French Oak Wood (*Quercus robur*) Extract (Robuvit) in Primary Lymphedema: A Supplement, Pilot, Registry Evaluation

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Abstract

The aim of this pilot supplement study was the evaluation of an oak wood extract (Robuvit, *Quercus robur* [QR], Horphag Research) in an 8-week registry study on lymphatic signs in primary lymphedema.

Subjects with primary lymphedema confined to a single leg without skin changes or ulcerations were followed for at least 8 weeks. Lymphedema was mainly present distally (below the knee). Three groups were formed: one group used only the standard management for lymphedema; one used the same management plus 300 mg Robuvit; and one used the standard management plus 600 mg of Robuvit.

The three groups were comparable. After 8 weeks the variation in leg volume was on average –6.2% with standard management, –15% in the QR 300 mg group, and –18.9% in the 600 mg group. The edema score was also significantly lower at 8 weeks in the two QR groups. The variation in proteins in the interstitial fluid in comparison with initial values was –14.8% in controls in comparison with –29.9% in QR 300 mg group and –36.9% in QR 600 mg group. Skin flux significantly improved (increased) in the two QR groups. Ultrasound pretibial skin thickness was decreased on average 6% in controls versus 10.3% in the low-dose QR group and 11.8% in the higher dose group. Perimalleolar thickness was decreased 7% in controls and more in the two QR groups. Ankle circumference was decreased 4.4% in controls and more in the two supplement groups.

This pilot registry indicates that Robuvit can be effective in the management of primary lymphedema. More patients and longer evaluation periods are needed.

Keywords

- ▶ lymphedema
- ▶ French oak wood
- ▶ Robuvit
- ▶ edema scale

Background

Lymphedema is usually characterized by swelling of the limbs. The condition often appears without a clear or defined medical history, and it is classically characterized by persisting, nonpitting edema.^{1–4} In some cases, previous and recurrent episodes of lymphangitis and cellulitis are known.^{1,3} Edema due to lymphatic disease does not generally respond promptly or effectively to rest or leg elevation.

The accumulation of interstitial fluid is caused either by congenital lymphatic abnormalities, by severe lymphatic

destruction (as in radiotherapy), or obstruction and compression. Different types of lymphedema progress in different ways and have several possible causes and aspects, and the clinical picture may be more evident in areas of the body where gravity affects its action more constantly.^{1–5} Developmental abnormalities of lymphatics and hypoplasia may be present in some 55% of the affected subjects, while varicose dilatation of lymphatic vessels may be observed in 24% of lymphatic patients.^{1,2} Lymphatic aplasia is observed in a limited number of patients. Rarely, lymphatic obstruction (which may also be functional due to compression) can also

be seen.¹ In some patients the dilatation of lymphatic vessels causes incompetence even with reverse flow (reflux).^{6,7} In different geographical areas different frequencies of disease can be observed (i.e., in relation to parasitic infestations).^{1,2} The treatment and control of lymphatic edema is based on several possible interventions. However, none are really fully effective and most are temporary (i.e., compression) unless used with great attention and persistence.^{8–10}

No specific drug for lymphedema has been developed so far.^{1,2,9–12} True lymphedema is a rare disease, and therefore very limited specific clinical and commercial interest is linked to this condition.^{1–3}

The aim of this pilot supplement study was the evaluation of an oak wood extract (Robuvit, *Quercus robur* [QR], Horphag Research) in a short-term evaluation (8 weeks) on lymphatic signs/symptoms and on some physiological functions linked to lymphatic functions.

Robuvit^{13–15} is a wood extract from QR including ellagitannins that have significant antioxidant and anti-inflammatory actions with an important effect on distal edema. Human absorption of roburins from a French oak wood extract (Robuvit) can be measured by evaluating the plasmatic increase of total phenols and the appearance of roburin metabolites. Supplementation increases plasma antioxidant capacity. Cell cultures have assessed the action of metabolites on gene expression modulation in endothelial, neuronal, and keratinocyte cell lines. Robuvit metabolites affect ribosome, cell cycle, and spliceosome pathways.¹⁴

Patients and Methods

Subjects with primary lymphedema confined to a single leg without skin changes or ulcerations were followed for at least 8 weeks. Lymphedema was mainly present distally (below the knee). The age at inclusion was between 35 and 55 years. The body mass index (BMI) was within normal values (< 26). No other significant venous or arterial disease was present. No other clinically significant disease, metabolic or bone/joint abnormality or condition requiring treatment was present at inclusion. The swelling had been present for at least 3 years with different levels of swelling and discomfort for an average of 4.4 years (range 3–6.5 years). None of these subjects had oncological problems or had been treated with radio or chemotherapy.

“Standard” lymphatic management^{1,2,5,8,10} was based on a five-step plan described as follows:

1. Strong (30–40 mm Hg at the ankle) elastic compression at least 9 h/d
2. Avoiding water retention and edema with exercise and, if needed, low-dose diuretics (furosemide 25 mg Cp, not more than once daily)
3. Control of salt (NaCl) in the diet
4. Antibiotic coverage for at least 2 weeks in case of any suspected inflammation or infection (redness, swelling, pain)
5. Repeated daily leg elevation, when possible, and constant exercise (mainly walking) and massage (mainly on the areas proximal and distal to the more affected areas)

Very careful hygiene of the foot and areas affected by lymphatic swelling was followed, and a hydrating cream was

applied to keep the skin moist and more elastic and less prone to skin breaks and subsequent infections. Education, compression, exercise, professional lymphatic drainage (when available), edema control, and foot cleaning procedures to avoid episodes of foot infections or lymphangitis were used intensively in both groups of patients.

Evaluation

The full vascular evaluation of the affected limb was performed with noninvasive tests and clinical evaluation.^{2–4,16} Venous or arterial problems were excluded. High-resolution ultrasound^{2,8} scans were performed every 4 weeks looking for any signs of further, localized edema or infections, and to exclude arterial or venous diseases.^{3,16} Black, low density, lymphatic spaces are visible in lymphatic patients (they were visible in all patients at inclusion).^{2–4,8} In our study, lymphoscintigraphy^{1,16} was considered not useful and potentially damaging for the residual lymphatics. Patients were asked to avoid any invasive procedure during the follow-up. No invasive procedure had been performed before.

Primary measurements were limb volume variations and the edema scale score as follows:

1. *Limb volume* was measured with immersion into a cylindrical, leg-shaped, Plexiglas container with water (30°C). Water displacement level at inclusion (the rise of water level to a defined volumetric mark) was arbitrarily indicated as 100% and subsequent variations adapted to this percentage.^{2–4,8,11,16,17} The length of the limb to be immersed in water was up to the lower limit of the patella (defined with ultrasound and indicated with a skin marker). After immersion and finding a stable standing position, water was added or removed to reach the level of the lower border of the patella. Each lymphedema limb had a volume 27.5; 3.3% larger on average than the healthy limb (range 25–44.4%).
2. The *edema scale* (►Table 1) included five items^{8,16,17} concerning the type of edema and four concerning the localization of edema. The sum of the two scores constituted the edema score. This study included patients with an edema score ranging between 3 and 5, excluding very mild (< 3) or very severe (5–8).

Supplementation

Robuvit is a wood extract from QR. This proprietary extract concentrates water-soluble components of the wood (ellagitannins) also found in wine resting in oak barrels.^{13–15} Flavors are imparted to wine as it ages in barrels. The use of oak has been prevalent in winemaking for centuries. Wine in the barrel acquires tannins (ellagitannins). Robuvit is specified to contain at least 20% of roburins (A, B, C, D, and E) and grandinin. Both components belong to the group of hydrolysable tannins (ellagitannins). Clinical investigation in healthy volunteers and patients have shown an increased antioxidant capacity of blood and a decrease in peripheral edema after supplementation with QR.^{13,14,18–23}

Three groups were formed: one group used only current management standards; one group used the same management plus 300 mg Robuvit (three 100 mg capsules, once a day

Table 1 The edema scale: the score ranges from 0 to 5 for the type of edema and 0 to 5 for the localization of edema

Type of edema	Score	Edema localization	Score
0: No edema			
1: Mild edema present only in the evening	1	Dorsum of foot	1
2: Edema present all day, partially reversible with rest	2	All foot, including ankle	2
3: Not reversible edema without functional impairment of limb	3	Edema involving all part of limb distal to middle joint (knee, elbow)	3
4: Permanent edema, severe functional impairment (limb volume > 200% of healthy limb)	4	All limb involved from proximal joint (hip, elbow)	4
5: As in type 4 with complications (i.e., ulcerations) or severe skin lesions	5	All limb	5

in the morning); and one group used the standard management plus 600 mg of Robuvit (three 100 mg capsules at 10 AM and 10 PM).

Supplement studies^{24–27} aim to define the field of activity of supplements and possible preventive, preferably nonclinical applications. The best fields of application for supplements are preclinical, borderline applications or the supplementary management of risk conditions. Unless there are specific claims, supplements are not generally used for treatment of signs/symptoms or clinical conditions.^{24,27} The aim of supplement studies is to produce supplementary data to be compared with “background” historical data (i.e., based on the “best management” for comparable subjects) or to other management plans. In this study, supplements were used according to the following rules:

1. The use of the supplement (Robuvit) was suggested to the evaluation subjects; its use was not prescribed but suggested as an option that would possibly improve the management of the risk condition
2. The supplement was used in addition to what was considered at the time the “standard” or best-management/care available for that condition, according to international guidelines
3. The use of the supplement should not have interfered with other treatments or preventive measures
4. The period of follow-up was variable, according to the needs and availability of the registry subjects. Ideally, the supplement administration should be used as long as needed to see results or changes
5. The type of evaluation for these studies is a registry

The evaluation of compliance concerning the use of the supplement is a significant measure of how many subjects are willing to use the product.

In supplement studies there is no defined group allocation and no randomization. Subjects decide on the basis of the initial briefing the management group they want to join. No placebo is used. Patients are always informed about the supplement or any treatment and management measure. A possible placebo effect is also carefully explained and considered. Data and results are analyzed only after the observation period; ideally, when sufficient evidence is collected or when

fund limitations would eventually stop the collection of the observations. The time needed to see differences among groups is also considered an evaluation target. In these types of studies, control groups, if present, are not necessarily parallel.

This study was basically a small-scale, independent, pilot, registry study; the evaluation product was recommended, not prescribed. All results and data were evaluated by an external reviewing panel, not in contact with the registry patients.

Secondary Target Measurements

Proteins in the Interstitial Fluid

Proteins in the interstitial fluid (PIF) were measured with a 23 gauge size butterfly needle inserted 2 to 3 mm in depth, at the dorsum of the foot. The interstitial fluid collecting in the tube (in 30 minutes) should have, in normal conditions, a protein concentration lower or equal to the concentration of proteins in blood (which is considered equal to 100%). An increased concentration indicates an abnormal accumulation of proteins in the interstitial fluid and is usually clinically associated with lymphatic edema.^{2–4}

Microcirculation

Skin flux was evaluated with a laser Doppler flowmeter (Laserflo, Vasamedics, St. Paul, MN) with a probe placed at the distal perimalleolar region. Flux measurements were the result of one average minute of measurement after stabilization. The test was made at standard environmental conditions (22°C) after 30 minutes of resting and acclimatization. In subjects with lymphedema, skin flux at the lower leg tends to be lower than in normal skin.²⁹

Limb Size Measurements

The initial circumference (ankle circumference = 100%; in cm), pretibial and perimalleolar tissue thickness (distance in mm between surface and periosteum) were measured at inclusion and at 8 weeks^{2–4,8} using high-resolution ultrasound (16 MHz linear probe, Preirus, Hitachi, Japan). Longitudinal (vertical) scans parallel to the tibia were used.

Statistics

Nonparametric tests (analysis of variance) were used to evaluate results. At least 20 subjects were evaluated in each group to compare the effects of the different management and to overcome the spontaneous variations in edema and other lymphedema-related measurements. The variability of lymphedema measurements (all nonparametric) may have an important interindividual and intraindividual value. Therefore, measurements were standardized as much as possible as to position, time of day, and environmental conditions, particularly temperature. All measurements were recorded before 11 AM in a room at standard temperature to avoid the inclusion of the edema present in the evening after standing. Results are shown as average and standard deviation.

Results

The three groups were comparable for age and sex distribution at 8 weeks (►Table 2). There were no dropouts or side effects.

Leg Volume

The first measurement defined the 100% (initial volume by water displacement). At the end of 8 weeks of evaluation the variation was on average –6.2% in controls with “standard” management; in the QR 300 mg group it was –15% and in the 600 mg group it was –18.9%. Both QR groups had better results than controls ($p < 0.05$). The higher dose was 2.9% more effective ($p < 0.05$) (►Table 3).

Edema Scale

The edema score was also significantly lower at 8 weeks in the two QR groups (6.7; 0.8 in controls in comparison with 4.3; 2.1 with low-dose QR, and 3.2; 1.8 in the higher dose group).

Interstitial Fluid Proteins

At inclusion the level of proteins in the interstitial fluid (PIF) was on average 18% higher than in plasma in controls; it was +17.6% in group B and +17.7% in group C (the three groups were comparable). At 8 weeks it was decreased to +3.2 in controls, –12.3% in group B, and –19.2% in group C. The difference between controls and all QR subjects was significant ($p < 0.05$). Also, the difference between the two QR groups was significant ($p < 0.05$). The variation in proteins in the interstitial fluid in comparison with initial values was 14.8% in controls in comparison with 29.9% in group B and 36.9% in group C.

Microcirculatory Variations

Laser Doppler flux was comparable at inclusion in the three groups. The skin was basically colder (on average more than 30%) than other body surfaces (i.e., hands, forehead). Skin flux significantly improved (increased) more in the two QR groups; the higher dose was associated with a higher skin flux at 8 weeks ($p < 0.05$) in comparison with the lower dose.

A comparable pattern was observed with transcutaneous skin P_{O_2} . At 8 weeks the two supplement groups had a significantly higher skin O_2 ($p < 0.05$) in comparison with controls, but there was a nonsignificant difference between the two dosages.

Limb Size

Considering clinical signs of lymphedema, ultrasound pretibial skin thickness was decreased on average 6% in controls versus 10.3% in the QR low-dose group and 11.8% in the high-dose group (QR was significantly more active; $p < 0.05$). Perimalleolar thickness was decreased by 7% in controls and significantly more ($p < 0.05$) in the two QR groups (there was no difference between the QR groups). Ankle circumference was decreased by 4.4% in controls and significantly more in the two supplement groups (7.5% in group B and 11% in group C; $p < 0.05$).

In the observation period there were minor episodes of localized fungal infections (all localized at toe or interdigital level) in 18.18% of the affected limbs in controls in comparison with 4.3% in the low-dose QR group and no infections in the high-dose group. Minor lymphangitic episodes were observed in 13% of controls in comparison with 4.54% in the lower dose QR and no episodes in the higher QR dose group.

Excluding perimalleolar thickness, all other parameters were significantly more affected by the higher dose of QR. There were no significant variations among patient groups and management groups concerning keratosis or areas of hyperpigmentation. Basically, this pilot evaluation was too short to detect significant changes in these aspects of lymphedema.

Compliance

Compliance with management was optimal (95%); compliance to QR was also very good (97% of the supplements correctly used); no patient in the Robuvit groups had to stop the supplementation. There were no changes in weight (and BMI) at 8 weeks. The tolerability was also very good, as no patient complained of side effects.

Table 2 Details of the 65 subjects completing 8 weeks of follow-up. There were no dropouts

Management groups	Number	Females	Mean age; SD	Observation period (d)
“Normal” management plan	22	13	38.3; 7	66; 2.2
Same plan + QR low dose	23	12	39.5; 3.2	64.3; 2
Same plan + QR high dose	20	12	39.9; 4.3	66.3; 2.1

Abbreviation: QR, *Quercus robur*.

Table 3 Summary table difference between controls and the two QR groups

		Group			P1	P2
		A	B	C		
		Controls	300 mg (QR low dose)	500 mg (QR high dose)		
Leg volume						
100% is the initial volume; 8 wk comparison as percentage of initial volume	Incl	100%	100%	100%	ns	
	8 wk	−6.2; 2.2%	−15; 2%	−18.9; 2.4%	^a	^a
Edema score						
	Incl	7.3; 1.6	7.2; 1.1	8.1; 1	ns	
	8 wk	6.7; 0.8	4.3; 2.1	3.2; 1.8	^a	^a
Interstitial proteins ^b						
Percentage comparison with plasma proteins	Incl	18.1; 1.6%	17.6; 2%	17.7; 2.1%	ns	
	8 wk	3.2; 1.1%	−12.3; 1.5%	−19.2; 2.2%	^a	^a
Microcirculation						
LDF flux units	Incl	0.92; 0.2	0.95; 0.1	0.93; 0.11	ns	
	8 wk	1.32; 0.1	1.94; 0.1	2.2; 0.1	^a	^a
Transcutaneous Po ₂ (mm Hg)	Incl	44.8; 3.2	45.2; 2.5	44.7; 3	ns	
	8 wk	46.7; 2	51.3; 3.3	53.4; 2.7	^a	ns
Limb sizes						
Pretibial thickness (mm)	Incl	13.3; 1.2	14.1; 2	13.9; 2.4	ns	
	8 wk	−6%	−10.3%	−11.8%	^a	ns
Perimalleolar thickness (mm)	Incl	15.3; 2	15.2; 3.2	16.4; 2.2	ns	
	8 wk	−7%	−13.2%	−13.8%	^a	ns
Ankle circumference (cm)	Incl	24.5; 3.5	25.1; 2.1	25.2; 2.6	ns	
	8 wk	−4.4%	−7.5%	−11%	^a	^a
Complications in 8 wk						
Fungal infections (episodes)	8 wk	4/22	1/23	0/20	^a	
Skin breaks	8 wk	11/22	2/23	2/20	^a	
Minor lymphangitic episodes	8 wk	3/22	1/23	0/20	ns	
Hyperkeratosis	Incl	4/22	4/23	3/20	ns	
	8 wk	4/22	4/23	2/20	ns	
Hyperpigmentation	Incl	4/22	5/23	4/20	ns	
	8 wk	No changes	No changes	No changes	ns	

Note: P₂ indicates a greater effect of the higher dose ($p < 0.05$).

^a $p < 0.05$.

^bReference range for total plasma protein is typically 60–80g/L.

Discussion

The medical treatment and control of primary lymphatic edema is based on several possible interventions, none of which, at present, seems to be definitive. Therapy and management should be individualized.^{11,16,30–32}

The variations in clinical pictures and the relative rarity of this disease (at least in our country) make it difficult to complete large studies with really comparable patients.

All studies should be based on long-term observations as the disease shows its worst characteristics of progression in time.^{8,16} An important step in lymphedema patients is the prevention of recurrent infections.^{1–4,33} This may stop further lymphatic damage but rarely improves the established disease. In most patients, good results are obtained before fibrosis develops altering the structure, perfusion, and nutrition at the level of the subcutaneous tissue.

Nonoperative management is used in all patients and is based on limb elevation repeated at intervals during the day, compression of the affected limb or sequential/intermittent compression with appropriate devices. Dietary sodium restriction is suggested, but its effects are questionable.^{2-4,34} The best possible hygiene to prevent minor infections and severe cellulitis can be associated with long-term selective prophylaxis with antibiotics. The prevalent bacteria in lymphedema are streptococci, but this may also be questionable (different countries may have different infective patterns), and cultures should be available when needed.^{1,33}

Surgery^{1-4,35} has been used only in a small percentage of subjects, including more severe cases, with significant results, but surgical techniques cannot be applied to all patients. The indications for surgery are, generally, a severely impaired limb function due to excessive size and weight, pain, recurrent infections, and the presence of lymphangiosarcoma and cosmetic considerations. Excisional procedures (i.e., resurfacing and plastic surgery with skin grafts, liposuction) are effective even at the price of some sensory loss and further swelling.¹⁻³ Also, many interventions may destroy the few remaining lymphatic channels. Lymphovenous anastomosis has been used for a few years using microvascular surgery (lymphatic-lymphatic anastomoses, microlymphatic by pass or lymph-venous connections). Good results have been reported in some 25% of operated (after accurate selection) patients,^{2,34,36} often in secondary lymphedema. Other methods such as the Thompson procedures, enteromesenteric bridge techniques, and omental pedicle flaps have been used for advanced patients but not widely accepted.^{1,36}

The prognosis for these patients is a gradual, steady progression leading to disability. The prevention of recurrent infections (i.e., using appropriate compression and shoes for foot protection) and the combination of treatments (exercise and lymph drainage) may be effective in controlling the problem.

A recent long-term study on autologous lymphatic transplant from our group³⁷ has shown promising results in a 10-year follow-up. New technology with lymphatic tissue grown in cultures allowing repeated, regular implant of tissue may be a significant possibility in the future.

Robuvit is the wood extract from QR concentrating water soluble components of the wood (ellagitannins).^{13,14} *Robuvit* is specified to contain at least 20% of roburins (A, B, C, D, and E) and grandinin¹⁸⁻²³ safe for humans and effective in decreasing plasma-free radicals, indicating a significant action on oxidative stress. Hydrolysable tannins (ellagitannins) included in *Robuvit* are effective in different preclinical and clinical conditions and have an anti-inflammatory action.¹⁵ Their antioxidant efficacy has been tested in healthy volunteers,¹⁴ in patients with hepatic failure,¹⁵ and in subjects with a combination of chronic fatigue syndrome and increase in oxidative stress.¹³ In several patients a decrease in peripheral edema after supplementation with QR¹³⁻¹⁵ has been observed.

Education and careful self-management are the key to managing lymphedema.³⁸ Volumetric changes and edema are the most visible signs for the patients. The evaluation of

proteins in interstitial fluid may be a significant quantitative evaluation, but this method should be better defined and evaluated in longitudinal studies.³⁹⁻⁴¹

Conclusions

This pilot study indicates that *Robuvit* can be effective in helping the management of lymphatic patients. The results appear to be related to dosages; however, 8 weeks is a short period for lymphedema. More patients and longer periods of observation are needed.

Conflict of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the article.

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