

# Using a twin herbal formula for the treatment of upper limb lymphoedema after breast cancer resection

Tor Wo Chiu, Darryl Andrew Tse, Violet Yee Kei Tsoi, Wen Ching Jeannette Ting, Shuk Kwan Chu, Chak Yeung, Ping Chook, Elaine Wat, King Fai Cheng and Ping Chung Leung

## Key words

Herbal formula; lymphoedema; quality of life

*Tor Wo Chiu, Darryl Andrew Tse and Wen Ching Jeannette Ting are at the Plastic, Reconstructive and Aesthetic Surgery Department, Burns Service, Prince of Wales Hospital, Shatin, Hong Kong, China. Violet Yee Kei Tsoi is at the Division of Surgery, North District Hospital, Hong Kong, China. Shuk Kwan Chu, Chak Yeung, Ping Chook, Elaine Wat, King Fai Cheng and Ping Chung Leung are at the Centre for Clinical Trials on Chinese Medicine, Institute of Chinese Medicine, the Chinese University of Hong Kong, and the State Key Laboratory of Research on Bioactivities and Clinical Applications of Medicinal Plants, the Chinese University of Hong Kong, Hong Kong, China.*

*Declaration of interest: The authors declare that there are no competing interests that could have influenced the work reported in this paper or its interpretation.*

*Trial registration: ChiCTR2100053004.*

*Acknowledgments: This work was supported by the State Key Laboratory Fund provided by the Innovation and Technology Commission of Hong Kong.*

Upper limb lymphoedema is a common complication after breast cancer surgery. It is reported that the incidence ranges from 6% to 30% (Sorani et al, 2006). With the implementation of adjuvant radiotherapy, the incidence has increased up to 90% (Erickson et al, 2001; Rupp et al, 2019). This is a chronic progressive disease, often accompanied by limb swelling, deformity and oedema. Symptoms include discomfort, limb heaviness, weakness, restricted shoulder mobility, burning pains, elevated skin temperature, deformities, social isolation and psychological morbidities.

The proportion of women developing

## Abstract

**Background:** Chronic lymphoedema is a common post-resection complication in breast cancer patients and its occurrence is related to surgical trauma and radiation therapy. Chronic lymphoedema can lead to generalised limb oedema, pain, cellulitis and joint stiffness, seriously affecting patients' quality of life. In addition, long-term lymphoedema can also lead to infection and skin ulceration, increasing the patient's mental burden and economic pressure. **Methods:** This study was conducted as a prospective self-controlled clinical trial. Participants were evaluated before treatment and followed up monthly for 6 months. Main outcome measures were limb volume, change in quality of life (QOL) for limb lymphoedema questionnaire (LYMQOL) score, hand grip strength test and tonometer for tissue indentation. **Results:** We enrolled 20 patients with breast cancer-related upper limb lymphoedema, from May 2018 to July 2023. After 6 months of treatment, the affected limb volume decreased by 4.1% compared to baseline. The LYMQOL improved after treatment, especially in the symptom domain ( $p=0.006$ ), with no changes in grip strength and tonometer measurement. **Conclusion:** After six months of treatment, the mean volume of affected limbs showed a decreasing trend over time; quality of life (LYMQOL) showed a significant improvement trend, especially in the symptom domain.

lymphoedema following surgical treatment of breast cancer ranges from 3% to 15% after sentinel lymph node biopsy and 40% to 65% after axillary lymph node dissection, following mastectomy (Armer, 2005). As breast cancer survival improves, the number of those at risk of lymphoedema also increases. Current treatment options are not wholly effective and the result is chronic progressive swelling with complications such as soft tissue fibrosis and even sarcomatous changes.

A study in Hong Kong demonstrated that calycosin and gallic acid from *Radix astragal* and *R paeoniae* can synergistically induce the expression of leukotriene B4 dehydrogenase (LTB4DH), thereby reducing the level of leukotriene B4 (LTB4; Cheng et al, 2015).

Ubenimex is a synthetic organic compound with the ability to promote lymphatic flow similar to benzopyranone, and entered Phase II clinical trials in the US in 2016. Ubenimex has been used as a chemotherapy adjunct for decades and has

known anti-inflammatory and antifibrotic activity, including inhibition of LTB4 production which has been shown to inhibit lymphomagenesis in *in vitro* models.

In 2015, a group of bioscientists in Hong Kong found that when chemical derivatives from two medicinal plants, calycosin and gallic acid, were mixed together, they attenuated the effects of LTB4 by increasing its metabolism through the induction of LTB4 dehydrogenase (Cheng et al, 2015). Calycosin and gallic acid are found in good quantities in the medicinal plants *Astragalus radix* and *Paeoniae* species, respectively. The two herbs are popular choices in herbal formulations (Nurlaila et al, 2022).

When *Peoniae rubra* and *Astragalus* are taken together, they initiate pharmacological effects similar to Ubenimex.

The aim of this study is to evaluate the effects of the oral consumption of a twin herbal formula containing *P rubra* and *Astragalus* in the control of post-mastectomy upper limb lymphoedema.

Chinese name	English name	Effects according to traditional Chinese medicine theory	Known pharmacological effects	Raw herb (g)/ per day
Huang qi 黄芪	Milk vetch (astragalus)	Invigorates vital energy to strengthen the body	Dilates coronary artery and capillaries	20
Mu dan pi 牡丹皮	Moutan cortex	Promotes blood circulation to remove blood stasis	Antibacterial and anti-inflammatory	10

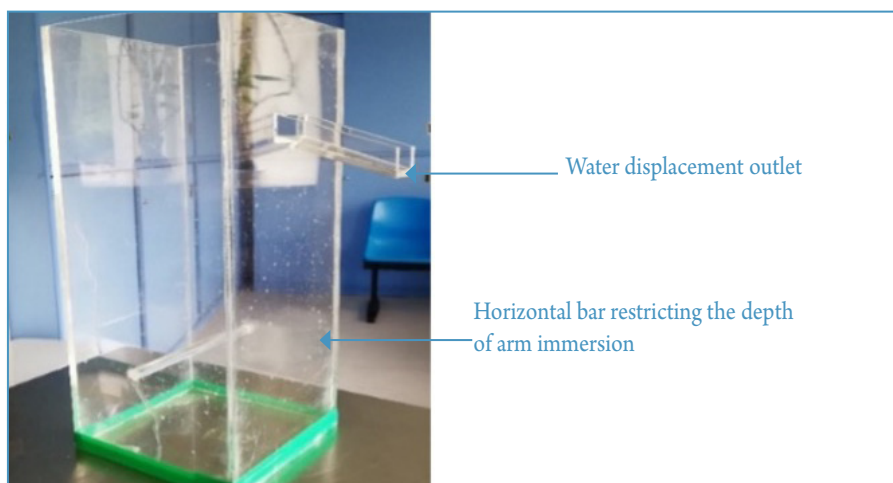


Figure 1. Standard container (for arm) water displacement tank.



Figure 2. Before treatment (left) and after 4 months of treatment (right).

## Methods

### Study objectives

The study was designed as a self-control open-label trial. The aim of the trial was to study the efficacy and safety of the dual herb formula in the treatment of lymphoedema resulting after mastectomy in breast cancer patients. The study was approved by the Clinical Research Ethics Committee (CREC Ref. No. 2020.715).

### Outcome measures

Outcome measures include displaced water volume measurement for the affected limb, quality of life (QOL) for limb lymphoedema questionnaire (LYMQOL; Keeley et al, 2010), hand grip strength test and tonometer evaluation for tissue indentation (Chen, 1988; Cantarero-

Villanueva et al, 2012). Measurements also included body weight and standard blood tests. All measurements were conducted at baseline and on monthly intervals.

### Participants

From May 2018 to July 2023, a total of 20 patients with breast cancer-related lymphoedema were included in the prospective self-control trial. Patients who underwent surgery for breast cancer and subsequently developed lymphoedema were recruited. Individuals with dermatitis or wounds on the affected area were excluded.

### Study procedures

After written consent was obtained, subjects were jointly monitored each

month by a surgeon, Chinese medicine practitioner and research assistant for regular assessments and safety checks.

### Study herbal formula

Two herbs, astragalus and moutan cortex, have been found to possess anti-fibrotic effects in both in vitro and in vivo experimental platforms. The powdered form with a carefully calculated dosage was administered to the clients 6 days a week for 6 months. The formula is shown in [Table 1](#).

### Intervention

The granule form of the herbal medicines with a carefully calculated dosage were administered to the participants orally six days a week for six months.

### Parameters of assessment

#### Displaced water volume (volume change of the affected limb)

The volume of lymphoedema was evaluated utilising both the water displacement method and circumferential measurements (Armer and Stewart, 2010; Velloso, 2011). Volumetric measurements are widely regarded as the gold standard for assessing limb volume (Mortimer, 1990; Boland and Adams, 1996). Despite also collecting circumferential measurements, we have reported the results using volumetric measurements.

The limbs were immersed into a standard container ([Figure 1](#)) filled with a standard volume of water. The amount of water displaced gave an objective measurement of the volume of the immersed part of the limb.

Monthly recordings of the lymphoedema of the affected extremity were achieved by measuring the displaced water volume. A decrease in the volume reflects the shrinkage of the lymphoedema.

At the same time, limb circumference was measured at a standard level.

Water displacement from a standard container after immersion of the affected limb has been reported to be reliable, with an intraclass correlation coefficient of 0.99 (Deltombe et al, 2007). The displaced volume was recorded in ml.

#### Lymphoedema Quality of Life

The Lymphoedema Quality of Life (LYMQOL) questionnaire contains four domains: function, symptoms, appearance and mood, as well as overall quality of life

**Table 2. Body weight changes (kg) at each visit.**

Visit	n	Mean	SD
Baseline	20	61.3	10.4
Month 1	17	60.0	9.5
Month 2	18	60.0	9.2
Month 3	17	60.0	9.5
Month 4	18	59.5	9.0
Month 5	16	59.4	9.6
Month 6	16	59.5	9.6
Change (%)	–	–2.9%	–

**Table 3. Affected limb displaced water volume (ml) at each visit**

Visit	n	Mean	SD	p-value
Baseline	20	1,303	485	–
Month 1	17	1,254	395	0.200
Month 2	18	1,308	465	0.346
Month 3	17	1,296	481	0.283
Month 4	18	1,248	462	0.055
Month 5	16	1,257	497	0.235
Month 6	16	1,250	486	0.068
Change (%)*	–	–4.1%	–	–

\*Compared with baseline

**Table 4. Pre- and post-treatment with twin-herb formula outcome summary.**

Variables	Pre-treatment	Post-treatment	p-value
Age (mean, year)	61.0 (49–73)	–	–
Lymphoedema duration (median, year)	5 (2–41)	–	–
Body weight (kg)	61.3 ± 10.4	59.5 ± 9.6	0.228
Body mass index (kg/m <sup>2</sup> )	24.3 ± 4.7	24.3 ± 4.6	0.916
Hand grip strength (affected arm, kg)	14.8 ± 4.0	15.3 ± 3.2	0.729
Tonometer measurement (affected arm)	20.7 ± 4.1	19.1 ± 3.2	0.259
Displaced water volume arm (ml)	1303.0 ± 485.1	1262.9 ± 447.0	0.068
Quality of life (QOL) function score, arm	0.81 ± 0.69	0.72 ± 0.55	0.555
QOL appearance score, arm	1.56 ± 0.85	1.24 ± 0.97	0.098
QOL symptoms score, arm	1.22 ± 0.54	0.80 ± 0.46	0.006
QOL mood score, arm	1.04 ± 0.64	0.71 ± 0.82	0.087
Overall QOL score, arm	6.19 ± 1.05	6.26 ± 1.77	0.868

(QOL). Each subscale is standardised on a 0 to 3 scale. The sum of answers for each area of function, symptoms, appearance and mood are added, then divided by the number of questions in that section to give a score for each parameter. A higher score denotes a lower quality of life associated with that parameter.

Total QOL score (overall) is recorded between 0–10, 10 being the best and 0 the worst.

**Hand grip strength**

Hand grip strength has been recognised as a valid measurement of functional mobility and QOL in patients and of physical activity in healthy female and male patients. Assessing muscle strength through hand-grip strength testing has been widely used under various conditions.

Hand grip strength was assessed by using a handheld grip dynamometer. Grip strength was assessed by applying pressure to the dynamometer with the non-affected, followed by the affected, hand. Measurement ceased at full strength. The best of three attempts was recorded in kg. A high score denotes stronger grip strength.

**Tonometer**

Tonometer measures the resistance of soft tissue to pressure, indicating the compliance of the skin surface and the compliance of the inner limb tissues.

Tonometry assesses the tissue tension (or tissue toughness), and is an index of fibrotic induration. The higher the tonometry reading, the ‘tougher’ the tissue.

**Statistical analysis**

Continuous variables were compared using the one-way ANOVA or paired t test where appropriate (to compare pre- and post-treatment or changes at each visit) and were described as mean (standard deviation).

General linear models (for repeated measures) and one-way ANOVA (for continuous outcome variables) were used to examine the change of displaced water volume and LYMQOL.

The overall quality of life, total score of LYMQOL and differences between baseline and each visit measurements in four domains were compared via one-way ANOVA test or paired t-test.

Hand grip and tonometry: The significance of differences was assessed with Student’s t-test for paired matched

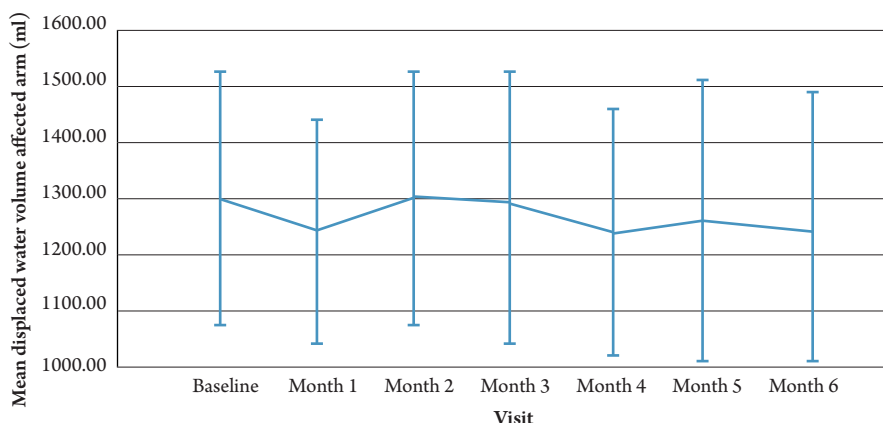


Figure 3. Affected limb mean water displacement volume (ml).

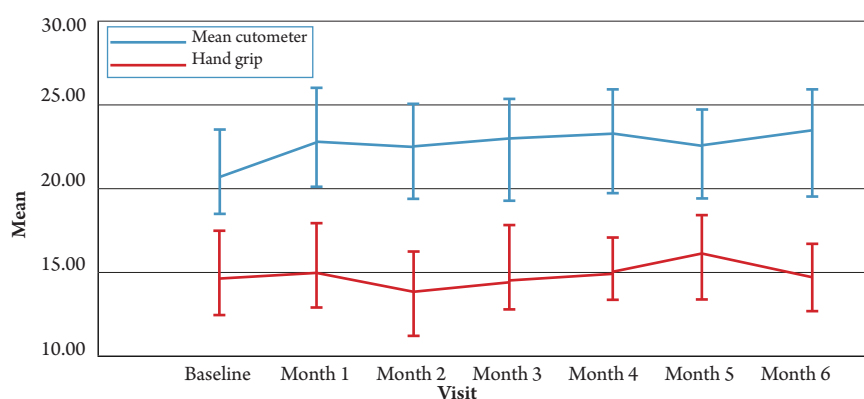


Figure 4. Changes of mean cutometer (A) and hand grip strength (B) at each visit.

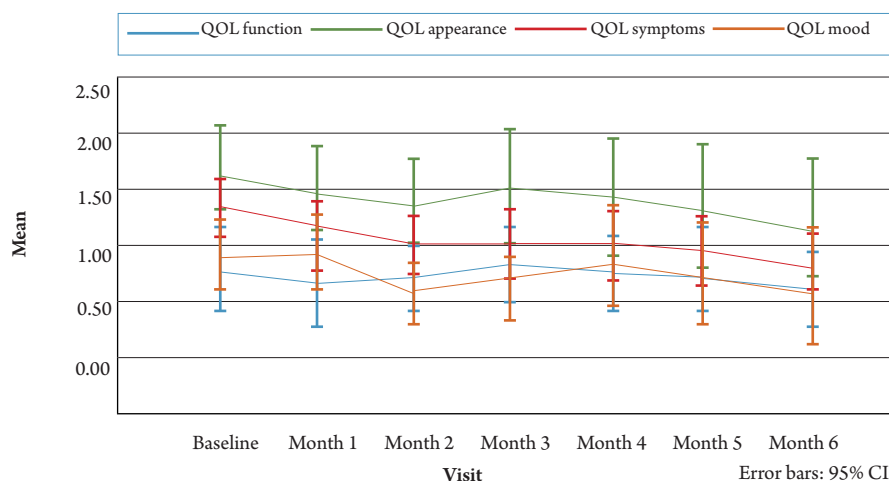


Figure 5. Changes of lymphoedema quality of life (LYMQOL) domains at each visit.

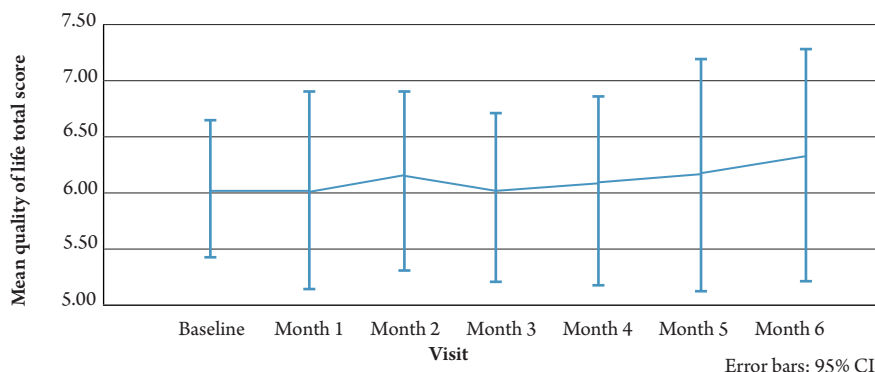


Figure 6. Changes of mean quality of life overall score at each visit.

observations when comparing pre- and post-treatment values.

A p-value <0.05 was considered to be statistically significant. Data were analysed using the Statistical Package for the Social Sciences 28 (Statistical Package for the Social Sciences, Chicago, IL).

## Results

For this pilot study report, a total of 20 subjects with established upper limb lymphoedema were included. The mean age of the participants was 60.9 years old (range 49–73 years). The median duration of lymphoedema was 5 years (2–41 years; Table 4).

### Body weight

Body weight remained stable during the study period (Table 2).

### Displaced water volume (lymphoedema volume change)

Overall volume change of affected arms decreased by 4.1% after 6 months of treatment (Table 3 and Figure 3).

The mean affected limb volume demonstrated a reduction trend over time after treatment (Figure 3). The most significant case experienced a reduction of 14.7% (Figure 2). The average reduction was 4.1% (Table 3).

The mean affected limb volume indicated a trend towards reduction over time after 6 months of treatment (Figure 3).

### Other measurements

#### Hand grip strength and tonometer

There were no remarkable changes in hand grip strength and tonometer readings during study period (Table 4 and Figure 4).

#### LYMQOL

Independent scales for function, symptoms, appearance and mood were included in the questionnaire. Each of these included several questions which were marked from 0 to 3, three being the worst.

The four domains and their corresponding questions are:

- Function.
- Appearance.
- Symptoms.
- Mood.

The overall quality of life (Q21) is scored as the value marked by the patient, between 0–10.

The summation of answers for each area of function, symptoms, appearance and mood were added, then divided by the number of questions in that section to give a score for each parameter. A higher score denoted a lower quality of life associated with that parameter.

Figure 5 and Table 4 show that independent scales for function, symptoms, appearance and mood were improved; among them, symptoms scales attained statistical significance ( $p=0.006$ ). Other quality of life domains, namely function, appearance, and mood scores, showed a trend towards improvement, although they did not reach statistical significance.

The overall quality of life of the participants showed a trend towards improvement, but it did not reach statistical significance. (Table 4 and Figure 6).

### Discussion

Persistent lymphoedema is a common complication in patients with breast cancer after surgical treatment. Surgical trauma and radiotherapy are the main causes. This complication can lead to severe limb swelling, pain and joint stiffness, seriously affecting the patient's quality of life. Long-term lymphoedema may also cause infections and skin ulcers, increasing the psychological burden and economic pressure on patients.

In order to evaluate the efficacy of an herbal formula for the treatment of breast cancer related lymphoedema, a prospective self-control clinical trial was conducted. A total of 20 patients with breast cancer-related lymphoedema were included in the trial and were treated for 6 months.

After 6 months of treatment, the affected

limb volume decreased by 4.1% on average, compared to baseline. In addition, the quality of life (LYMQOL) improved after treatment, especially in the symptom domain ( $p=0.006$ ). However, there was no significant change in other less specific evaluations.

The results of this study indicated that the herbal formula might be an effective method for the treatment of breast cancer-related lymphoedema. However, this study has some limitations, such as the small sample size, and the short treatment period. Further study is needed to further validate the results.

During the study period, no adverse events were reported, indicating that the herbal preparation was well-tolerated by the participants.

### Conclusion

In conclusion, this prospective self-controlled clinical trial has provided preliminary evidences for the efficacy of the herbal formula in the treatment of breast cancer related lymphoedema, but bigger series with longer treatment are needed to confirm its efficacy.

The limitations of this study included the small sample size, the absence of a proper control group, and the limited reliance on more objective measurement methods. Due to the COVID-19 pandemic, the clinical trial was disrupted for nearly 3 years. Future studies should consider using a larger sample size, including a control group, and incorporating more objective measurement methods such as bioimpedance spectroscopy (BIS) technology to improve the accuracy and reliability of the results.

### References

- Armer JM (2005) The problem of post-breast cancer lymphedema: impact and measurement issues. *Cancer Invest* 23(1): 76–83
- Armer JM, Stewart BR (2010) Post-breast cancer lymphedema: incidence increases from 12 to 30 to 60 months. *Lymphology* 43(3): 118–27
- Boland R, Adams R (1996) Development and evaluation of a precision forearm and hand volumeter and measuring cylinder. *J Hand Ther* 9(4): 349–58
- Cantarero-Villanueva I, Fernández-Lao C, Díaz-Rodríguez L et al (2012) The handgrip strength test as a measure of function in breast cancer survivors. *Am J Phys Med Rehabil* 91(9): 774–82
- Chen HC, O'Brine BM, Pribaz JJ, Roberts AHN (1988) The use of tonometry in the assessment of upper extremity lymphoedema. *Br J Plastic Surg* 41(4): 399–402
- Cheng Y, Zhao J, Tse HF et al (2015) Plant natural products calycosin and gallic acid synergistically attenuate neutrophil infiltration and subsequent injury in isoproterenol-induced myocardial infarction: a possible role for leukotriene B4 12-hydroxydehydrogenase? *Oxid Med Cell Longev* 2015: 434052
- Deltombe T, Jamart J, Recloux S et al (2007) Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. *Lymphology* 40(1): 26–34
- Erickson VS, Pearson ML, Ganz PA et al (2001) Arm edema in breast cancer patients. *J Natl Cancer Inst* 93(2): 96–111
- Keeley V, Crooks S, Locke J et al (2010) A quality of life measure for limb lymphoedema (LYMQOL). *J Lymphoedema* 5(1): 26–37
- Mortimer PS (1990) Investigation and management of lymphoedema. *Vasc Med Rev* 1(1): 1–20
- Nurlaila I, Roh K, Yeom CH et al (2022) Acquired lymphedema: Molecular contributors and future directions for developing intervention strategies. *Front Pharmacol* 13: 873650
- Rupp J, Hadamitzky C, Henkenberens C et al (2019) Frequency and risk factors for arm lymphedema after multimodal breast-conserving treatment of nodal positive breast cancer – a long-term observation. *Radiation Oncology* 14(1): 39
- Soran A, D'Angelo G, Begovic M et al (2006) Breast cancer-related lymphedema—what are the significant predictors and how they affect the severity of lymphedema? *Breast J* 12(6): 536–43
- Velloso FS, Barra AA, Dias RC (2011) Functional performance of upper limb and quality of life after sentinel lymph node biopsy of breast cancer. *Rev Bras Fisioter* 15(2): 146–53