**e Supplementary Material**

**Study procedures**

We used the previously validated standard patient evaluation of eye dryness (SPEED) questionnaire, which consists of 2 questions on frequency and severity of dry eye graded on a scale of 0-3 on frequency, and grades 0-4 on severity. Scores from all sub-questions were added, and the greater the total score (0-28), the more frequent or severe the dry eye.[[1](#_ENREF_1)]

The Oculus keratographer 5M (Oculus, Wetzlar, Germany) was used to perform the non-invasive tear break up time (NIBUT).[[2](#_ENREF_2)] Briefly, seated patients blinked freely while fixing on a target ahead. Once ready, patients blinked twice and then refrained from blinking. The fully automated instrument captured any break or distortion in the image of the projected rings on the cornea and the timings recorded. Three readings were taken per eye and averaged, higher readings indicate more tear stability.[[3](#_ENREF_3)]
Schirmer test was done with the standard 5 mm wide Test Strips (Clement Clark) with a notch for folding, without prior anaesthesia. The strips were positioned over the inferior temporal half of the lower lid margin in both eyes, and participants’ eyes were then closed. The extent of the wetting was recorded after 5 minutes, and strips were stored at -80˚C until further analysis.[[4](#_ENREF_4)]

Fluorescein staining was performed as previously described.[[4](#_ENREF_4)] A drop of saline was instilled on the fluorescein strip (Fluorets) then shaken off so that no visible drop remained. The cornea staining was imaged by Keratograph 5M and scored in 5 corneal zones as in the CCLRU system. In each zone, the grade was 0-4, with 0.5 unit intervening steps, a greater number indicated more intense or greater area of staining.

Conjunctival redness was measured by the Keratograph 5M. After scanning the ocular surface and images captured, grading of the conjunctival hyperemia (0-4) was automatically performed with subtraction of major conjunctival blood vessels, and temporal bulbar, nasal bulbar and average readings were obtained. Higher redness scores indicate more hyperemia.[[5](#_ENREF_5)]

Tear evaporation rates were derived from ocular surface temperature recordings for each eye. The procedure and principle of this measurement have been published.[[6](#_ENREF_6)] Briefly, recordings were performed for 20 seconds per eye, with participants blinking freely. The recorded data were used to derive the evaporation rate using a thermodynamics mathematical model. The technique is robust and sensitive to treatment-induced changes because we have shown reduction in tear evaporation after another kind of intervention in the eye.[[7](#_ENREF_7)]

# Tear osmolarity was measured with the TearLab system (OcuSense, San Diego, CA), a simple and highly specific point-of-care method of measuring tear osmolarity in mOsM.[[8](#_ENREF_8)] Briefly, a non-traumatic touch pen was applied to the lower tear meniscus of each eye, and as little as 50 nL of tear was collected instantly. After docking the pen into the reader, the result was obtained within seconds. The average of 3 osmolarity readings on each eye was analysed.

**Details of study treatment**

All participants were asked to use one drop of artificial tear with a prolonged gelling property (Systane ultra) 4 times a day each eye, with intervals of >=2 hours between drops and if necessary, additional normal saline eye drops at least 5 minutes apart from other medications. A diary chart was given at the commencement of the study and entries entered by participants whenever drops were instilled during the study.

One of the six designed TCM physicians performed AC twice weekly for 30 days, over 8 sessions. The acupuncture points used included 5 points around the eyes (ST1 (cheng qi) 承泣, BL2 (cuan zhu) 攒竹, GB20 (feng chi) 风池, Tai Yang 太阳, 3 tear needles 泪三针) and 3 points on the limbs (SP6 (san yin jiao) 三阴交, LI4 (he gu) 合谷, ST36(zu san li) 足三里) **(e Figure 2)**. Since we used the same comparative group (AT) for the AC and HB groups, sham acupuncture was not used. The needles around the eyes had dimensions of 0.25 (diameter) x 13mm (length), while 0.25 x 25mm needles were used behind the ear (feng chi) and 0.30 X 25mm needles on the upper and lower limbs. These needles remained in the points for 20 minutes during each treatment session, with a depth of penetration of about 1-2 mm.

The herbal formulation used is the standard concoction for lung-kidney yin deficiency type of dry eye patients used in SCHMI developed by the senior TCM coauthor (WQP). This formulation is called 杞菊甘露饮 (qi ju gan lu yin) or Lycium berry, a chrysanthemum beverage. This is a modified version of “qi ju di huang wan” published previously.[[9](#_ENREF_9)] The ingredients of this formulation were: *Lycium barbarum* *L. (10 g),* *Chrysanthemum morifolium Ramat.(10 g), Pseudostellaria heterrophylla (Miq.)(20 g), Lilium brownie F.E.Brown.(15 g), Ophiopogon japonicus (L.f.)Ker-Gawl (10 g), Dendrobium loddigesii Rolfe. (10 g), Rehmannia glutinosa Libosch (15 g), Citrus reticulata Blanco (10 g) and Citrus aurantium L. (10 g)* **(e Table 2)*.***

The above ingredients were prepared in granules concentrated to a 1:10 ratio. A total of 11g of granules, dissolved in hot water, were orally consumed twice daily after food by each participant over 30 days. The medications were dispensed on a weekly basis.

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**e Table 1. Usage of artificial tears prior to commencement of trial**

|  |  |
| --- | --- |
|   | **No of participants using the eyedrop prior to study** |
|   | **HB** | **AC** | **AT** |
| Eyemo | 2 | 1 | 0 |
| Tears naturale free | 7 | 5 | 7 |
| Tears naturale II | 0 | 1 | 1 |
| Refresh | 1 | 6 | 2 |
| Refresh plus | 1 | 2 | 0 |
| Genteal | 1 | 1 | 1 |
| Systane gel drop | 1 | 0 | 0 |
| Systane ultra  | 1 | 0 | 1 |
| Endura | 0 | 1 | 0 |
| Normal Saline | 0 | 1 | 0 |
| Optive UD | 0 | 1 | 0 |
| B&L Moisture Eye | 0 | 0 | 1 |
| Hialid | 0 | 0 | 1 |

**e Table 2.** Functions of the herbs

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Herb** | Chinese character | **Latin name** | **Amt.** | **Functions** | **Meridian related to:** |
| **Gou qi zi** | 枸杞子 | *Lycium barbarum L.* | 10g | * Nourish liver, kidney and lung
 | * Liver
* Kidney
 |
| **Mai dong** | 麦冬 | *Ophiopogon japonicus (L.f.)Ker-Gawl* | 10g | * Nourish *yin* and promote fluid production
* Moisten lung and clear heart
 | * Lung
* Kidney
 |
| **Bai He** | 百合 | *Lilium brownie F.E.Brown.* | 15g | * Nourish *yin* and moisten lung
* Induce tranquillity by clearing heart
 | * Heart
* Lung
 |
| **Shi hu** | 石斛 | *Dendrobium loddigesii Rolfe.* | 10g | * Strengthen stomach and promote fluid production
* Nourish *yin* and clear heat
 | * Stomach
* Kidney
 |
| **Sheng Di Huang** | 生地黄 | *Rehmannia glutinosa Libosch* | 15g | * Clear heat and cool blood
* Nourish *yin* and promote fluid production.
 | * Heart
* Liver
* Kidney
 |
| **Chen Pi** | 陈皮 | *Citrus reticulata Blanco* | 10g | * Regulate qi and invigorate spleen
* Dry dampness and resolve phelgm
 | * Lung
* Spleen
 |
| **Zhi Qiao**  | 枳壳 | *Citrus aurantium L.* | 10g | * Regulates *qi*
* Promotes digestion
 | * Spleen
* Stomach
 |
| **Ju hua** | 菊花 | *Chrysanthemum morifolium Ramat.* | 10g | * Clear lung heat and moisten dryness
* Clear liver heat and improve vision
* Relieve toxicity.
 | * Lung
* Liver
 |
| **Tai Zi Shen** | 太子参 | *Pseudostellaria heterrophylla (Miq.)* | 20g | * Promote spleen *qi*
* Promote fluid production and nourish lung
 | * Spleen
* Lung
 |

**e Table 3:** Outcome measures at week 4

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|   |   | Herbs | Acupuncture | Artificial tears | Herbs vs Artificial tears(p value) | Acupuncture vs Artificial tears(p value) |
| Number |  | 49 | 50 | 50 |  |  |
| **SPEED** | mean±SD | 7.14±4.32 | 7.18±4.25 | 7.08±4.08 | 0.94 | 0.90 |
|  |  |  |  |  |  |  |
| **NIBUT (s)** | mean±SD | 8.28±5.63 | 6.91±5.08 | 9.79±6.33 | 0.21 | 0.01\* |
|  |  |  |  |  |  |  |
|  **Schirmer I (mm)** | mean±SD | 14.5±10.2 | 11.4±8.3 | 12.4±9.0 | 0.31 | 0.70 |
|  |  |  |  |  |  |  |
| **Cornea staining** |  |  |  |  |  |  |
| Central | mean±SD | 0.07±0.29 | 0.19±0.65 | 0.21±0.61 | 0.16 | 0.88 |
|  |  |  |  |  |  |  |
| Inferior | mean±SD | 0.82±0.74 | 1.1±0.95 | 0.82±0.74 | 0.98 | 0.10 |
|  |  |  |  |  |  |  |
| Superior | mean±SD | 0.31±0.5 | 0.34±0.63 | 0.32±0.47 | 0.89 | 0.86 |
|  |  |  |  |  |  |  |
| Temporal | mean±SD | 0.28±0.6 | 0.3±0.53 | 0.29±0.66 | 0.94 | 0.91 |
|  |  |  |  |  |  |  |
| Nasal | mean±SD | 0.37±0.74 | 0.64±0.78 | 0.58±0.91 | 0.20 | 0.72 |
|  |  |  |  |  |  |  |
| **Tear Osmolarity (mOsM)** | mean±SD | 301±9.6 | 303±15.2 | 302±13.5 | 0.71 | 0.82 |
|  |  |  |  |  |  |  |
| **Conjunctival Redness** | mean±SD | 1.19±0.41 | 1.15±0.40 | 1.23±0.37 | 0.57 | 0.30 |
|   |  |  |  |  |   |   |

\*p<0.01

† Standard patient evaluation of eye dryness : greater number (0-28) indicates more severe/frequent dry eye symptoms

†† Non-invasive tear break up time

**e Table 4.**  Lung-kidney yin deficiency scores and dry eye symptomatic response

|  |  |  |  |
| --- | --- | --- | --- |
|   | Responder†††n=119 | Non-respondern=30 | p-value |
| pre-treatmentTCM score†mean±SD | 14.8±5.1 | 13.5±4.5 | 0.11 |
| post-treatmentTCM scoremean±SD | 9.0±4.2 | 11.8±4.7 | <0.001\* |
| Change in TCM score††Post-Pre Treatmentmean±SD |  -5.9±3.3 |  -1.7±2.8 | <0.001\* |
|  |  |  |  |
| \*p-value<0.05 |  |  |  |

† a higher traditional Chinese medicine (TCM) score indicates greater lung-kidney yin deficiency

†† these results are for all treatment groups combined, when the analysis was repeated for only participants (n=99) treated with acupuncture and herbal medications, the same conclusion was obtained (p=0.006, data not shown)

††† based on the difference in SPEED questionnaire result at Week 4- Baseline. A negative result indicates symptomatic response, ie., decrease in dry eye symptoms at week 4 compared to baseline

**e Table 5.** Further analysis of basline tear osmolarity (first 2 rows) and outcomes of a subset analysis of participants with baseline osmolarity above 306 mOsm.

|  |  |  |  |
| --- | --- | --- | --- |
|   | **HB** | **AC** | **AT** |
| Worse osmolarity of 2 eyes *(mean±SD)* | 305±15 | 299±46 | 311±21 |
| No (percent) > 306 mOsm | 17 (54) | 18 (36) | 27 (54) |
| **Outcomes** |  |  |  |
| SPEED 1 month *(mean±SD)* | 7.5±5.0 | 7.1±4.6 | 6.9±4.4 |
| NIBUT 1 month *(mean±SD)* | 6.1±2.7 | 5.9±5.0 | 9.2±6.0 |
| Conj redness 1 month (mean±SD) | 1.2±0.3 | 1.1±0.3 | 1.0±0.4 |
| Osmolarity (worse of 2) 1 month *(mean±SD)* | 307±10 | 317±16 | 308±20 |
| Change in osmolarity *(mean±SD)* | -14.1±15.3 | -5.4±13.6 | -15.8±23.1 |
| Schirmer 1 month *(mean±SD)* | 11.2±8.3 | 11.5±6.6 | 11.0±8.0 |
| Inferior cornea staining (1 month) *(mean±SD)* | 0.79±0.69 | 1.36±0.61 | 0.74±0.63 |
| Central cornea staining (1 month) *(mean±SD)* | 0.00±0.00 | 0.23±0.69 | 0.13±0.38 |
| Change in SPEED from baseline *(mean±SD)* | -4.0±4.2 | -5.0±4.0 | -4.2±4.2 |
| Number(%) with improved symptoms | 13 (26) | 17 (34) | 19 (38) |

 **e Table 6.** Baseline values of cytokines (normalized to 1 mm Schirmer) in pg/mL [mean ± SD]

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|   | **AT** | **AC** | **HB** | **HB vs AC(p value)** | **HB vs AT(p value)** | **AC vs AT(p value)** |
| IFN-γ | 0.142 ± | 0.282 | 0.21 ± | 0.32 | 0.192 ± | 0.345 | 0.786 | 0.434 | 0.264 |
| IL-10 | 0.119 ±  | 0.14 | 0.166 ± | 0.185 | 0.175 ± | 0.294 | 0.852 | 0.228 | 0.158 |
| IL-12 | 0.197 ± | 0.366 | 0.267 ± | 0.395 | 0.268 ± | 0.606 | 0.991 | 0.478 | 0.359 |
| IL-13 | 1.305 ± | 1.315 | 1.591 ± | 1.671 | 1.622 ± | 2.408 | 0.941 | 0.417 | 0.344 |
| IL-17A  | 0.000 ± | 0.000 | 0.005 ± | 0.022 | 0.003 ± | 0.013 | 0.543 | 0.163 | 0.125 |
| IL-2  | 0.062 ± | 0.101 | 0.073 ± | 0.106 | 0.065 ± | 0.099 | 0.707 | 0.891 | 0.613 |
| IL-4 | 0.243 ± | 0.416 | 0.619 ± | 1.091 | 0.537 ± | 1.281 | 0.731 | 0.127 | 0.025\* |
| IL-6 | 0.565 ± | 0.698 | 0.59 ± | 1.337 | 0.532 ± | 0.744 | 0.79 | 0.819 | 0.907 |
| IL-8  | 12.25 ± | 19.57 | 21.58 ± | 54.05 | 12.79 ± | 22.31 | 0.294 | 0.898 | 0.254 |
| IP-10 | 558.98 ± | 483.31 | 594.9 ± | 527.93 | 666.54 ± | 607.61 | 0.532 | 0.332 | 0.723 |
| MCP1  | 27.61 ± | 37.24 | 24.2 ± | 23.89 | 13.04 ± | 14.2 | 0.006\* | 0.012\* | 0.587 |
| RANTES  | 2.451 ± | 5.559 | 2.706 ± | 4.584 | 2.760 ± | 4.982 | 0.955 | 0.772 | 0.803 |
| TNFα | 0.015 ± | 0.04 | 0.045 ± | 0.118 | 0.018 ± | 0.044 | 0.139 | 0.729 | 0.094 |
| IL-1β | 0.05 ± | 0.058 | 0.064 ± | 0.061 | 0.062 ± | 0.077 | 0.876 | 0.362 | 0.22 |
| MIP-1A | 0.34 ± | 0.582 | 0.503 ± | 1.157 | 0.337 ± | 0.73 | 0.396 | 0.98 | 0.376 |

\*p<0.05**e Table 7**. Cytokine concentrations in the tear (normalized to 1 mm Schirmer) in pg/mL [mean ± SD] at 4 weeks.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|   | **AT** | **AC** | **HB** | **HB vs AC(p value)** | **HB vs AT(p value)** | **AC vs AT(p value)** |
| IFN-γ | 0.125 ± | 0.26 | 0.141 ± | 0.235 | 0.106 ± | 0.194 | 0.208 | 0.341 | 0.371 |
| IL-10 | 0.123 **±** | 0.174 | 0.122 ± | 0.133 | 0.095 ± | 0.124 | 0.179 | 0.18 | 0.447 |
| IL-12 | 0.221 ± | 0.38 | 0.231 ± | 0.413 | 0.091 ± | 0.145 | 0.016\* | 0.014\* | 0.475 |
| IL-13 | 1.172 ± | 0.988 | 1.416 ± | 1.396 | 1.179 ± | 1.381 | 0.19 | 0.489 | 0.149 |
| IL-17A  | 0.009 ± | 0.062 | 0.002 ± | 0.012 | 0.000 ± | 0.001 | 0.189 | 0.168 | 0.215 |
| IL-2  | 0.055 ± | 0.099 | 0.064 ± | 0.124 | 0.033 ± | 0.055 | 0.059 | 0.084 | 0.365 |
| IL-4 | 0.276 ± | 0.555 | 0.364 ± | 0.693 | 0.283 ± | 0.603 | 0.252 | 0.478 | 0.228 |
| IL-6 | 0.618 ± | 1.304 | 0.592 ± | 1.434 | 0.444 ± | 1.13 | 0.293 | 0.24 | 0.452 |
| IL-8  | 8.628 ± | 15.722 | 7.308 ± | 7.72 | 6.93 ± | 11.023 | 0.438 | 0.268 | 0.286 |
| IP-10 | 415.103 ± | 342.756 | 550.674 ± | 489.125 | 596.95 ± | 917.252 | 0.404 | 0.096 | 0.044 |
| MCP1  | 16.225 ± | 19.271 | 29.868 ± | 53.312 | 11.579 ± | 16.958 | 0.013\* | 0.103 | 0.05 |
| RANTES  | 1.96 ± | 2.459 | 2.438 ± | 3.646 | 1.23 ± | 1.316 | 0.017\* | 0.035\* | 0.236 |
| TNFα | 0.021 ± | 0.058 | 0.021 ± | 0.057 | 0.011 ± | 0.031 | 0.146 | 0.152 | 0.497 |
| IL-1β | 0.052 ± | 0.08 | 0.054 ± | 0.118 | 0.039 ± | 0.059 | 0.225 | 0.18 | 0.479 |
| MIP-1A | 0.345 ± | 0.907 | 0.243 ± | 0.329 | 0.293 ± | 1.019 | 0.358 | 0.396 | 0.218 |

\*p<0.05

**e Table 8.** The number and proportion of participants with downregulation of each cytokine at the one month visit

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  **AT N(%)** | **AC N(%)** | **HB N(%)** | **AT vs HB†(p value)** | **AC vs AT†(p value)** | **AC vs HB†(p value)** |
| IFN-γ | 21 | (42) | 20 | (40) | 24 | (48) | 0.55 | 1 | 0.089 |
| IL-10 | 14 | (28) | 19 | (38) | 24 | (48) | **0.039** | 0.4 | 0.42 |
| IL-12 | 18 | (36) | 20 | (40) | 26 | (52) | 0.11 | 0.84 | 0.32 |
| IL-13 | 23 | (46) | 27 | (54) | 30 | (60) | 0.16 | 0.55 | 0.69 |
| IL-17A  | 0 | (0) | 5 | (10) | 2 | (4) | - | - | - |
| IL-2  | 21 | (42) | 26 | (52) | 27 | (54) | 0.23 | 0.42 | 1 |
| IL-4 | 18 | (36) | 24 | (48) | 23 | (46) | 0.31 | 0.31 | 1 |
| IL-6 | 30 | (60) | 31 | (62) | 33 | (66) | 0.53 | 0.84 | 0.84 |
| IL-8  | 31 | (62) | 32 | (64) | 37 | (74) | 0.2 | 1 | 0.39 |
| IP-10 | 35 | (70) | 27 | (54) | 31 | (62) | 0.4 | 0.15 | 0.54 |
| MCP1  | 31 | (62) | 25 | (50) | 30 | (60) | 0.84 | 0.31 | 0.42 |
| RANTES  | 27 | (54) | 31 | (62) | 36 | (72) | 0.097 | 0.54 | 0.4 |
| TNFα  | 10 | (20) | 16 | (32) | 15 | (30) | 0.36 | 0.25 | 1 |
| IL-1β | 25 | (50) | 37 | (74) | 33 | (66) | 0.16 | **0.023** | 0.51 |
| MIP-1A | 42 | (84) | 42 | (84) | 39 | (78) | 0.61 | 1 | 0.61 |
| **†**The right 3 columns show p values of chi square tests or Fishers exact tests |  |

**e Supplementary Figures:**

**e Figure 1.** Translated English version of scoring sheet for lung-kidney yin deficiency.

**e Figure 2**. Illustration of acupuncture points

**e Figure 3.** Change in symptom score and conjunctival redness in each of the treatment group

**e Figure 4. A.** Tear osmolarity measurments at baseline and 4 weeks. **B**. Tear evaporation rates derived from thermography at baseline and 4 weeks.

 **e Figure 5.** Change in tear cytokines level in each treatment group

**e Figure 6.** Changes in the tear concentration of IP-10 and IL-1β in individual participants (p values: from paired T tests)