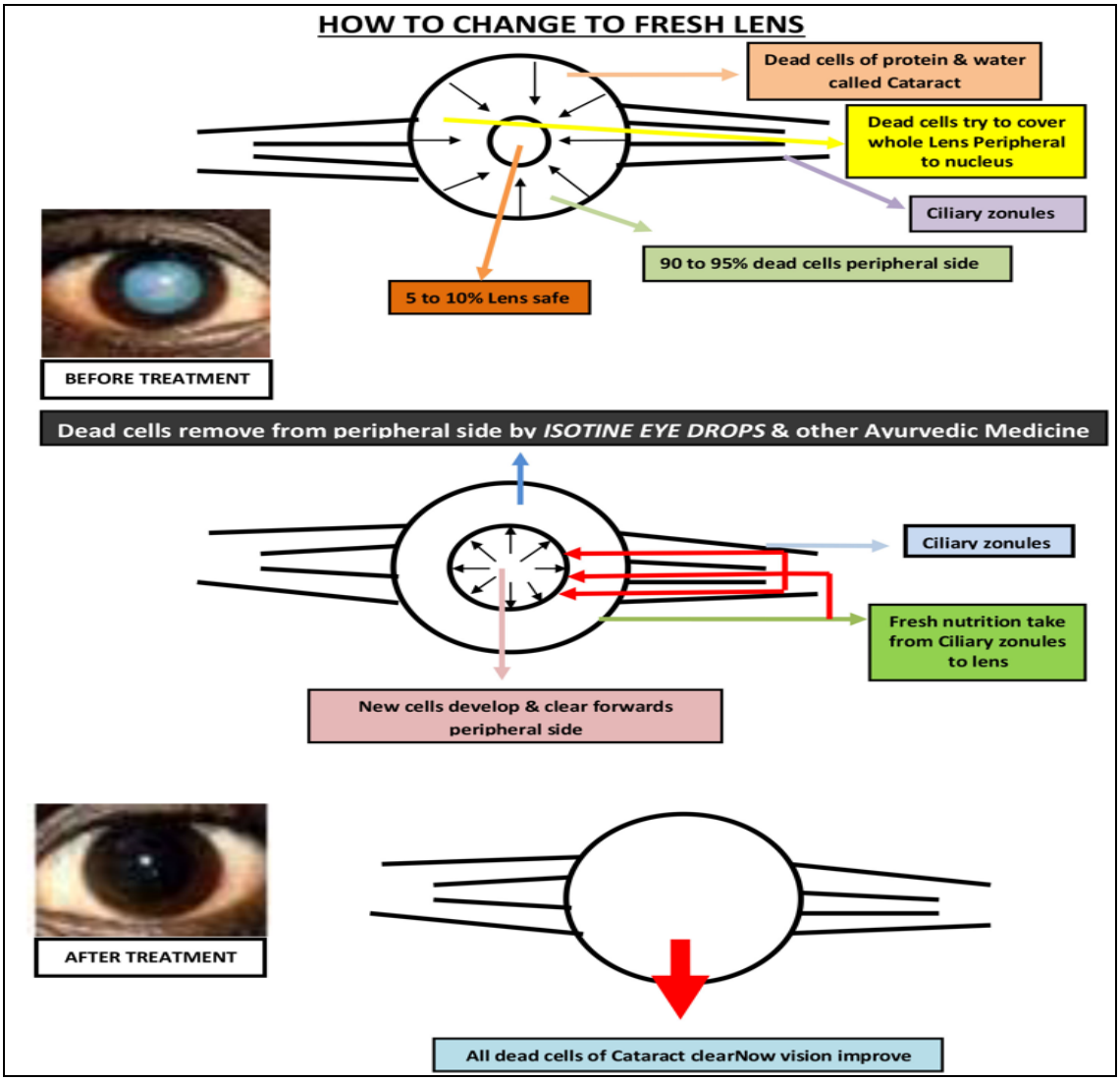

FIG. 7: ABSTRACT DIAGRAM, SHOWING THE POSSIBLE MECHANISM OF ACTION OF ISOTINE, TOWARDS ITS ROLE IN REGENERATION OF NEW CELLS IN THE EYE LENS. THE NUTRITION IS BEING SUPPLIED TO THE NUCLEUS THROUGH THE CILIARY MUSCLE AND CANAL OF SHELAM BODY. THIS ACTIVATES THE FORMATION OF NEW CELLS, THAT GOES TO THE PERIPHERY AND THE OLD DEAD CELLS (APOPTOSIS) RETURN TO THE NUCLEUS FOR THEIR OUSTER FROM THE LENS, THERE BY MAINTAINING THE VOLUME OF THE LENS TO NORMAL

Though surgery is the most accepted medical intervention for cataracts, post-cataract-surgical complications and secondary cataract development due to posterior capsule opacification (PCO) are common. This situation is attributed to aberrant growth of lens epithelial cells, which are left behind in the capsular bag. Uncontrolled activity of Transforming growth factor β (TGFβ) is mainly involved in developing fibrotic PCO, which is due to delayed inhibitory action of Sprouty (Spry) 1 and Spry2 [15]. The expression of FGF-1 and its receptors, FGFR-2 and FGFR-3 has been reported to play a significant role. Thus, factors could modulate the signalling pathways involved in the concentration and activity of proteins like FGF, BMP/TGF-β, Notch, and Wnt signaling proteins, retinoic acid, and Hedgehog pathways, would be effective. Similarly, Spred, like Sprouty (Spry) and also Sef proteins, acting through receptor tyrosine kinase (RTK)-mediated MAPK/ERK-signaling, are involved [16].

Isotine has shown promising results in cataract patients by enhancing their visual acuity, but its mechanism of action is unclear. More experiments and bioinformatics are needed to solve this complex issue. Still, the presence of minerals in Isotine, might be playing an important role in regulating the signalling steps involved in lens growth or regeneration. However, here we can hypothesize that isotine ingredients give nourishment to the nuclear cells, through the ciliary muscle and canal of shelam body, which activates the formation of new cells that goes to the periphery. At the same time, old dead cells (Apoptosis) return to the nucleus for getting a passage to get ousted from the lens, thereby maintaining the volume of the lens to normal **Fig. 7.**

The Yashad Bhashm contains Zinc; Fitkari Bhashm-alum); Tutth Bhashm" (copper sulphate) might be playing significant role as cofactors for various enzymes, involved in signalling pathways of anti-inflammatory, antioxidant, matrix metalloproteinases, enhancing autophagy [17, 18]. Rapid wound healing [19], inhibition of Phospholipase A2 activity [20] and antimicrobial activities. Zinc is reported to reduce macular degeneration, night blindness, and cataract, by being the constituent of transcription factor III A, Zn-metalloproteases, "carbonate dehydrogenase" and fructose 1, 6 biphosphatase. Recently, carbonic anhydrase inhibitors have been reported to reduce eye pressure by decreasing the production of intraocular fluid, thus helping in glaucoma management [21]. The Zinc supplements may provide the nutrition for lens and cornea and improve the functioning of synaptic sites within the retina and CNS, especially at glutamatergic nerve terminals[22]. TheBorax might be active through optimizing the angiogenesis in the eye. The alum controls bleeding and activates healing [23] micro-damages in the eye. Copper, the component of superoxide dismutase, maintains the cellular antioxidant's level in the eye. These metals might also be acting as an adjuvant to enhance the absorption of secondary metabolites of plant constituents of Isotine, which have a primary role in enhancing the pathways for protease activation, growth of lens, and retinal repair, though not enough reports are available in this context, collectively they might be active on epithelial cells, which are directly involved in these processes and showing additive or synergistic responses.

Though there is no direct evidence for the reversal of cataracts, there could be the possibility of forming new cells in the lens, pushing out the old cells, filled with deformed crystalline proteins, attributing to the opaqueness of the lens. Further experiments are needed to support this claim. This study clearly indicates the reversal of severely impaired vision without any surgical intervention. This novel finding has never been reported earlier with any other medicine. This opens a ray of hope to reduce the cases of cataract-induced blindness in society. More animal experiments are needed to explain its mechanism of action but based on the reported effect of its ingredient; it can be hypothesized that it is acting through reduction of the opaqueness of lens, growth of lens, improved retinal sensitivity, though enhanced antioxidant, anti-inflammatory and protease activity.

CONCLUSION: Isotine an herbal eye drop, already in clinical practice for more than 36 years, with 3 months of treatment, is significantly reversing the poor vision and severely impaired vision induced by cataracts, categorized as blindness as per WHO classification. It also reduces the power of the eyeglass and removes the

eyeglass completely by normalizing the eye physiology. The possible mechanism of action of Isotine could be attributed to its antioxidant, anti-inflammatory, and protease activation potentials.

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Ethical Approval: Ethical clearance for the study of Isotine has been given by our Institute Banaras Hindu University ethical committee (dean/2021/EC/2408, dated 15th February 2021).

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