Pharmacologic vitreolysis of vitreous floaters by 3-month pineapple supplement in Taiwan: A pilot study

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Abstract: Purpose: This survey is the first one in the world to evaluate the pharmacologic effects of pineapples for floaters. In different designs, we followed the results of patients who took various doses of pineapples each day for 3 months. **Methods**: The studies and sources of crude pineapples were all scheduled between March and June 2016 in Southern Taiwan, including Tainan, Kaohsiung and Ping-Tung Cities. The famous, beneficial and delicious pineapples were supplied by the local farmers selling to the world since 1900. In this study, 388 participants were arranged to undergo a series of ocular examinations during the series of experiments. In experiment 1, 190 subjects were classified into group 1 (one floater) and group 2 (multiple floaters); all participants took 2 pieces of pineapple after lunch every day for 3 months. In experiment 2, the 198 eyes with various vitreous floaters were classified into 3 groups by chance, according to the extent of pineapple intake, including the low pineapple group (LPA), middle pineapple group (MPA) and high pineapple group (HPA). In all the experiments, our staff members cut into one piece of pineapple with 100 g. Regular intake of pineapples is good for health-promotion and even cancer-prevention; however, to prevent higher blood glucose and ensure daily caloric restriction, the reasonable amount of pineapple is 2-3 pieces within healthy persons. In experiment 2, the amounts of oral pineapples in LPA, MPA, and HMP were 1, 2, and 3 pieces after lunch each day, respectively. **Results**: In experiment 1,100% subjects of one floater (120 eyes) subsides to only 29.2% (35/120) after 3-month-therapy. Besides, 70 participants with multiple floaters decreased to 19 cases (27.1%; 19/70) three months later. In a world, the extract pineapple may enhance floaters disappearance. In experiment 2, groups 1-3, (each group = 66 eyes) were choose randomly to different supplements including the LAP, MAP and HAP intake also for 3 months. It is surprised that from pineapple may increase the rate of disappearance of vitreous opacity. The percentage of decrease of floaters by taking the pineapples was 45.5%, 37.8% and 30.2% and 1, 2, 3 pieces, respectively. It also showed that pineapples for treating the patients with floaters with dose-dependent manner. In addition, the protocols for therapy of the floaters were no special side effects. Furthermore, the mechanisms of dissolving floaters may be to cut and clear the vitreous fibrils and to scavenge the free radicals which could result in hyaluronic acid degradation and vitreous floater formation. **Conclusion**: We found that taking pineapples should diminish the persistence of floaters, posterior vitreous detachment and even extracellular matrixes which could impact the disturbance of vision and even associated complications.

[Chi-Ting Horng, Fu-An Chen, Daih-Huang Kuo, Li-Chai Chen, Shou-Shan Yeh, and Po-Chuen Shieh. **Pharmacologic vitreolysis of vitreous floaters by 3-month pineapple supplement in Taiwan: A pilot study**. J Am Sci 2019;15(4):17-30]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org. 3. doi:10.7537/marsjas150419.03.

Keywords: pineapple, vitreous floater, bromelain

Introduction

The vitreous is highly hydrated gel-like structure (> 98% water) that is acellular, apart from a few cells called hyalocytes in the vitreous cortex. Besides, the gel state is maintained by a network of long thin collagen fibrils that are approximately 15 nm in diameter. Filling the space is a network of hyaluronan; this glycosaminoglycan (polysaccharide) may attract water and generate swelling pressure that inflates the gel. The collagen fibrils are composed of collagen type II, V, XI and IX. They are organized into small bundles, and interconnections between these bundles allow the formation of an extended network that maintains the gel state.

During aging, the vitreous progressively liquefies and pockets of liquid form in the gel. In the adult eye, 20% of vitreous is liquid, then after the age of 40 years there is increasing liquefaction so that by 80 to 90 years of age more than half of vitreous is liquid (1). The vitreous liquefaction, in conjunction with age-related weakening of postbasal vitreous-retinal adhesion, then results in posterior vitreous detachment (PVD). In clinics, the symptom of PVD is the most common cause of acute-onset floaters. A recent paper by van Overdam and his co-workers suggests that patients with isolated PVD, vitreous floaters, vitreous hemorrhages or retinal hemorrhages at initial presentation need to be rescheduled for a follow-up visit (2). All the persons were instructed to return if the number of floaters increased. However, the majority of PVD is benign regarding physiological change. For those older than 40 years of age, PVD gradually impacts the visual axis. Moreover, the prevalence of PVD is up to 24% among those aged 50–59 years, increasing to 87% among people older than 80 years. In PVD, the vitreous shrinks and detaches from the retina, leading to floaters. In 14% of cases, tractional forces from the vitreous jelly over the retina sometimes cause retinal tears. However, left untreated, the tears which result in breakage may allow fluid to enter the sub-retinal space and could progress to retinal detachment (RD) and even blindness. Therefore, wiping out vitreous floaters early is very important for eyesight preservation (3).

Physiologically, the vitreous requires a complex biochemical and structural procedure. It is completely attached to the retina. Floaters usually begin as a few small spots, curtains and clouds, becoming much denser over time. In most cases, vitreous opacities occur as a result of degenerative changes. The vitreous liquefaction should provoke condensation of vitreous collagen fibers and PVD which show floaters. In a more dramatic condition, the existence of floaters is induced. In humans, most ocular floaters are small flecks of a protein called collagen in the back of your eye. As you age, the protein fibers that make up the vitreous shrink down to little shreds that clump together. The shadows they cast on your retina are floaters. If you further see a flash, it's because the vitreous has pulled away from the retina. Besides, posterior uveitis or bleeding in the eye is another reason for ocular floaters, which is a serious condition of the eyes (4). At times, the symptoms of floaters may occur when patients suffer from high fever, head injuries or influenza at times and the troublesome problem should recover spontaneously after two weeks. However, after aged 40, the vitreous gel should begin to liquefy involving nearly 50% by age 80, a process called synchysis. When the lysis forms, the posterior scaffold should detach from the retina with the intervening space (5). Generally speaking, monocular floaters in patients often reflect some underlying ocular disease. For example, the major causes of monocular floaters include: PVD, vitreomacular traction (VMT) and vitreous hemorrhage. Additionally, although less likely, monocular causes of floaters also include Endophthalmitis, uveitis, vitreous lymphoma, and retinal degeneration. According to past studies, the relationship between ocular floaters and PVD is a close one. The presence of complete PVD is highly associated with symptomatic vitreous floaters. Therefore, it is very important to realize the pathophysiology of the vitreoretinal interface for determining how to separate, remove the vitreous from the retina safely and prevent associated complications such as retinal detachment (RD) and full-thickness macular holes (FTMHs).

The probability of PVD becoming complicated by a retinal break or rhegmatogenous RD (RDD) is influenced by the presence of high myopia, cataract surgery, peripheral retinal degeneration, trauma, previous RDD, and a positive family history.

There are several high risks of developing floaters such as age > 50 years old, nearsightedness, eye trauma, complications from cataract surgery, eye inflammation and diabetic retinopathy. Ocular floaters sometimes may be accompanied with flashes, signifying the possibility of retinal tears, incomplete detachment or an adhesion of the vitreous body on the internal limiting membrane (ILM), VMA, vitreomacular traction (VMT) with separation between the vitreous and the macula, FTMHs and resulting in retinal detachment. In addition, it sometimes can increase the macular thickness and decrease best-correct visual acuity. Therefore, it is very important to differentiate from the physiological condition to avoid emergent floaters (5).

In this study, we focus on the age-related eye changes of the vitreous and the vitreous liquefaction; afterwards, separation from the internal limiting membrane (ILM) of the retina will happen with the process mediated by the aggregation of collagen fibrils and degeneration of extracellular matrix component at the vitreo-retinal interface.

In optometry, floaters are the opacities in the vitreous body which cast shadows onto the retina. The patients see them as small moving spots or specks in the visual field. Floaters move as the eye moves, but do not precisely follow eye movements. When attempted to look directly at them, the floaters seem to move away, and blinking does not get rid of them. They are mostly seen when looking at something bright like white paper, plain white or blue sky. The floaters may appear as various shapes of lines, circles, dots, cobwebs, clouds, and flies. In our study, some shapes of retinal images were considered as similar ones. Finally, we counted the numbers of total floaters as the prognostic factors related to the effectiveness of pineapple treatment. Following an exact diagnosis, the patients complaining of floaters were usually managed conservatively with the reassuring suggestion that over time they will adapt to the visual axis.

Traditionally there were two main management options: pars plana vitrectomy (PPV) or observation. For the latter, stable mild disease does not justify the risks of surgery, and will resolve spontaneously in some eyes with VMT (6). Even if the spontaneous resolution of VMT and fibril strands could happen, more aggressive therapies are indicated for the possibility of vision loss. Observation may have disadvantages, with a natural history study reporting that only 11% of patients' eyes showed spontaneous dissociation over a mean follow-up of 5-years, whereas 64% of eyes lost at least 2 Snellen lines over this timeframe. In addition, VMT can also progress to FTMH during observation. However, the patients who experience persistent or severe symptomology may undergo PPV. Equally, PPV for VMT may have various disadvantages, with only one-third of eyes gaining 2 or more Snellen lines. Furthermore, PPV is associated with postoperative patient burden and serious complications such as endophthalmitis and increased intraocular pressure (IOP) (7). Furthermore, postoperative retinal detachment occurs in 2.4%, and 92% of phakic eyes are likely to develop cataracts within 3 years of PPV (8). Some newly techniques, for instance, Nd:YAG laser vitreolysis, pharmacological vitreolysis and even 25-gauge vitrectomy developed (9). For example, Nd:YAG laser vitreolysis is commonly used in treating the vitreous opacities located near the posterior retina. Some reports claim that the success rates in existing studies are highly variable, ranging from 0% to 100% (10). However, the shock from the Nd:YAG laser used to break the vitreous floaters may sometimes damage the human retina and impact the visual loss (11).

Recently, a new method of enzymatic vitreolysis with intravitreal ocriplasmin (Jetrea; Thrombogenics USA, Alcon), which is a recombinant and truncated form of the human serine protease plasmin has been employed. Recently, ocriplasmin (microplasmin) is a potential alternative treatment for patients with symptomatic VMT and macular hole that could also remove fibril strands and vitreous opacity by pars plana vitrectomy (12). The ocriplasmin induced the smaller fragment of the plasmin enzyme and was approved as the first non-surgical treatment for patients with VMT by the Food and Drug Administration (FDA, USA) in 2012 (13,14). A total of 26.5% of subjects receiving a single intravitreal ocriplasmin (125μm) achieved the primary end point of pharmacologic VMA resolution at day 28 compared with 10.1% of placebo (15). The medical effect of ocriplasmin is enzymatically degradation of the protein scaffold in the vitreo-retinal interface and cleave collagen, fibronectin, and laminin which are the major components of the vitreous strands and floaters. It may lead to various degrees of vitreous liquefaction and loosening of vitreoretinal attachment which would decrease the development of epi-retinal membrane, VMT, and RRD (16), the same idea as the effectiveness of ocriplasmin for treating the vitreous body-associated overgrowth tissues (17). The similar method may be used to cut the extracellular matrices and clear the useless vitreous fibrils.

How to use the concepts of proteinases, for example, trypsin, chymotrypsin, papain and some hydrolytic enzymes to dissolve the vitreous strands and floaters is an advanced option in the future. Bromelain is extracted from stems and fruits of the pineapple; it contains various proteolytic enzymes such as anti-inflammatory, analgesics, anti-thrombotic and antifibrinolytic properties (18). In clinics, it is now prescribed as the treatment of several diseases, for example, osteoarthritis, dental pain and post-operative swelling (19). During our experiences, pineapple may also be a good source of fruit which would supply hydrolytic enzymes to interact with the vitreous contents and treat patients with vitreous opacities. Pineapple (Ananas comosus) is a delicious crown shaped fruit that grows on the tropical plant of the same name. It is a good source of a number of essential nutrients, vitamins, minerals, phytonutrients, antioxidants, etc., and the presence of these nutrients makes it a wonderful fruit for our health, skin and hair. Pineapple is the common name of Ananas comosus and the leading edible members of the family *Bromeliaceae*, growing in the tropical and subtropical areas including Taiwan, Southern China, Philippines, Thailand, Indonesia, Malaysia, Kenya, and India. Pineapple has been used as a medical plant in several native cultures. Its main component is a sulfhydryl protease, with traces of acid phosphate, peroxidase inhibitors and several low molecule weight compounds.

The stems and fruits from the pineapple contain protease, a particular bromelain, a non-proteolytic component which is mainly responsible for complete debridement and dissolving the over-growth connective tissues, including several proteins and mucopolysaccharide substrates from the human body (20). When we analyzed the proliferative phase in humans, we found that this event fosters the production of proangiogenic factors. Vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF-2), and PDGF2 are initially released by platelets and then by resident cells. Besides, endothelial progenitor cells (EPCs) also play an important role which is mediated by MMP and other factors for matrix remodeling and even scar formation (18). Moreover, the protease, including Matrix Metalloproteinases (MMPs) would be found in the vitreous level in the proliferative diabetic retinopathy, which could degrade the ECM and growth factors. Therefore, we suggest that the autolytic, biological, and enzymatic factors be used in the biological activities of bromelain in removing vitreous constitutes and floaters (21).

In this study, we evaluated the effectiveness of the pineapple plant to treat patients with ocular floaters and some VTMs for the restoration of visual axis and even recovery from the baseline.

Methods and Materials

This institutional review board (IRB) approved this retrospective study, which included 388 consecutive eyes of 388 patients complaining about floaters in Southern Taiwan. This study followed the tents of the Declaration of Helsinki. Moreover, patients were included if they were at least 18 years of age and did not suffer from the ocular floaters after trauma or major disorders within 6 months. The reason is that some medical reports demonstrate that quick liquefaction occurred, and the inner contents should result in changes after trauma or other disorders. Interestingly, in experiment 1, when these ocular images of high conscious subjects mentioned at least 1 image interpreter, the diagnosis of vitreous opacities, PVD and some symptomatic SMV subjects were confirmed by indirect ophthalmoscopy, B-San (ultrasonography) and spectral domain optical coherence tomography (SD-OCT) of all participants (22). Ultrasonography is routinely used to diagnose PVD and vitreous floaters, because of their characteristics of dense collage matrix. Besides, OCTs allow detailed imaging of the transverse and coronal aspects of the vitreoretinal interface. It may also easily and clearly detect the vitreous floaters. Therefore, a dilated examination of the ocular fundus is mandatory, so only patients with stable and solid vitreous opacity and PVD were enrolled in our experiment. However, the floaters forming blood clots or unexpected incomplete PVD were all excluded in our experiments (23). Besides, all the systemic diseases; hypertension, DM, hyperglycemia and connective tissue disorders may impact the normal physiological PVD. Moreover, age, and lens status showed significantly positive impact on floaters. The vitreous hemorrhage in proliferative retinopathies include: diabetic retinopathy, sickle cells, venous occlusion, Eales disease, intraocular inflammation, trauma surgery, asteroid hyalosis (AH), as well as myopia (high myopia > 8D). The above were excluded from our study because of the complicated vitreous-retinal pathophysiology.

Any similar shadow shapes of floaters were considered as one image. In addition, those with ocular floaters greater than one image were included in the group of patients with multiple floaters. Patients were excluded if the signs from the examinations were not apparent when they subjectively suffered floaters. The persistence of vitreous floaters from the patients' description and the object findings (focal echodensities) from the B-scan ultrasonography and ophthalmoscopy were all confirmed together. Ultrasonography provides real-time imaging of internal and peripheral vitreous structure, and expands the evaluation of the patients with floaters (24). When subject complaints and the exact diagnosis were consistent, the subjects were enrolled in the study. All 288 participants were divided by the number of ocular floaters as one or multiple (> 1). Therefore, the patients were all asked to take various pieces of pineapple, and the time of endpoint study time was three months. After they began to eat the pieces of pineapple prepared by our medical staffs, the patients returned for a series of check-up examinations every month. All the crude pineapples were from Southern Taiwan including Ping-Tung, Kaohsiung and Tainan and cut open to several pieces (Fig. 1). After weighing, every piece of the pineapple was mean 100 g. All 388 patients took the pieces of pineapple according to various designs. The 190 and 199 subjects were randomly enrolled in experiment 1 and 2. At first (experiment 1), 190 patients were separated into 2 subgroups: one floater and multiple floaters (> 1) in experiment 1. Secondarily (experiment 2), 199 subjects with one or multiple floaters would be divided into 3 subgroups randomly, and they received various (low, middle, high) treatments in the experiment 2. When the floater numbers decreased, the positive findings were confirmed as successful therapy. Afterwards, we compared the results of the pineapples to the treatment of the ocular floaters in experiments 1 & 2 before and after 3 months.

The schedule was between 2016 March with June in 2016 for heidig the "bright: survey about the concent for treating ocular floaters, which was an incurable disease in the past decade. All 388 participants were arranged to undergo a series of ocular examinations. The whole study was completed in 3 months and we compared with the outcomes after 3-month supplement. In fact, the bromelain was obtained from the stem or fruit of the pineapple. It is sold in the form of a powder, cream, tablet, or capsule. In our study, we directly cut the whole pineapple into several pieces horizontally; each piece may contain stems and fruits. In experiment 1, the 190 participates were separated to one floater (group 1) and multiple floaters (group 2). Hence, all 190 subjects were asked to eat 2 pieces of pineapple every day prepared by our staffs. In experiment 2, 198 patients with 198 eyes were placed in 3 subgroups: low pineapple group (LPA), middle pineapple group (MPA) and high pineapple group (HPA) for various pieces of the designed supplement. Taking too much pineapple is harmful to DM patients as it may elevate the glucose level in the blood, so the maximal amount of the pineapple in our experiment is eating 3 pieces (about 300 g) each day, which is safe. Therefore, we designed for 2 pieces of pineapples (around 200 mg/day) for the management strategies for everybody in experiment 1. Besides, in experiment 2, all 199 patients were divided to 3 subgroups and received various doses treatment: the low-, middle-, and high-dose pineapples (LDP, MDP, HDP; 1, 2, 3 pieces, respectively). Afterwards, we compared the outcomes of the pineapples to the treatment of ocular floaters after the 3–month treatment. In experiments 1 and 2, the participants all took the pineapple after the lunch. Besides, all subjects were arranged to return to receive a series of examinations to follow their ocular condition every month.

All patient charts were reviewed for age, gender, lens status, chief complaint, number of ocular floaters, any discomfort, and side effects. Besides, all the data were measured and the statistical differences were measured for the effect of pineapples with the use of SAS 9.0 (SAS Inst., Cary, NC, USA). The *P* value < 0.05 was considered statistically significant.

Fig. 1. The pineapple is abundant in Taiwan. In our study, the whole pineapple would be divided into several pieces to treat the patients with ocular floaters.

Results

In the whole study, no retinal damage or ocular inflammation was observed. Besides, the intraocular pressure and blood sugar of all the participants were normal. The vision of all the participants remained stable and the angle of chamber, lens status corneal and zonular fibers all showed normal by means of a slit lamp (SL-D7; NIDEK) and anterior segment OCT (Heidelberg OCT) (25).

Furthermore, no participants suffered any discomfort or side effects from the pineapple supplement. The definition of the case "success" is that the floaters and retinal shadows were no longer visible by indirect ophthalmoscopy and even SD-OCT detection. Besides, some of the participants told us that they could see the scene beautifully without black image blacking after 3 months.

In experiment 1 (2 pieces /day for every one), the percentage of 120 patients with one floater successfully disappeared decreased to only 35 subjects (29.2%; 35 /120) (P < 0.05). Besides, 70 patients with multiple floaters decreased to only 19 patients (27.2%; 19 /70) with regular supplement of pineapples for 3 months (P < 0.05) (Table 1).

In experiment 2, the final results of various floaters in the 3 groups with LPA, MPA, and HPA treatment were compared after they took different doses of pineapple for 3 months. Firstly, we found that 66 patients with LPA treatment taking one piece of pineapple every day in subgroup 1 decreased to 33 subjects (45.5%; 30/66) after 3 months (P < 0.05). Secondly, 66 participants with MPA treatment taking two pieces of pineapple every day in subgroup 2 significantly decreased to 22 subjects complaining about decreased shadow of retinal image (33.3%; 25/66) after the whole 3-month-peroid therapy (P < 0.05). In subgroup 3, 66 patients were asked to take 3 pieces of pineapples each day. Three months later, the patients with lower floaters dramatically changed to 17 patients (25.8%; 17/66). During the series of examinations, we found that the vitreous opacity had improved without further blocking the visual axis (Table 2). Furthermore, it is reported that the greater amounts of pineapple taken, the fewer the patients retaining vitreous opacities and floaters. According to the maximal doses of pineapple supplement, the greater the effectiveness in treating floaters and enhanced vitreous opacity showed lysis. In summary, treating the patients with ocular floaters by pineapple supplements revealed the dose-dependent manner. It was interesting to find that the patients with floaters during a 3-month-peroid therapy were 45.5%, 33.3% and 25.8% and 1, 2, 3 pieces of pineapple, respectively. We concluded that pineapple intake may decrease the aggregation of collagen fibrils forming fibers and the rates of symptomatic floaters. Furthermore, we suggest that bromelain is advantageous over the firm PVD easily separated from the vitreo-retinal interface. Therefore, pineapple supplement is good for the patients with various floaters.

Table 1: The change of various floaters before and after eating over a period of 3 months

Ocular floater numbers	**Before**	**1st month**	**2nd month**	**3rd month**

One	120	119	88	35* (29.2%)
Multiple	70	68	52	19* (27.1%)

N= 190 eyes

1. Multiple floaters denote patients with at least 2 floaters.
2. After treatment, the patients with multiple floaters may completely or incompletely disappear. Therefore, the multiple floaters would change into 1 or 0 floaters.

*3. We compared the results at the basal time and 3 months by ANOVA. If p value is less than 0.05, it showed significant difference.

Table 2: The change of ocular floaters before and after taking pineapples over a period of 3 months

Numbers of pineapple	**Before**	**1st month**	**2nd month**	**3rd month**
1 pieces	66	66	54	30* (45.5%)
2 pieces	66	66	56	22* (33.3%)
3 pieces	66	60	58	17* (25.8%)

1. Group 1 (N= 66 eyes): the patients took 1 piece of pineapple

Group 2 (N= 66 eyes): the patients took 2 pieces of pineapple

Group 3 (N= 66 eyes): the patients took 3 pieces of the pineapples

*2. We compared the results at the basal time and 3 months by ANOVA. If the p value is less 0.05, it showed significant difference.

Discussion

Vitreous is a dilute meshwork of collagen fibrils interspersed with extensive arrays of hyaluronan molecules. Besides, hyaluronan is the major macromolecules of vitreous which is an unbranched polymer of repeated disaccharides linked by glycosidic bonds in physiology. Moreover, hyaluronan is also covalent to a protein core; the ensemble is called proteoglycan. Further analysis showed vitreous contains collagen type II, a hybrid of type V/XI, and IX collagen in a molar ratio of 75:10, 15, respectively. The vitreous collagens are organized into fibrils, with type V/Xi residing in the core, type II collagen surrounding the core, and the IX collagen on the surface of the fibrils.

In anatomy, vitreous consists of hepatocytes, collagens (type I, IX, V/XI and VI collagens), GAGs, PGs, and other extracellular matrix molecules (fibrillin. Optcin, VIT-1). The collagen molecules are coiled by three α polypeptide chains coiled into a left-hand helix. The three chains then warp around each other into a right amino acid, which is a glycine-residual that creates Glycine-X-Yn amino acid repeat. The X-and Y-repeats can be any amino acid, but X is often alanine or proline, and the Y is at times hydroxyproline. Besides, collagens are also rich in lysine. All collagens have non-triple-helical region bonds and stabilize the structure of the collagen triple. Hydroxyproline forms hydrogen bonds and stabilizes. The lysine and hydroxylysine residues are necessary for the flotation of intramolecular cross-link, which stabilizes the collagen fibrils. Hydroxylysine also provides potential sites for posttranslational glycosylamines. To date, nearly 30 different types of collagen molecules for more than 40 genes have been characterized. Interestingly, vitreous collagens resemble collagen fibrils.

The onset of floaters is often secondary to PVD and possible complications. When patients complain about floaters, they should be referred to special ophthalmologists for detailed examination to exclude the more peripheral region of retinal tear or detachment. Moreover, the physicians should identify the possible "vitreous floaters' as their urgent approach. According to previous studies, acute onset of floaters and even PVD would develop into the retinal break within six weeks. However, early diagnosis and possible treatment for the floaters and PVD becomes very serious.

The nature and composition of the vitreous humor change over the course of life. In adolescence, the vitreous cortex becomes denser and vitreous tracts develop; in adulthood, the tracts become better defined and sinuous. Central vitreous liquefies, fibrillar degeneration occurs, and the tracts break up. The coarse strands develop with ageing. The gel decreases with age and the liquid volume increases. Cortex may disappear at sites, leading to liquid vitreous extruding into the potential space between the vitreous cortex and retina. Therefore, vitreous floaters may be the symptoms or signs of people leading to the ghosts of blindness by the side (26). A follow-up visit for patients with an isolated PVD or floaters can be justified to detect the small percentage of asymptomatic retinal breaks.

Vitreous opacities may affect patients at any age whereby they experience eye floaters. Most floaters are small spots that drift through the field of human vision. Moreover, they may stand out when they look at something bright, like white paper or a blue sky. Visual floaters are visual phenomena caused by degenerative changes of the vitreous gel. Over time, the vitreous collagen type IX decreases, resulting in the surface exposure of "sticky" type II collagen.

Hence, these result in the vitreous collagen fibrils aggregating and liquefying, while accompanied vitreous shrinkage and clumping make tiny shadows on the retina (27). The PVD entails the collapse of the vitreous body and anterior displacement of the posterior vitreous cortex, and is the most common cause of floaters. The symptoms might annoy some people and shouldn't interfere with their eyesight. However, the floaters sometimes may impair the ability to read, use the computer and smartphone, and drive. The impact is more challenging for some high detail visual requirements, particularly in dynamic settings, for instance performing from sheet music. It even appears in the peripheral vision, giving the sensation of people approaching from behind or from the side. Efforts to temporarily alleviate visual interference include eye blinking, rubbing eyes, closing one eye, or moving the head. These maneuvers only give short windows of visual clarity. Vitreous floater symptoms usually subside with the passage of time; however, some patients with floaters may suffer from persisting discomfort, and psychological distress; they then seek medical care. Hence, the constant struggle to achieve adequate visual transparency for some peoples impacts their emotional and physical resilience as well (28). Interference of the floaters with the visual axis results in patients' discomfort. Besides, the contrast sensitivity may decrease to 67% starlight increase in eyes which would induce unhappiness (29). Recent studies indicate that vitreous floaters can have a significant negative impact on visual function and in turn the quality of life (30). Although in most patients the floaters are minimal, they can cause various significant impairments in the vision-related quality of life, affecting a small population of patients. Now, a new definition of floaters as "symptomatic vitreous opacities (SVO)" was further made. Ivanosva et al. conclude that the SVO could also lead to intermittent blurred vision, glare and even haze attributable to migration of vitreous opacities into the visual axis. This event interferes with many important activities of daily life such as reading, driving, and performing close work (31). Wagle and his co-workers reported that patients with floaters and PVD were willing to take an 11% risk of death and a 7% risk of blindness just to get rid of the bothersome floaters due to impaired driving (30). Therefore, determining how to decrease the numbers of vitreous floaters has become an important issue. Besides, they also raise the demand for healthcare for ophthalmic professionals and extend the range of their service provision (32).

The vitreous liquefaction destabilizes collagen fibrils at the age of 4 years, and 12.5% of the vitreous is liquefied at the age of 18. The most common etiologic cause of floaters is age-related and myopia-induced liquefaction of the vitreous gel; liquefaction induces collagen into visible fibrils and leads to the collapse of the vitreous body. According to further research, most macromolecules in vitreous are collagens II and collagens IX, glycosaminoglycans (GAGs) like hyaluronic acids (hyaluronan; HA), proteoglycan (PGs) and non-collagenous glyco-proteins. Because water may bind to HA, the ageing process could lead to two structural changes: (1) depolymerization of HA which causes water structural changes and (2); loss of collagens IX which provokes aggregation of collagens II fibrils and further leads to the formation of fluid filled with lacunae. Therefore, collagen filament aggregation and condensation result in the formation of larger fibrils, which float in lacunas of liquefied vitreous giving the patients the perception of floaters. The speed at which these vitreous changes happen depends on the people's age, environmental factors, exposure to sunlight, oxidative stress, and HA-collagen interaction. As for age, among patients > 70 years old, we find that at least 50% of the vitreous is liquefied. In summary, the floaters do not impact the human visual acuity; and the numbers sometime increase with age.

In youth, the vitreous is a clear gel that fills the vitreous cavity, occupying approximately 80% of the volume of the globe, so called "myopic vitreopathy". In nature, the vitreous consists mostly of water (99%) as well as hyaluronic acid and a meshwork of fine collagen fibrils. An important area is the vitreous base, a 3- to 4-mm-wide circumferential zone of vitreous that straddles the ora serrata. In the vitreous base, the collagen fibers are firmly attached to the underlying peripheral retina posterior to the ora serrate, and to the pars plana epithelium anteriorly. Other areas of firm vitreous attachment are at the edges of retinal scars, in areas of lattice and other vitreoretinal degenerations, at the optic disc, and along the major vascular arcades. The prevalence of PVD increases with age, axial length, and following cataract surgery and trauma. Vitreous floaters are a part of the PVD in clinic. Some articles demonstrate that myopic people should experience floaters and PVD approximately 10 years earlier than those with emmetropia or hyperopia. Besides, human lens removal allows hyaluronic acid to diffuse more easily out of the vitreous into the anterior chamber and subsequently out of the eye. The unsupported collagen fibers then collapse together. Indeed, the posterior capsule may induce an effective barrier to hyaluronic acid, and the procedure of posterior capsulotomy may easily enhance floaters and possible PVD. This event occurs as a result of liquefaction. With increasing age, an opening ultimately develops in the posterior vitreous through which the central liquefied vitreous passes suddenly into the retro-vitreous space, rapidly dissecting a plane and separating the posterior hyaloid from the retina. Furthermore, floaters and PVD are involved as inciting events in most cases of RRD (33). Typical symptoms of PVD are floaters which are described as cobwebs, spots or hair in the field of vision; they are caused by vitreous opacities, for instance, the peripapillary glial tissues torn from the optic disc, condensations of vitreous collagen, and/or blood. However, acute symptomatic retinal breaks resulting from severe PVD have a high risk of RD with visual loss. Moreover, incomplete PVD may also induce the formation of VTM. If left untreated, partial VTM may improve through spontaneous resolution; however, some patients unfortunately experience deterioration in their vision. Therefore, removal of vitreous floaters becomes the mainstay treatment in the unexpected development of ocular diseases.

Current treatment options for vitreous opacity, PVD, and symptomatic VMT in patients include: observation, pneumatic vitreolysis, Nd:YAG laser vitreolysis, pars plana vitrectomy and nearly developing pharmacologic vitreolysis. At first, close observation by the experienced ophthalmologists at a regular time indicates if the patients with limited vision are relatively too young or too old to treat. Indeed only a close follow-up is certainly a reasonable initial approach, as the progress of VMT is known to spontaneously ease in some patients. Therefore, early preservation of the human body and even ophthalmic acuity is very important. The VMA always develops when the traction forces exerted on the area of adhesion are sufficient to produce anatomical distortion of the macula, resulting in severe VMT and even FTMHs formation. The symptoms and signs of patients with VTM and FTMHs include ocular floaters such as metamorphopsia, visual acuity changes, lower contrast sensitivity and central visual fields defects. As for the timing of operation, in Japan, most vitreo-surgeons favor emergent operation until observation when the patients' best-corrected visual acuity drops to 6/30 (12).

Patients with vitreous floaters and mild PVD can receive close follow-up. Although almost all patients accept the conservative management option, there is a small subset of patients who may desire more aggressive treatment intervention to resolve their visual symptoms (21). However, if they do not spontaneously relieve, aggressive treatment, including surgery should be taken into consideration. For example, vitrectomy is indicated for the common choice. Till today, various methods were arranged to treat the vitreous floaters: complete or incomplete PVD, and symptomatic VMT. Vitreous floaters are a common complaint in the ophthalmic care setting. However, most conditions are benign, so ophthalmic care practitioners have little to offer regarding treatment options. The majority of cases encountered are managed with patient education and reassurance. Now, there are several therapies in solving the above vitreous problems including vitrectomy, pneumatic vitreolysis, Nd:YAG laser vitreolysis, and pharmacologic vitreolysis (34).

Pars plana vitrectomy is an effective treatment for the surgical removal of the vitreous opacities, incomplete fibril strands, firm VMA, symptomatic VMT and even FTMHs until 1991. Some surgeons even use the gas tamponade (SF6 or C3F8) for as long as possible in an attempt to enhance closure rates. Kelly and Wendel postulate that vitrectomy would remove traction around the hole and this, combined with gas tamponade, would result in the ring of perifoveal detachment flattening with some (58%) improvement of vision (35). There is a relationship between these two choices: gas choice and postsurgical requirement, related to the amount of time of time that gas still bridges the severe VMT or holes. The combined gas (air-fluid exchange) could cross the defect of a macular hole without face-down positioning in an upright position; if the gas fill exceeds 50%, a long-acting tamponade will maintain >50% gas fill for a longer time than air or short-acting gases. Unfortunately, vitrectomy could also carry significant surgical risks, including cataract, glaucoma and RD, which may limit the broad indication of vitrectomy for floaters (36).

As for the method of pneumatic vitreolysis (PVL), the small quantity of expansible gas is injected into the vitreous cavity to achieve focal VMT release for eyes with symptomatic VMT. The method of pneumatic vitreolysis since 1993 is the intravitreal injection of a small quantity of expansible gas for the purpose of achieving focal VMT release for eyes with floaters, VMT, or inducing VMT release and closure of macular defect. The success rates of VMT release have ranged from 60% to 100%, and the rates of closure of small macular holes have ranged from 50% to 80% following PVL, which is a promising, low-cost therapeutic option, with the potential for managing symptomatic VMT and vitreous floaters on a global scale. The intravitreal special gas (i.e.: C_3F_8) bubble creates an intragenic PVD that relieves VMT in some patients. However, the success rates of VMT release range broadly. Besides, the danger of intravitreal injection includes: intragenic cataract, glaucoma, Endophthalmitis, retinal breaks, and the development of RD (37).

Nd:YAG laser vitreolysis is attractive because it is relatively simple and effective for treating the mid-, posterior floaters and even Weiss ring floaters (38). The mechanism of laser vitreolysis would be used for the lysis of fibers and rhexis of aggregates, followed by displacement out of the visual axis which could be offered to treat symptomatic vitreous floaters. Recently, this method has been widely used to collagenous vitreous strands, transvitreal sheets or bands, and mostly to break the vitreous opacities. This is generally performed by focusing the laser onto the vitreous opacities visible at the slit-lamp. Typically, only opacities relatively far from the retina are treated, thus, these represent a subset of floaters that might be appropriate to treat with Nd:YAG laser. Unlike vitrectomy, the laser is closed eye obviating the risk of endophthalmitis, rapid progression of cataracts, elevated intraocular pressure leading to glaucoma, posterior capsule defects, retinal tear or hemorrhage and even severe RD. This non-aggressive alternative method is more dedicated and safer than vitrectomy. Therefore, amorphous floaters in the mid- to posterior vitreous are clinically significant and difficult to visualize and treat by Nd:YAG laser.

Medical therapeutic treatment evolved from surgery to pharmacotherapy and then to prevention as a result of increased knowledge about the origin and pathophysiology of diseases. The treatment of vitreo-retinal diseases is currently undergoing the first stage of this paradigm shift with development of pharmacologic vitreolysis. Hence, the concepts of proteolytic and collagenotic enzymes attempt to remove and dissolve of burn or traumatic eschar and proliferative tissues for years. It is interesting to find that the stem of the pineapple plants also contains a number of protease (particular bromelain) and non-proteolytic component enzymes (for the complete debridement of burns). Current options show the decreased vitreous cells and proliferative tissues. Therefore, intravitreal injection with Ocriplasmin is a potential alternative therapy for floaters, and VMT. The enzymatic activity of ocriplasmin at the vitreoretinal interface facilitates release of VMT in some patients and must simultaneously liquefy the gel liquid and weakening the VMA. A randomized, controlled trial (called MIVI-TRUST) examined the use of ocriplasmin for pharmacologic treatment of VMT in 652 eyes. Stalmans et al. reported that the success of traction release was achieved at 26.5% on day 28, significantly better compared with only 10.1% in the control group. The vitreous floaters and VMT are the pathologic consequence of vitreous attachment with structure disturbance of retina which would be successfully dissolved by ocriplasmin (22). Grandorf et al. report dose- and time-dependent cleavage by ocriplasmin between posterior vitreous cortex and the ILM in both human cadaver and feline eyes (38). Recently, ocriplasmin is even considered as cost-effective in patients without epiretinal membrane or full thickness macular hole which is useless to utilize vitreolysis and absorbing the extracellular matrix and proliferative tissues such as vitreous floaters (so called vitreous balls).

The reason for sudden onsets in patients 50 years or older has been related to PVD in 95% cases. Furthermore, in the pathogenesis of PVD, after vitreous liquefaction, the second most important event is the age-related weakening of the adhesions between the posterior hyaloid membrane and the internal limiting membrane, which leads to the separation of these two structures, shrinking and collapse of the vitreous body) (39). In patients with high myopia, vitreous liquefaction, floater liquefaction floaters-related PVD occurs much earlier compared to the same age patients, with emmetropia or hyperopia (40). Early vitreous liquefaction and PVD describe ion conditions following trauma, phakia, intraocular inflammation, vitreous hemorrhage and retinal venous diseases (41). During ageing, the vitreous degenerates in time, collapses and detaches from the retina, which may induce complete or incomplete PVD. The most common complications of age-related total PVD are retinal tear; vitreous, retinal, and optic-disc hemorrhage; as well as RDD.

Because the association between vitreous floaters and PVD is very close, it is very important to realize the epidemiology. In patients with acute onset of floaters as a consequence of PVD, the incidence of the retinal tear 14.5% and that of vitreous and/or retinal hemorrhage is 22.7% (42). Besides, visual impairment was found to be a predictor for retinal pathology, which is in accordance with previous studies where 67% of patients with decreased visual acuity had retinal tears or detachments, whereas 19% of patients with floaters or flashes alone had these conditions (22). A previous study showed floaters in 42%, flashes in 18%, and both floaters and flashes in 20% of PVD and secondary retinal pathology. The incidence of retinal rupture increased from 4%–5% with only floaters to 10%–11% with flashes with/without floaters. However, floaters alone should not be discarded as unimportant; 26.7% of the retinal tears or RD occurs with floaters alone. It has been shown that PVD usually occurs in the other eye within 6 months to 2 years after the first eye (19). It is likely that PVD is a parallel process in both eyes; thus, the patient should be informed of possible pathologies not only in the eye with the present pathology but also in the other eye as well. Hence, the presence of a retinal tear should trigger special attention to the retinal status of such patients in the future. Therefore, we had better approach the floaters when they happen, even though some of them indicate waiting.

Besides, patients with uncomplicated PVD have a 3.4% chance of rapid retinal tear within 6 weeks. However, it could reveal floaters shown for prevention from doctor and permanent vision loss if left untreated (42). Hence, early quantifying of the association between relevant clinical variables and risk of retinal tear in patients presenting acute-onset floaters and its treatment becomes very important. According to Byer's study, the prompt and conscientious vitreo-retinal examination of each patient older than 45 years of age who experiences vitreous floater is the most effective way for preventing RRD. Of 163 patients who had one to two floaters as their presenting symptom, with or without light flashes, the retinal tear should develop in 7.3% of total patients. Therefore, Byre concluded that in this early floaters stage when the symptom was detectable, it is crucial in terms of providing an opportunity for early treatment of vitreous floaters that might prevent RD formation (43). Furthermore, Dayan and his colleagues also report that retinal tear may be found in 26.7% of patients with PVD presenting floaters alone. In their study, 295 patients with floaters were reviewed: 64% had only isolated PVD (the most common), 16.6% had DR and 31% had flat retinal tear. They further commented that floaters were predictors of vitreo-retinal pathology (26). Sharma and his co-workers found that vitreous floaters are the presenting symptoms of patients with PVD-related cases, flashes in 62% and both in 51% of cases within duration of less than 1 month (44). Now, due to the overuse of computers and smartphone, the case of condition of pre-mature cataracts, PVD and vitreous floater are increasing. PVD is even more accelerated after cataract surgery and 75.8% eyes without preoperative PVD or lattice degeneration showing higher incidence of RD after cataract surgery were noted. Furthermore, the incidence of RD with post-operative PVD, uneventful for phacoemulsification was 21.2%. The onset of postoperative PVD should be considered an important risk factor for the development of RD after cataract surgery, particularly in eyes with lattice areas. We collected all the results and concluded that patients with vitreous floaters or any fibril strands should arrange a series of management according to the amounts and location of the "trouble" vitreous opacities (45).

In the past, observation was deemed a negative concept because of the advanced vitrectomy techniques which could easily remove vitreous collagen and hyaluron with smaller instruments. Current surgical techniques are sutureless because highly shelved small gauge sclerotomies are self-sealing, obviating the need for sutures. Aspiration setting and cut rates are the same as typically used for vitrectomy, that is, between 400 and 600 aspirations and 1800 to 2500 cuts per minute. The amount of vitreous removed varies from extensive with surgical induction of PVD, to limited without PVD induction and with preservation of 3 to 4 mm of retrolental vitreous. The preservation of retrolental vitreous is thought by some to mitigate cataract formation post-op. In addition, the amount of vitreous removed determines how much balanced salt solution is infused, varying from more than 10-15 ml in extensive vitrectomies around 5 ml for limited vitrectomies. Future further enhanced control will determine how much and which parts of the vitreous body are to be removed (46). Although survey results show the percentage of satisfied participants ranged from 85% to 100%, most people prefer food or nutrition supplement for treating floaters than an operation (47).

There are many uses for pineapple and its derived ingredients. Along with papain, bromelain is one of the most popular proteases to use for cooking meat. The potential medical uses of the bromelain may be due to its proteases. However, bromelain has not been scientifically proven to be effective in treating any diseases and has not been approved by the U.S. Food and Drug Administration for the treatment of any disorder. In the US, the passage of the Dietary Supplement Health and Education Act allows the sale of bromelain-containing dietary supplements, even though efficacy has not been confirmed. However, bromelain could be used as a known allergen. Currently, bromelain is used as a dietary supplement for nasal swelling, inflammation, osteoarthritis, poor digestion, osteoarthritis (knee), increased heart rate, adjusting menstrual problems, cardiovascular disease, burn, wound care, pain control, antithrombotic, anti-inflammatory, various anti-cancer effects, acute rhinosinusitis, preventing pulmonary edema, stimulating contraction, slowing the clotting system, improving the absorption of antibiotics, preventing cancer, reducing labor, and assisting the body in eliminating fat, improving antibiotic absorption, minimizing muscle soreness after intense exercise, relieving pain related to arthritis and knee concern, gout, bruises, ulcerative colitis, tendonitis, carpal tunnel syndrome and inhibiting the ability of colorectal cancer [48,49,50,51,52,53,54]. Moreover, bromelain is also claimed as a tooth plaque removal enhancer in toothpastes. Furthermore, systemic enzyme therapy consisting of combinations of proteolytic enzymes such as bromelain, trypsin, chymotrypsin, and papain were also prescribed. However, some people may induce allergic reactions to pineapples and we should pay attention to the phenomena. Fortunately, there were no special side effects or discomfort in our treatment with pineapples.

Plant proteases play an essential role in many regulatory processes associated with events in tissue growth and environmental change. In addition, the proteases are important in responding to various stresses such as wounding or the proliferative phase. For example, the new protease “Anti-acanthin” was isolated from the “Bromeliaceae” which may be used to dissolve the proliferative fibrils in vitreous (55). The cysteine protease is the most abundant in Bromeliaceae, including papain, bromelain and ficin (56). In eclectic microscopy, we could easily find that insoluble fibrils could be de-polymerized into a soluble form by several proteolytic enzymes such as pepsin and ficin. Furthermore, the swollen fibrils should be found after digestion by pyrolytic enzymes. The above evidence should be used to explain why the patients taking pineapples may decrease their vitreous floaters. In fact, pineapples have a long tradition as a medicinal plant among the natives of South and Central America. Isolation of bromelain was recorded by the Venezuelan chemist Vicente Marcano in 1891 by fermenting the fruit of pineapple. In 1892, some authors investigated the matters more completely, and called it 'bromelin'. Later, the term 'bromelain' was introduced and originally applied to any protease from the plant family Bromeliaceae. Bromelain from the pineapple is a mixture of protein-digesting (proteolytic) enzymes and several other substances in smaller quantities. Moreover, the proteolytic enzymes are sulfhydryl proteases; a free sulfhydryl group of a cysteineamino acidside chain is required for function. Now several researchers all found that bromelain is present in parts of the pineapple plant, but the stem is the most common commercial source, because us-able quantities are readily extractable after the fruit has been harvested (57, 58). According to classifications (E.C number): bromelain may be separated into 2 major extract components: stem bromelain (EC 3.4.22.32) and fruit bromelain (EC 3.4.22.33). However, stem-bromelain is distinguished from fruit-bromelain, previously called bromelain. These 2 enzyme numbers are not the same; in other words, various biochemistry activities should be different in usage. Pineapples are mainly grown in Thailand, Malaysia and Taiwan. Bromelain is extracted from the peel, stem, leaves or waste of the pineapple plant after processing the fruit for juice or other purposes. The starting material is blended and pressed through a filter to obtain a supernatant liquid containing the soluble bromelain enzyme. Further processing includes purification and concentration of the enzyme.

Vitreous may maintain the transparency for maximal photon transmission to the retina. Besides, vitreous may also maintain lens transparency by mitigating the effects of reactive oxygen species on lens proteins, thus preventing cataracts. This antioxidant effect is primarily the result of high concentrations of ascorbate in vitreous, an observation originally made in 1944 by Friedenwald and colleagues. Therefore, another pathway to dissolve the vitreous opacities may be by the theory of reactive oxygenase species (ROS) which is very popular in many studies. For example, Yeh et al. found that ROS levels were significantly elevated in the vitreous fluid of proliferative diabetic retinopathy (PDR) patients, and patients with a more advanced clinical PDR appearance had higher ROS levels. Moreover, the ROS theories and oxidative stress might be correlated with PDR severity (59). Besides, Akiba demonstrated that ROS may contribute to vitreous liquefaction which is a part of the normal ocular aging process and associated with vitreoretinal pathology. It is found that the hyaluronic acid, one of the main components of vitreous gel, could be degraded by ROS, including free radicals. It is believed that the structural changes in vitreous may be caused by ROS (60). Upon inflammation, the vitreous gel contracted and released a water-like liquid. In addition, superoxide dismutase can suppress the liquefaction; the destruction of the vitreous gel structure resulted from ROS generated by inflammatory cells. Although many unknown factors contribute to vitreous liquefaction, ROS may be the main cause of vitreous structure alterations. Recently, Bromelain was found to have anticancer effects; the mechanisms were explored by assessing the role in inducing ROS, superoxide, autophagosomes, and lysosomes. Therefore, the abilities to lower the higher levels of ROS in pineapple were considered as the possible mechanisms of treating vitreous floaters by the effectiveness of bromelain (62). Müller and his co-workers also found that bromelain, cysteine proteases from pineapple have the biochemical activities to decrease oxidative stress, which may induce the rapid progression of floaters and PVD in vitreous cavity. As for the pathways, inhibiting NFκB/AMPK signaling as well as their downstream signaling proteins such as p-AKT, p-ERK, and p-Stat3 play the key role. Additionally, MMP9 and other epithelial mesenchymal-transition markers were partially found to be downregulated. Apoptosis was induced after bromelain treatment (62). Hence, our therapeutic option might reveal new insights for the treatment of human floaters, PVD and associated vitreous fibrils. Our studies revealed that the pineapple supplement every day can offer a cheap alternative to current therapies for the vitreous floaters, which is the first report in the world.

There are several limitations in our study. Firstly, the amount of pineapple which we used included 1, 2 or 3 pieces (each piece was approximate 120 g) which is easily calculated but the total amount taken deserved doubt. In the future, we may select another dedicated method to ensure an exact food supplement. Secondarily, in the whole studies, the pineapples were obtained from Kaohsiung, Tainan, and Ping-Tung cities, and randomly separated to the different groups for various treatments. We did not further trace the different extracts from the distinct geographic areas. Besides, we did not know if the bromelain from the 3 cities and its associated hydrolytic enzymes were similar. Lastly, we did not further extract the more detailed biochemistry substances and the exact hydrolytic enzymes for lysing the vitreous floaters and strains. We will analyze the associated problems and find true answers in the future.

Conclusion

To our knowledge, this is the first proven study showing that pineapple would effectively cut and clear the vitreous opacities and the associated vitreous strands which impact various physiological and psychological effects of eyes.

Furthermore, this study found that pineapple may significantly dissolve and remove vitreous floaters. For the patients with acute–onset floaters and even flashes, it sometimes led to severe VMT, macular holes and even RD which would induce blindness. In the experiments of our survey, we found that pharmacyte vitreolysis from the regular intake of pineapple could decrease the rate of the vitreous floaters with less complication. Moreover, we believe that pineapple supplement is suitable for patients presenting floaters and the associated vitreous problems. Besides, we will further find the exact biochemical properties and real pathway in dissolving vitreous floaters.

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4/12/2019