


**A SYSTEMATIC REVIEW OF POST-BREAST CANCER LYMPHOEDEMA
AND ITS TREATMENT WITH NATURAL MEDICINE.**

Jesica Graciela Massaro-Zygmunt

A minithesis submitted in partial fulfilment of the requirements for the degree of
Magister of Curationis in the Department of Community and Health Sciences at the



University of the Western Cape
WESTERN CAPE

Supervisor: Prof. Dr. C. Nikodem

Co-supervisor: Dr. J. Armer (University of Missouri)

November 2008

**A SYSTEMATIC REVIEW OF POST-BREAST CANCER LYMPHOEDEMA
AND ITS TREATMENT WITH NATURAL MEDICINE.**

Jesica Graciela Massaro-Zygmunt

KEYWORDS:

Lymphoedema

Secondary lymphoedema

Homeopathy

Systematic review

Breast cancer

Lymphatic system

Natural medicine

Herbs

Review Manager 5

Radiotherapy

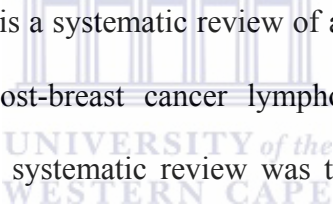


ABSTRACT

A SYSTEMATIC REVIEW OF POST-BREAST CANCER LYMPHOEDEMA AND ITS TREATMENT WITH NATURAL MEDICINE.

J.G. Massaro-Zygmunt

M.Cur. minithesis, Department of Community and Health Sciences, University of the
Western Cape




In this minithesis a systematic review of all of the available contemporary literature on post-breast cancer lymphoedema was undertaken. The purpose of this systematic review was to search for, collate, synthesize and thereby provide the reader with a comprehensive, evidence-based account of all the available research published between 1988 and 2008 on the treatment of post-breast cancer lymphoedema with natural medicine.

Because the large number of articles published every year across a plethora of biomedical journals makes it incredibly difficult for practitioners to keep up-to-date within their specialized areas, systematic reviews are particularly useful as they summarize high quality, contemporary scientific knowledge on a topic in one place (Antman, Lau, Kupelnik, Mosteller & Chalmers, 1992). One such topic on which many

health practitioners have a paucity of information regarding management and risk reduction in lymphoedema (Radina, Armer, Culbertson & Dusold, 2004)

The primary objective of this research project was to assess the effects of natural medicine on post-breast cancer lymphoedema in regard to 1) life style improvement including any signs and symptoms related to the condition such as heaviness, tightness, pain, ache, itch, mobility of the affected arm, skin texture as well as psychological symptoms like distress; 2) arm volume changes of the affected limb; 3) adverse effects; and 4) modification or cessation of treatment.



Several online databases were searched for articles that contain the term lymphoedema, lymphedema, limb swelling or "linfedema" (Spanish and Portuguese); thereby including all possible spellings in English, Spanish and Portuguese. Relevant information was extracted and recorded in tabular format. The quality of each study was analysed using a checklist, which was drawn up by the primary researcher and study supervisor based on the CONSORT guidelines (Altman, 1996).

To ensure quality, only randomized controlled trials, quasi-randomized controlled trials or clinical trials that met the inclusion or exclusion criteria, reporting benefits or adverse effects of natural medicines for the

treatment of post-breast cancer lymphoedema were included. In addition, studies had to focus on natural medicine versus placebo or routine treatment or no treatment as types of intervention; and participants had to include women of all ages that had been diagnosed with post-breast cancer lymphoedema.

The relevant data from included studies was entered into Review Manager 5 (Revman 5) software for meta-analysis. The primary studies included in this systematic review generally suffered from small sample sizes, varied somewhat in their operationalisation of outcomes and the format for presenting results, making meta-analysis very difficult. However, results suggest that sodium selenite taken orally and CYCLO 3 FORT also taken orally are effective in the reduction of limb volume. The results also suggested that aromatherapy using an intervention cream containing wheat germ oil and essential oils of fennel, sage, geranium, black pepper and juniper; and vitamin E plus pentoxifylline taken orally are not effective. Seeing as these results are drawn from single studies with heterogeneous outcome variables, they should be seen as tentative until they are confirmed by replication. Gaps in the literature regarding natural medicine as a treatment for post-breast cancer lymphoedema were identified, and recommendations for further research are proposed.

DECLARATION

I declare that, *A systematic review of post-breast cancer lymphoedema and its treatment with natural medicine* is my own work, and that it has not been submitted before for any examination in any other university, and that all sources I have used or quoted have been indicated and acknowledged by complete reference.

Jesica Graciela Massaro-Zygmunt

November 2008



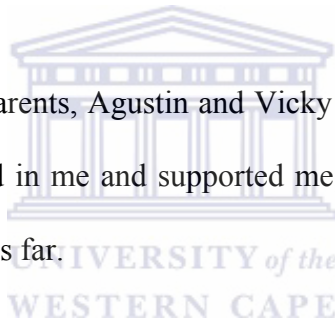
Signed:.....

ACKNOWLEDGEMENTS

First of all I want to thank God for His infinite love and mercy, for being with me every step of the way. All the glory is to Him.

I would like to thank my husband, Conrad Zygmunt, for his never ending support and love, for being always there for me encouraging me through the process. You are the greatest blessing in my life and I love you very much!

I also want to thank my parents, Agustin and Vicky Massaro, despite being far away they have always believed in me and supported me, without them I would not have been able to have come this far.



I would like to extend my appreciation to my supervisor, Professor Cheryl Nikodem for making a way for me to assist to the Cochrane systematic review and RevMan 5 workshop and to the first lymphoedema course presented in South Africa.

I would also like to express my gratitude to Professor Jane Armer, my co-supervisor from the University of Missouri, whom I had the pleasure meeting at the lymphoedema course in South Africa. Thank you for always being so quick to answer my questions and for always being ready to help.

Finally I would like to thank my relatives and friends in Argentina, South Africa, and other countries, for their prayers and continuous love. I am grateful that you got me to de-stress when it was much needed and for just being there for me.



CONTENTS

Title Page		i
Keywords		ii
Abstract		ii
Declaration		vi
Acknowledgements		vii
CHAPTER 1	Introduction	1
	1.1 Introduction	1
	1.2 Background literature	2
	1.3 Research problem	4
	1.4 Research objectives	5
	1.5 Research question	6
	1.6 Research statement	6
	1.7 Definitions	7
	1.7.1 Lymphoedema	7
	1.7.2 Primary lymphoedema	7
	1.7.3 Secondary lymphoedema	8
	1.7.4 Lymphatic system	9
	1.7.5 Systematic reviews	10
	1.7.6 Mastectomy	10
	1.7.7 Cancer	11

1.7.8 Breast cancer conserving surgery	12
1.7.9 Axillary lymph node dissection (ALND)	12
1.7.10 Sentinel lymph node biopsy (SLNB)	12
1.7.11 Oncology	14
1.7.12 Radiotherapy	14
1.7.13 Chemotherapy	15
1.7.14 Review Manager (RevMan) 5	15
1.7.15 Randomized controlled trial	16
1.7.16 Natural medicine	16
1.7.17 Aromatherapy	17
1.8 Research design and methodology	17
1.8.1 Types of studies	17
1.8.2 Types of participants	18
1.8.3 Types of interventions	18
1.8.4 Types of outcomes measures	18
1.8.5 Search strategy for identification of studies	18
1.8.6 Methods of the review – Validity and reliability	19
1.8.7 Data analysis	19
1.9 Relevance of the study	20
1.10 Ethics statement	20
1.11 Chapter outlines	21
1.12 Time line	21
1.13 Budget	22

1.14	Summary	23
CHAPTER 2	Literature Review	24
2.1	Introduction	24
2.2	Anatomy	25
2.3	Physiology	26
2.4	Pathophysiology of breast cancer related lymphoedema	27
2.5	Incidence and prevalence of lymphoedema	28
2.6	Classifications of lymphoedema	29
2.6.1	Primary lymphoedema	30
2.6.2	Secondary lymphoedema	31
2.6.2.1	Lymphoedema associated with post-breast cancer treatment	31
2.7	Causes of lymphoedema	33
2.8	Predisposing factors associated with lymphoedema	34
2.9	Symptoms of lymphoedema	35
2.10	Diagnosis of lymphoedema	35
2.11	Stages of lymphoedema	36
2.12	Treatments for lymphoedema	37
2.12.1	Treatments overview	37
2.12.2	Complete decongestive therapy (CDT)	39
2.12.3	Manual lymphatic drainage (MLD) and Simple lymphatic drainage (SLD)	40

2.12.4	Intermittent pneumatic compression (IPC)	41
2.12.5	Surgical treatments	41
2.12.6	Pharmacotherapy	43
2.12.7	Low-level laser therapy	44
2.12.8	Flowave	45
2.12.9	Other complementary and alternative therapies	45
2.13	Natural medicine and lymphoedema	47
2.13.1	Horse chestnut seed extract	48
2.13.2	Selenium	49
2.13.3	Bromelain (from pineapple)	50
2.13.4	Aromatherapy	50
2.13.5	Vitamin E supplement	50
2.13.6	Mulberry leaf	51
2.13.7	Pycnogenol (from pine bark) and Procyanidins	51
2.13.8	Butcher's broom (<i>Ruscus aculeatus</i>)	52
2.14	Post-breast cancer lymphoedema lack of information / education	53
2.14.1	Patient's lack of information / education	53
2.14.2	Health care providers' lack of information / education	54
2.15	Summary	54

CHAPTER 3	Research Design & Methodology	56
3.1	Introduction	56
3.2	The Review Manager (RevMan) 5	57
3.3	Systematic reviews	57
3.4	Rational for systematic reviews	58
3.5	Systematic reviews as scientific research	59
3.6	Main features of systematic reviews	59
3.7	Advantages of systematic reviews	60
3.8	Limitations of systematic reviews	61
3.9	Ensuring quality of systematic reviews	62
3.10	Criteria for selection of studies for this review	62
3.11	Search strategy	67
3.12	Methodology quality, validity and reliability	67
3.13	Limitations of this systematic review	69
3.14	Data collection	69
3.15	Data analysis	70
3.15.1	Dichotomous data	71
3.15.2	Continuous data	73
3.16	Characteristics of included studies	74
3.17	Excluded studies	81
3.18	Summary	84

CHAPTER 4	Results	85
4.1	Introduction	85
4.2	Life style improvement	87
4.2.1	Comparison 01: post-breast cancer group	87
4.2.2	Comparison 02: post-cancer group	89
4.3	Changes in arm volume (of the affected limb)	90
4.3.1	Comparison 01: post-breast cancer group	90
4.3.2	Comparison 02: post-cancer group	92
4.4	Adverse effects	92
4.4.1	Comparison 01: post-breast cancer group	93
4.4.2	Comparison 02: post-cancer group	93
4.4.3	Comparison 01 and 02 combined	94
4.5	Modification or cessation of treatment	95
4.5.1	Comparison 01: post-breast cancer group	95
4.5.2	Comparison 02: post-cancer group	96
4.6	Summary results	97
CHAPTER 5	Discussion	98
5.1	Introduction	98
5.2	Discussion	100
5.3	Implications for practice	102
5.4	Implications for future research	103
5.5	Conclusion	105

BIBLIOGRAPHY	107
---------------------	-----

APPENDICES	118
-------------------	-----

LIST OF FIGURES

1.1 Primary lymphoedema of the lower limbs	7
1.2 Secondary lymphoedema post-breast cancer treatment	8
1.3 The lymphatic system	9
1.4 Sentinel lymph node biopsy of axillary lymph nodes	13
2.1 Causes of lymphoedema	33
4.1 Forest plot of comparison 01: changes in induration fibrosis using vitamin E plus pentoxifylline	87
4.2 Forest plot of comparison 02: symptom improvement using aromatherapy cream	89
4.3 Forest plot of comparison 02: well-being using aromatherapy cream	90
4.4 Forest plot of comparison 01: adverse effects using vitamin E plus pentoxifylline of CYCLO 3 FORT	93
4.5 Forest plot of comparison 02: adverse effects using aromatherapy cream	94
4.6 Forest plot of both comparison groups: adverse effects using vitamin E plus pentoxifylline or CYCLO 3 FORT or aromatherapy cream	95

4.7 Forest plot of comparison 01: modification or cessation of treatment using vitamin E plus pentoxifylline or CYCLO 3 FORT	96
--	----

LIST OF TABLES

1.1 Time line for the completion of the systematic review	21
1.2 Proposed budget for the present systematic review	22
2.1 Stages of lymphoedema	36
3.1 Selection criteria for post-breast cancer lymphoedema and its treatment with natural medicine	65
3.2 Comparison 01: post-breast cancer group (Cluzan et al., 1996)	75
3.3 Comparison 01: post-breast cancer group (Gothard et al., 2004)	76
3.4 Comparison 02: post-cancer group (Barclay et al., 2006)	78
3.5 Comparison 02: post-cancer group (Micke et al., 2003)	80
3.6 Excluded studies (Hutson et al., 2004)	81
3.7 Excluded studies (Kirshbaum, 1996)	82
3.8 Excluded studies (Hutson, 2004)	82
3.9 Excluded studies (Kasseroller, 1997)	83
4.1 Symptom improvement using CYCLO 3 FORT (Cluzan et al., 1996)	88

CHAPTER ONE

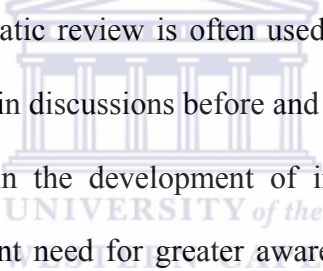
Introduction

1.1 Introduction

It is estimated that approximately 30% of breast cancer survivors develop lymphoedema after undergoing breast cancer treatment (Bumpers, Best, Norman & Weaver, 2002). There is an urgent need for greater awareness and understanding of the experiences of women who have undergone breast cancer treatment and develop lymphoedema following the treatment. Awareness needs to expand especially amongst health practitioners that appear to have a lack of understanding regarding the risk reduction and treatment of lymphoedema (Radina, Armer, Culbertson & Dusold, 2004). In addition research suggests that breast cancer patients often make use of alternative or complementary medicines in their treatment of lymphoedema symptoms, especially in cases with heavy swelling, despite a lack of supporting evidence based literature documenting its effectiveness (Ashikaga, Bosompra, O'Brien & Nelson, 2002; Fouladbakhsh, Stommel, Given & Given, 2005). It was hoped that this systematic review would result in a greater understanding of the management of post-breast cancer lymphoedema with natural remedies after meta-analyses of all the data collected via the defined search strategy.

1.2 Background literature

More than two million articles get published every year in over 20,000 biomedical journals, which makes it impossible to keep up-to-date even within a specialized area. This is why systematic reviews are so important - they help practitioners or anyone interested in a specific topic to keep up to date with contemporary information, as they include high quality literature about the relevant topic (Antman, Lau, Kupelnik, Mosteller & Chalmers, 1992).



A comprehensive systematic review is often used as evidence based research to guide nurses and doctors in discussions before and after surgery with their patients and could be included in the development of information leaflets or consent forms. There is an urgent need for greater awareness and understanding of the experiences of patients who have undergone breast cancer treatment and develop lymphoedema thereafter. Many health practitioners lack the understanding of lymphoedema management and have little or no information on risk reduction related to lymphoedema (Radina et al., 2004). This uncertainty is transferred to patients. For example, a South African patient while being interviewed regarding the knowledge of her condition stated: “...*They said the swelling would be there forever. I'm not expecting a bigger arm like this, but they tell me it's going to get bigger, and then it is going to get bigger, then it's going to be like burst... this arm will be so much blood and trickle will start...*” (Ester, personal communication, July 2008). This knowledge is especially important for nurses, as

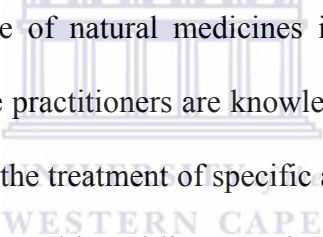
nursing care has a major impact on the patient's outcomes, with nurses being responsible for monitoring for the presence of this disease so that they can rapidly intervene and thus minimize the extent of the problem (Marrs, 2007).

It is estimated that approximately 30% of breast cancer survivors develop lymphoedema after undergoing breast cancer treatment (Bumpers et al., 2002). It is important to determine the incidence and prevalence levels of post-breast cancer lymphoedema. Increases in incidence may guide clinicians to do further research, while a decrease may show that policies that address the problem are implemented successfully. Without some statistics regarding the incidence of lymphoedema, it may be difficult for clinicians to empirically determine the extent of the problem and impossible to evaluate the effectiveness of interventions (Webb, Bain, & Pirozzo, 2005). Descriptive statistics are often used by researchers to compare ratios across different contexts, which may give information regarding the causes of lymphoedema amongst groups with different environmental, treatment, co-morbid or genetic characteristics. Finally, although not a specific aim of the present study, the information generated during the literature search may also be useful for predicting the natural course and progression of lymphoedema following breast cancer treatment (Webb, Bain, & Pirozzo, 2005).

This review is based on all obtainable literature from databases that were available to the reviewer concerning this topic, and it is hoped to encourage a better

understanding of lymphoedema in general. Special attention is given to studies that are concerned with herbal and natural or homeopathic compounds to treat secondary lymphoedema post-breast cancer as interest in the use of complementary and alternative medicine (CAM) to treat ailments has grown among the public (Olson, 2001).

1.3 Research problem



Public interest in the use of natural medicines is growing, and it is therefore important that health care practitioners are knowledgeable of the use and efficacy of natural medications in the treatment of specific ailments such as lymphoedema. However, scientific evidenced based literature is scarce, and popular literature is often unscientific and/or ambiguous (e.g. Bone, 2008; Brady, no date; Brady, 1996a; Brady, 1996b; Dharmananda, 2000; Herbs2000.com, 2008; Lymphedema People, 2008a; Lymphedema People, 2008b; Medifocus Health, 2008; O'Connor, 2008; Sims, 2006). This is especially the case in the use of natural medicines for the treatment of lymphoedema. Therefore, the present study was conducted to provide a comprehensive, evidence-based account of information on the efficacy of natural medicines in the treatment of post-breast cancer lymphoedema.

1.4 Research objectives

The primary objective of this research project was to assess the effectiveness of natural medicines in comparison to conventional treatment, no treatment or placebo for the treatment of post-breast cancer lymphoedema by doing a systematic review and meta analyses of the results of all the literature available to the reviewer. The specific objectives that were considered, in order to assess the effectiveness of natural medicines were:

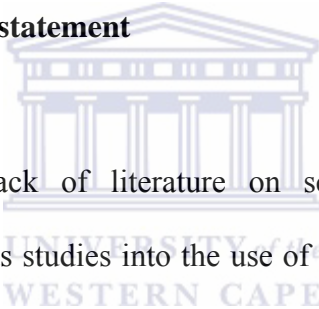
- The effects on life style improvement (including any signs and symptoms related to the condition such as: heaviness, tightness, pain, ache, itch, mobility of the affected arm, skin texture, as well as psychological symptoms like distress).
- The effects on arm volume changes (of the affected limb).
- Adverse effects.
- Modification or cessation of treatment.

The literature regarding post-breast cancer lymphoedema and its treatment with natural medicine was searched and collated in order to provide a comprehensive summary of contemporary knowledge on the topic. Gaps in the literature regarding natural medicine as a treatment for post-breast cancer lymphoedema were identified, and recommendations for further research were proposed.

1.5 Research question

What are the effects of natural medicines / therapies on quality of life (including signs and symptoms), arm volume changes (of affected limb), adverse effects, modification or cessation of treatment in post-breast cancer lymphoedema patients?

1.6 Research statement



Currently there is a lack of literature on scientific, evidence based and methodologically rigorous studies into the use of natural medicines as part of the treatment of lymphoedema. A systematic review with meta-analysis of available clinical trial data allows for greater validity, reduction of systematic errors or bias, and greater generalizability of results across various settings. Furthermore, it may result in an increased understanding of the effectiveness of natural medicines as part of the treatment of post-breast cancer lymphoedema for both the person suffering from lymphoedema and the health care worker responsible for the care.

1.7 Definitions

1.7.1 Lymphoedema

Lymphoedema is the “accumulation of lymph in the interstitial spaces, usually in the peripheral tissue, due to some interference with the lymphatic return. Since it is a one-way system, this fluid has no way to get out of the tissues and accumulates” (Pratt, 1956, p. 1548). It can be classified into primary or secondary lymphoedema (Weissleder & Schuchhardt, 2008).

1.7.2 Primary lymphoedema

Primary lymphoedema results from a genetic or congenital abnormality of lymph of the lymphatic system (Casley-Smith & Casley-Smith, 1992 cited by McCallin, Johnston, & Bassett, 2005). See figure 1.1 below:



Figure 1.1: Primary lymphoedema of the lower limbs (The Jacksonville Lymphedema Clinic, 2005).

1.7.3 Secondary lymphoedema

Secondary lymphoedema may be caused by “trauma, such as axillary lymph node dissection during surgery for breast cancer, or by filariasis, which is a parasitic infection of the lymphatic system occurring in the tropical and equatorial parts of the world” (Casley-Smith & Casley-Smith, 1992 cited by McCallin, Johnston & Basset, 2005, p. 101). See figure 1.2 below:



Courtesy of BioCompression Systems Inc.

Figure 1.2: Secondary lymphoedema post-breast cancer treatment (Storer, 2006).

1.7.4 Lymphatic system

It is described as the “systems of vessels and glands through which the lymph is returned to the circulation system” (Weller, 2001, p. 244). See figure 1.3 below:

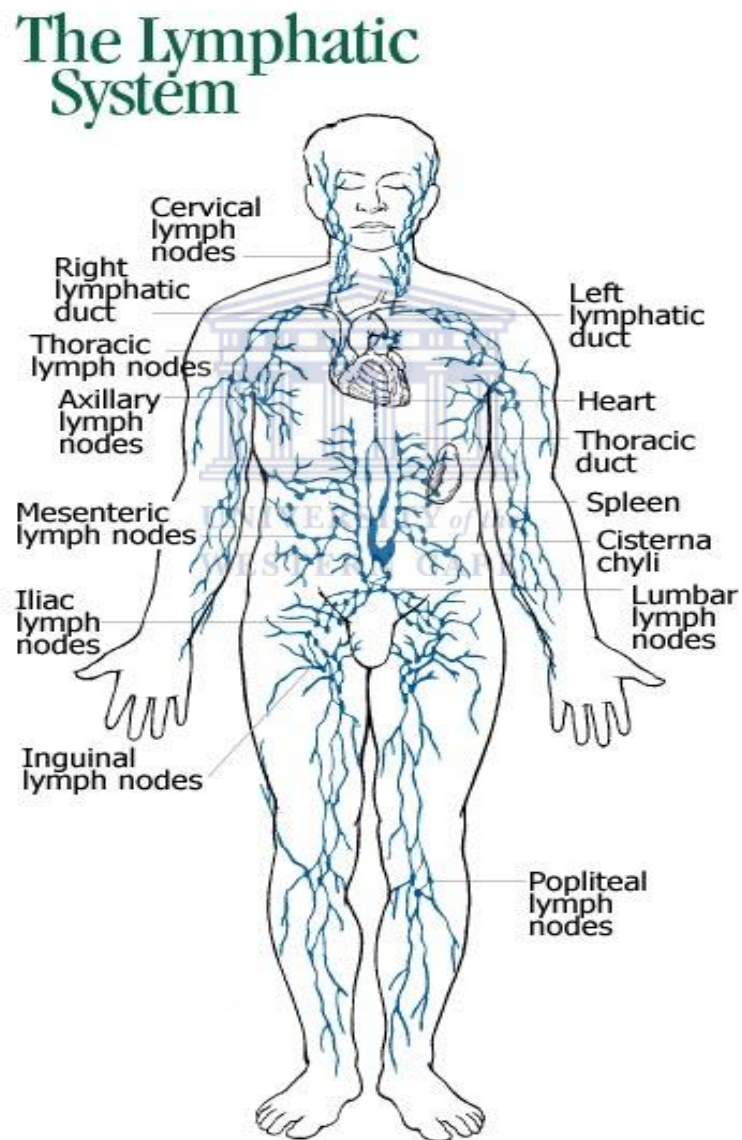


Figure 1.3: The lymphatic system (Lymphedema Treatment Center, no date).

1.7.5 Systematic reviews

“Systematic reviews attempt to collate all evidence that fits pre-specified eligibility criteria in order to answer a specific research question” (Higgins & Green, 2008, p. 4). A systematic review is a selection and collection of data from primary studies, in which the primary studies are analysed and where the results may be presented in narrative form, quantitative form (using meta-analysis) or both. Preference is given to randomized controlled trials over other types of studies for inclusion in the review (Higgins & Green, 2008; Jadad & McQuay, 1996).



1.7.6 Mastectomy

Mastectomy is a surgical procedure that is often performed as a treatment for breast cancer (Gale Encyclopaedia of Cancer, 2006). Radical mastectomy, an approach attributed to William Halsted, which involves the en bloc removal of the breast, muscles of the chest wall, and contents of the axilla was the standard surgical procedure for the treatment of breast cancer for much of the 20th century (Fisher, Jeong, Anderson, Bryant, Fisher, & Wolmark, 2002). This approach was later discarded for a more moderate approach called modified radical mastectomy. In this approach all of the breast tissue, its overlying skin and the contents of the axilla nodes are removed. The procedure is less debilitating than radical

mastectomy seeing as pectoral muscles are not removed, and post-operative oedema of the arm less likely (Schachter & Neuhauser, 1981).

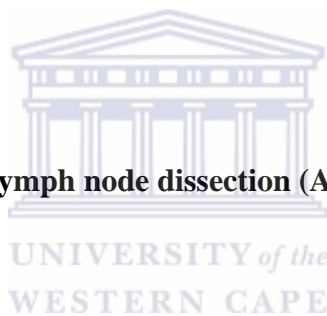
1.7.7 Cancer

Cancer is a general term to describe malignant growths in tissues. There are many different types of cancers. For example, carcinoma refers to cancers of the epithelial tissue, while sarcoma refers to cancers of connective tissue origin, as in bone and muscle. The basic aetiology of cancer remains unknown; however, many potential causes and contributing factors have been identified. Some of these include cigarette smoking, ionizing radiation, exposure to certain chemicals and overexposure to the sun. Hereditary factors also play an important part in the development of cancers. A cancerous growth is one that is “not encapsulated, but infiltrates surrounding tissues, the cells of which it replaces by its own. It is spread by the lymph and blood vessels and may lead to metastases in other parts of the body. Death is caused by destruction of organs to a degree incompatible with life, by extreme debility and anaemia, or by haemorrhage” (Weller, 2001, p. 69).

1.7.8 Breast cancer conserving surgery

Breast conserving surgery is an operation that removes the breast cancer along with a margin of normal breast tissue around it, while attempting to conserve as much of the normal breast tissue as possible. There are three main ways this surgery is done: lumpectomy, quadrantectomy, and segmental mastectomy (Breastcancer.org, 2007a). A sentinel lymph node biopsy is often conducted on proximal axillary lymph nodes, which are then either removed or left intact if the sentinel nodes are found to be negative.

1.7.9 Axillary lymph node dissection (ALND)



Axillary lymph node dissection (ALND) is a surgical procedure used to assess breast cancer and its need for further treatment (Encyclopedia of Surgery, 2007), and/or to take out lymph nodes from the armpit area (Breastcancer.org, 2007b).

1.7.10 Sentinel lymph node biopsy (SLNB)

Sentinel lymph node biopsy (SLNB) is a procedure in which a dye and/or radioactive substance is injected into the proximity of the cancer tumour and subsequently drains into the lymph nodes. The first lymph node that the dye

comes to is called the sentinel lymph node, as it has the highest probability of coming into contact with cancer cells that might spread after breaking away from the main cancer in the breast. Sometimes there is more than one sentinel node. The radioactive substance or dye makes it possible for clinicians to identify the sentinel lymph node, or nodes, which are then removed and checked to see if there are cancer cells in them (Breastcancer.org, 2007c). Refer to figure 1.4 below:

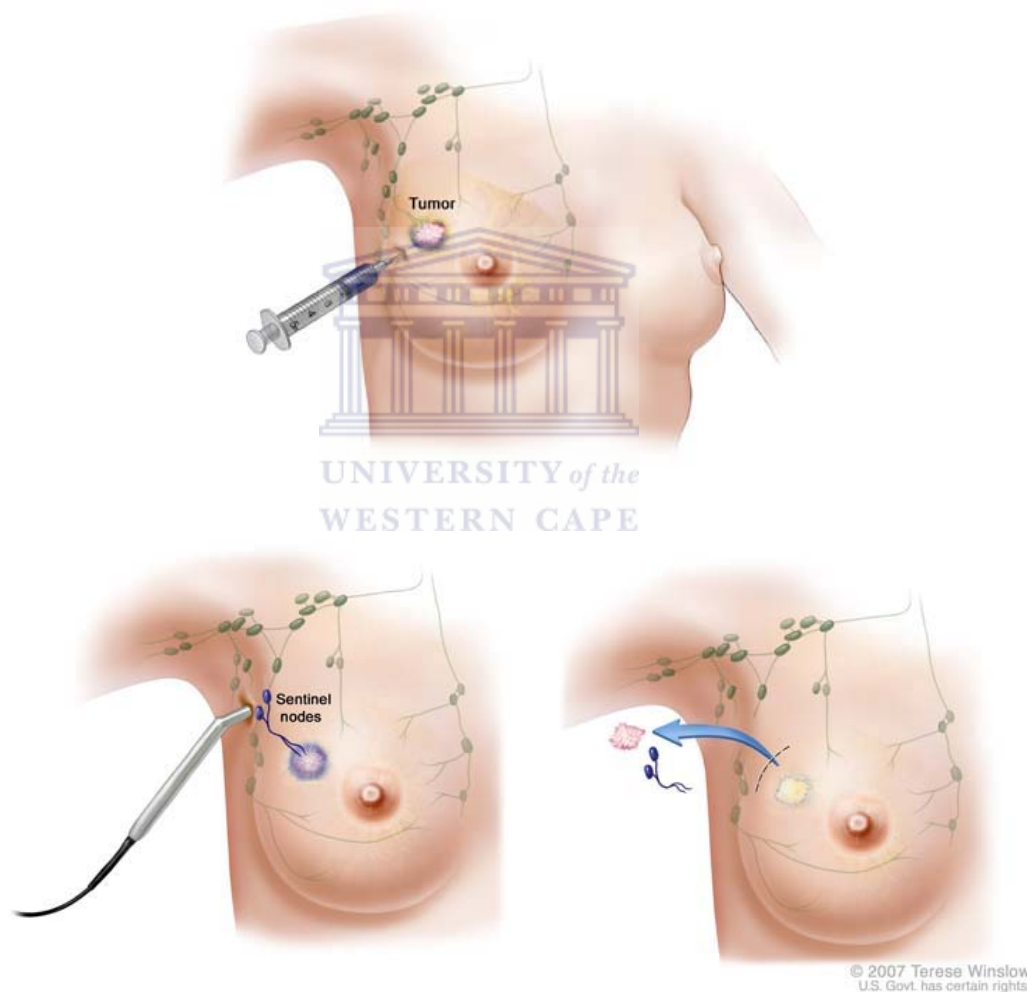


Figure 1.4: Sentinel lymph node biopsy of the axillary lymph nodes (National Cancer Institute, 2008).

1.7.11 Oncology

Oncology is the section of science that concerns itself with the study of tumours (Weller, 2001).

1.7.12 Radiotherapy

Radiotherapy is the treatment of disease by radiation or radioactive isotopes (Weller, 2001). It is broadly categorised into two approaches, teletherapy in which the source of radiation is further away from the tumour and in which X-rays are typically used, and brachytherapy that describes approaches in which the source is either within or very close to the tumour and tends to utilize radioactive sources (Cherry & Duxbury, 1998). In treatment of breast cancer external beam radiation is the type most frequently used, typically at a schedule of 50 Gy, delivered in 25 fractions of 2.0 Gy over 5 weeks, but research findings do suggest that lower doses in a smaller number of fractions could deliver the same required effects (The START Trialists' Group, 2008).

1.7.13 Chemotherapy

Chemotherapy can be loosely defined as the specific treatment of disease by the administration of chemical compounds that most often have cytotoxic effects (Weller, 2001). The first of such compounds that could be considered the historical antecedent of modern chemotherapy was used from 1630 by the Jesuits who made a tea from the bark of the chinchona tree to treat malaria. However, the advances made in the use of chemotherapy in the treatment of cancer only came about in the early twentieth century when Paul Ehrlich coined the term chemotherapy to describe the use of specific drugs for the treatment of infectious disease and cancer (Ingwersen, 2001). One use of chemotherapy, which is particularly useful in the treatment of breast cancer in women with a high risk of recurrence, is adjuvant chemotherapy that takes place after primary surgery has taken place and is targeted at micrometastases. It is common to use a combination of two to five drugs together although dosage and duration depend heavily on the regimen. For example, six months seems adequate for a CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) regimen, whereas three to four months would suffice for doxorubicin regimens (Stein, 1998).

1.7.14 Review Manager (RevMan) 5

Review Manager 5 (RevMan 5) is a software tool used to aid in the process of producing a systematic review. It is a computer program developed by The

Cochrane Collaboration Programme intended to help authors prepare and keep up-to-date Cochrane Systematic reviews. This software assists in the development of protocols and full reviews. Furthermore, RevMan 5 may also be used to calculate meta-analyses of the data entered into it, thus showing the results in a graphical form (The Cochrane Collaboration, 2008).

1.7.15 Randomized controlled trial

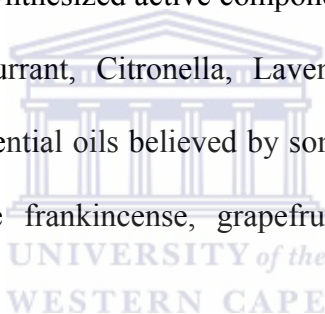
A randomized controlled trial is any experimental study in which “investigators randomly allocate eligible people to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the treatment and control groups” (Cochrane Reviewers’ Handbook Glossary, no page number).

1.7.16 Natural medicine

For the purpose of this thesis, natural medicine will be defined as a complementary and alternative medicine that uses preparations made from plants, herbs, vitamins or foods to prevent and treat diseases and ailments or to promote health and healing.

1.7.17 Aromatherapy

Aromatherapy can be described as the therapeutic use of essential oils based on the perceived pharmacological, psychological or neurological effects of the ‘active components’ of such oils. Essential oils are effectively obtained by various processes of distillation that attempts to maintain them in their natural form. Within the field there is a strong belief in the synergistic pharmacology of the chemical constituents of essential oils, and thus essential oils in their natural state are favoured over synthesized active components. Examples of essential oils are Ambrette, Black currant, Citronella, Lavender, Myrrh, Orris and Ylang (Schnaubelt, 1999). Essential oils believed by some to be useful in the treatment of lymphedema include frankincense, grapefruit, hyssop, safflower oil and lavender.



1.8 Research design and methodology

1.8.1 Types of studies

All randomized controlled trials, quasi-randomized controlled trials or clinical trials that met the inclusion or exclusion criteria, reporting benefits or adverse effects of natural medicines for the treatment of post-breast cancer lymphoedema.

1.8.2 Types of participants

Women of all ages diagnosed with post-breast cancer lymphoedema.

1.8.3 Types of intervention

Any use of natural medicine versus placebo or routine treatment or no treatment.

1.8.4 Types of outcomes measures

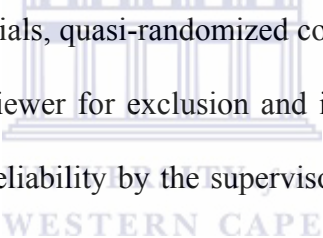
The primary outcomes refers to any type of life style improvement such as: any signs and symptoms related the condition e.g. heaviness, tightness, pain, ache, itch, mobility of affected arm, skin texture, as well as psychological symptoms like distress followed by arm volume changes of the affected limb, adverse effects, cessation or modification of treatment.

1.8.5 Search strategy for identification of studies

The databases Blackwell Synergy, CINAHL, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, EBSCOhost, InfoTrac, JSTOR, PubMed, Medline, ProQuest, ScienceDirect, LILACS, Wiley InterScience, and Google Scholar were searched for articles that contain the term lymphoedema, lymphedema, limb swelling and "linfedema" (Spanish and Portuguese); thereby

including all possible spellings in English, Spanish and Portuguese. Articles between the year 1988 and 2008 were included for analysis. Relevant information was extracted, including the quality of the study, and recorded in tabular format. The quality of each study was analysed using a checklist, which was drawn up by the study supervisor and the primary researcher based on the CONSORT guidelines (Altman, 1996).

1.8.6 Methods of the review – Validity and reliability



Randomized controlled trials, quasi-randomized controlled trials and clinical trials were selected by the reviewer for exclusion and inclusion, and were checked to ensure consistency and reliability by the supervisor and co-supervisor. The data were carefully entered and doubled checked to ensure accuracy. The studies that were not included in this systematic review were captured into a record and the reasons for exclusion are provided.

1.8.7 Data Analysis

Scientific articles that met the inclusion and exclusion criteria were reviewed by the reviewer and the supervisors for inclusion in the review. The information was then entered onto Review Manager 5 (RevMan 5) software to systematically

meta-analyse the information. Data analysis in this systematic review included both a narrative description of the results of included studies and a quantitative (statistical) analysis of the results wherever it was possible and/or appropriate.

1.9 Relevancy of the study

It is hoped that the results of this systematic review will help to define the effects of natural medicines on post-breast cancer lymphoedema patients.

1.10 Ethics statement



The study proposal was sent for ethical review to the University of the Western Cape Faculty of Community and Health Sciences Higher Degrees Committee and Senate. Since the present study is a systematic review, it was not subject to certain ethical concerns such as voluntary participation and informed consent as other designs may be. This systematic review will be sent to The Cochrane Collaboration as a scientific article for possible publication where it will be peer reviewed. It is important that the reviewer makes all selection criteria for inclusion, exclusion and methods of analysis explicit in order to avoid bias. These are clearly defined in more detail in section 3.10.

1.11 Chapter outlines

Chapter one gives a summary outline in the form of a proposal. Current literature concerning lymphoedema is discussed in chapter two. Chapter three describes the methodology of the review. In chapter four the results are given. Chapter five contains the discussion of the results with conclusions and possible implications for future research.

1.12 Time line



Table 1.1

Time line for the completion of the systematic review

Writing proposal	June-August 2007
Submission of proposal to higher degree	August 2007
Approval of proposal	August 2007
Selecting and sorting of articles	September 2007-June 2008
Analysis of data	June - September 2008
Formatting conclusions	September - October 2008
Complete writing of thesis	October -November 2008
Submission of thesis	November 2008

1.13 Budget

Below is a breakdown of the expenses incurred in the process of completing this research study. The study supervisor allocated funds for the RevMan workshop and Lymphoedema course, while the rest of the expenses were covered by the researcher.

Table 1.2

Proposed budget for the present systematic review

RevMan 5 workshop	R500
Lymphoedema course	R2800
Photocopying	R1000
Printing	R2000
Stationary	R500
Internet	R1200
Petrol	R3000
Total	11000

The above expenditures made it possible for the reviewer to gain access to online journals, print the articles so that they were easy to read and mark, collate the data in a systematic manner, learn to use the RevMan 5 software, gain more in-depth knowledge regarding lymphoedema, and travel from home to the university in order to meet with the study supervisor and make use of the library facilities.

1.14 Summary

In this chapter is found a short introduction of the topic of this systematic review. The principal objective of this review is to evaluate the effectiveness or adverse effects of natural medicines as a part of treatment for post-breast cancer lymphoedema.



CHAPTER TWO

Literature Review

2.1 Introduction

Lymphoedema is a lifelong condition characterised by protein-rich oedema in a part of the body as a result of the accumulation of lymphatic fluid due to obstruction or abnormalities in the lymph nodes of the lymphatic system (Pratt, 1956). This condition may result from treatments for breast cancer, such as lymph node dissection, surgery and/or radiation and can be reduced in severity if detected early and treated. However, it is generally under reported and under treated (Marrs, 2007). Presently there is no cure for cancer related lymphedema (Liao, Huang, Li, Chen, Wei, Kuo, Chen & Hsu, 2004).

The present literature review focuses on post-breast cancer lymphoedema and its treatment with natural medicines. Information is included that is relevant to all classifications of lymphoedema, such as the incidence and prevalence in South Africa and some other countries, the classifications (with emphasis placed where post-breast cancer treatment lymphoedema is classified), the possible causes, predisposing factors, symptoms, diagnostic methods, stages through which a patient may typically progress, and all available treatments – placing emphasis on natural medicines as alternative/ complementary treatments. The review will

however begin with a discussion of the anatomy, physiology and pathophysiology of breast cancer related lymphedema.

2.2 Anatomy

The lymphatic system consists of different vessel systems and interspersed lymph nodes, acting as a drainage and transport system for the body. A diagrammatic representation of this system is displayed in Figure 1.3. Initial lymphatic sinuses, which are endothelial ducts with an average lumen diameter of $56.0 \pm 10.0 \mu\text{m}$, make up the beginning of the lymphatic system. Following on there are precollectors, which are sections of lymphatic vessels between the initial lymphatic sinuses and the collectors that contain incomplete valves and trabeculae, creating turbulence in the lymphatic flow and thereby fostering reabsorption and immunological properties. These precollectors also tend to lie in close contact to rhythmically pulsating arterial blood vessels that in conjunction with muscle contractions assist lymphatic flow. The lymph collectors are vessels consisting of three layers separated by sheets of elastic fibres and contain valves interspersed at distances of between 6 to 20 mm that control the direction of flow. These connect seamlessly with lymphatic trunks that filter the lymph into the venous blood via lymphovenous anastomoses from both superficial and deep lymphatic systems that share various connections allowing the transport of lymph from distal to proximal, and also from the superficial to the deep systems and visa

versa. The thoracic duct is the main collector of the lymphatic system. Variations in vessel course are frequent, which explains why a functional collateral circulation can develop after removal of the axillary lymph nodes following breast cancer therapy. The axillary lymph nodes constitute a small number of the roughly 600 lymph nodes distributed about the body, which receive both lymph and arterial vessels and can contain cross-connections between neighbouring lymph nodes (Zöltzer, Weissleder, & Schuchhardt, 2008).

2.3 Physiology



The main function of the lymphatic system is to circulate interstitial fluid back into venous circulation. As a part of this process water and large molecules such as proteins and waste are removed from the body fluids and transported back into the vascular system, lymphocytes and other defence cells are re-circulated, oedema is prevented, various nutrients that have been taken up via the bowel's lymphatics are transported, and the body's inner balance is maintained. The three most important mechanisms responsible for generating and maintaining lymphatic flow include diffusion, filtration or re-absorption, and pinocytosis or endocytosis. Within this system the lymph nodes act as biological filter stations responsible for the concentration or dilution of lymph, cell-mediated and humoral immunity, storage of pigments and other agents, and for acting as an intralymphatic filter

between the interstitial and the blood systems (Schuchhardt, Weissleder, & Zoltzer, 2008).

2.4 Pathophysiology of breast cancer related lymphoedema

Lymphoedema of the arm is the most common complication following curative treatment of breast cancer, and results from damage of the auxiliary lymphatic system by lymph node extirpation and/or percutaneous radiation therapy of the regional lymph drainage areas. As a consequence the transport capacity of the lymphatic system is compromised and the volume of protein and water is greater than compensatory mechanisms can handle, and a mechanical lesion results. Protein accumulates in the tissues with the potential of developing into fibrosclerosis if not treated properly, while metabolic processes in the interstitium are disturbed and inflammatory processes are facilitated further hampering lymph circulation (Weissleder & Schuchhardt, 2008).

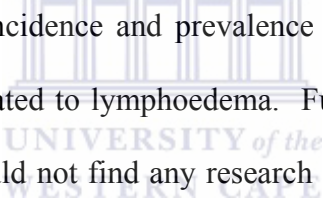
2.5 Incidence and prevalence of lymphoedema

The true incidence (Bicego, Brown, Ruddick, Storey, Wong, & Harris, 2006; Paskett & Stark, 2000) and prevalence of lymphoedema worldwide is not known (Ferrel & Coyle, 2001), but it is speculated that the total incidence of secondary lymphoedema alone is more than 100 million cases. These are mainly due to an infectious process known as filariasis in underdeveloped parts of the world, and trauma such as breast cancer treatment in developed countries. The incidence has been shown to increase each year after initial breast cancer treatment (Morrell, Halyard, Schild, Ali, Gunderson & Pockaj, 2005), thus it is believed that an increase in breast cancer incidence would result in an increase in secondary lymphoedema (Hayes, 2008). It is estimated that approximately 30% of breast cancer survivors develop lymphoedema after undergoing breast cancer treatment (Bumpers et al., 2002), and approximately 25% after a mastectomy, with an increase to 38% for those who also undergo radiation (Bicego et al., 2006; Paskett & Stark, 2000). Lymphoedema can develop almost immediately after surgery or it could take up to 30 years for the symptoms of lymphoedema to begin, so “the cumulative incidence depends on the period of time over which women are followed and the method used to estimate incidence” (Geller, Vacek, O’Brian, & Secker-Walker, 2005, p. 925).

Filariasis, classified as secondary lymphoedema (transmitted by mosquitoes), occurs mainly in underdeveloped countries and it is the most common type of

secondary lymphoedema in countries such as Brazil, several countries in the North of Africa, India, and South-East Asia (Zuther, 2004).

Cancer treatment, trauma and surgery are the major causes of secondary lymphoedema in developed countries (Ferrell & Coyle, 2001). For example, the United States have the highest incidence of secondary lymphoedema as a result of breast cancer surgery (Zuther, 2004), while Australia have the highest incidence of secondary lymphoedema due to melanoma treatment (Hayes, 2008).



Currently there are no incidence and prevalence statistics for South Africa and many other countries related to lymphoedema. Furthermore, the reviewer in her very thorough search could not find any research done in South Africa related to post-cancer lymphoedema from 1988 till 2008.

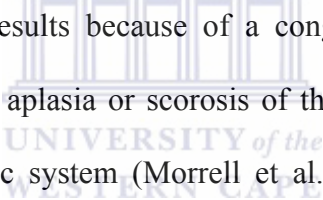
2.6 Classifications of lymphoedema

Lymphoedema is a lifelong condition characterised by protein-rich oedema in a part of the body as a result of the accumulation of lymphatic fluid due to obstruction or abnormalities in the lymph nodes of the lymphatic system (Pratt,

1956). This condition may result from treatments for breast cancer, such as lymph node dissection, surgery and/or radiation (Marrs, 2007).

Lymphoedema is commonly classified into primary or secondary lymphoedema. These two classifications will be discussed in more detail below.

2.6.1 Primary lymphoedema




Primary lymphoedema results because of a congenital or genetic abnormality (hyperplasia, hypoplasia, aplasia or sclerosis of the lymph nodes) in structure or function of the lymphatic system (Morrell et al., 2005; Zuther, 1999). These hereditary lymphoedema include: congenital lymphoedema, lymphoedema praecox, and lymphoedema tarda (Morrell et al., 2005). If primary lymphoedema occurs before the patient reaches the age of 35 it is known as lymphoedema praecox, which accounts for 83% of primary lymphoedema cases, whereas if it occurs after the age of 35 it is known as lymphoedema tardum (Norton School of Lymphatic Therapy, 2008).

2.6.2 Secondary lymphoedema

Sometimes called acquired lymphoedema, is associated with lymph node dissections, radiation of lymph nodes, surgery such as mastectomy, trauma and infections. Secondary lymphoedema is the most common type worldwide; as previously stated, this is mainly due to filariasis in underdeveloped parts of the world, and trauma such as breast cancer treatment in developed countries. (Morrell et al., 2005).

2.6.2.1 Lymphoedema associated with post-breast cancer treatment

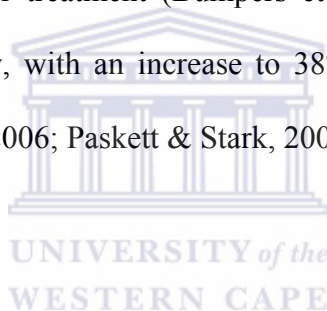


Lymphoedema onset following the diagnosis and treatment of breast cancer is usually associated with breast cancer therapy such as surgery and radiotherapy, but has also been linked with advanced disease from tumour compression or a lymphatic vessel being obstructed (Morrell et al., 2005). It can be exacerbated by adjuvant radiotherapy. Under standard protocol, patients with breast cancer normally receive adjuvant radiotherapy after breast conserving surgery if there is high risk of local or regional reappearance (Morrell et al., 2005).

Mastectomy is the complete removal of a breast, and is often the treatment of choice when there is more than one site of cancer in the breast. On the other hand,

when there is only one site and the cancer is under 4cm and has clear margin, breast-conserving surgery such as a lumpectomy can be performed. A lumpectomy involves the removal of a limited amount of tissue that leaves the breast relatively intact and may be followed by radiation treatment (Breastcancer.org, 2007d).

The true incidence of lymphoedema is not known but it is estimated that approximately 30% of breast cancer survivors develop lymphoedema after undergoing breast cancer treatment (Bumpers et al., 2002), and approximately 25% after a mastectomy, with an increase to 38% for those who also undergo radiation (Bicego et al., 2006; Paskett & Stark, 2000).



Numerous researchers cited by McCallin, Johnston, and Bassett (2005) suggest that newer improved surgical protocols techniques, such as sentinel lymph node biopsy (SLNB), may possibly reduce the incidence of lymphoedema given that greater numbers of lymph node removal are unnecessary if the sentinel lymph nodes are negative. These preventive and early detection strategies might help patients from developing morbidities related to more chronic and severe conditions or from progressing to advanced lymphoedema stages. It will also help practitioners understand the long-term impact of this progressive condition providing direction for future service development.

2.7 Causes of lymphoedema

The causes of lymphoedema differ depending on the type of lymphoedema, and the age of onset. Figure 2.1 below, illustrates the different causes of primary and secondary lymphoedema.

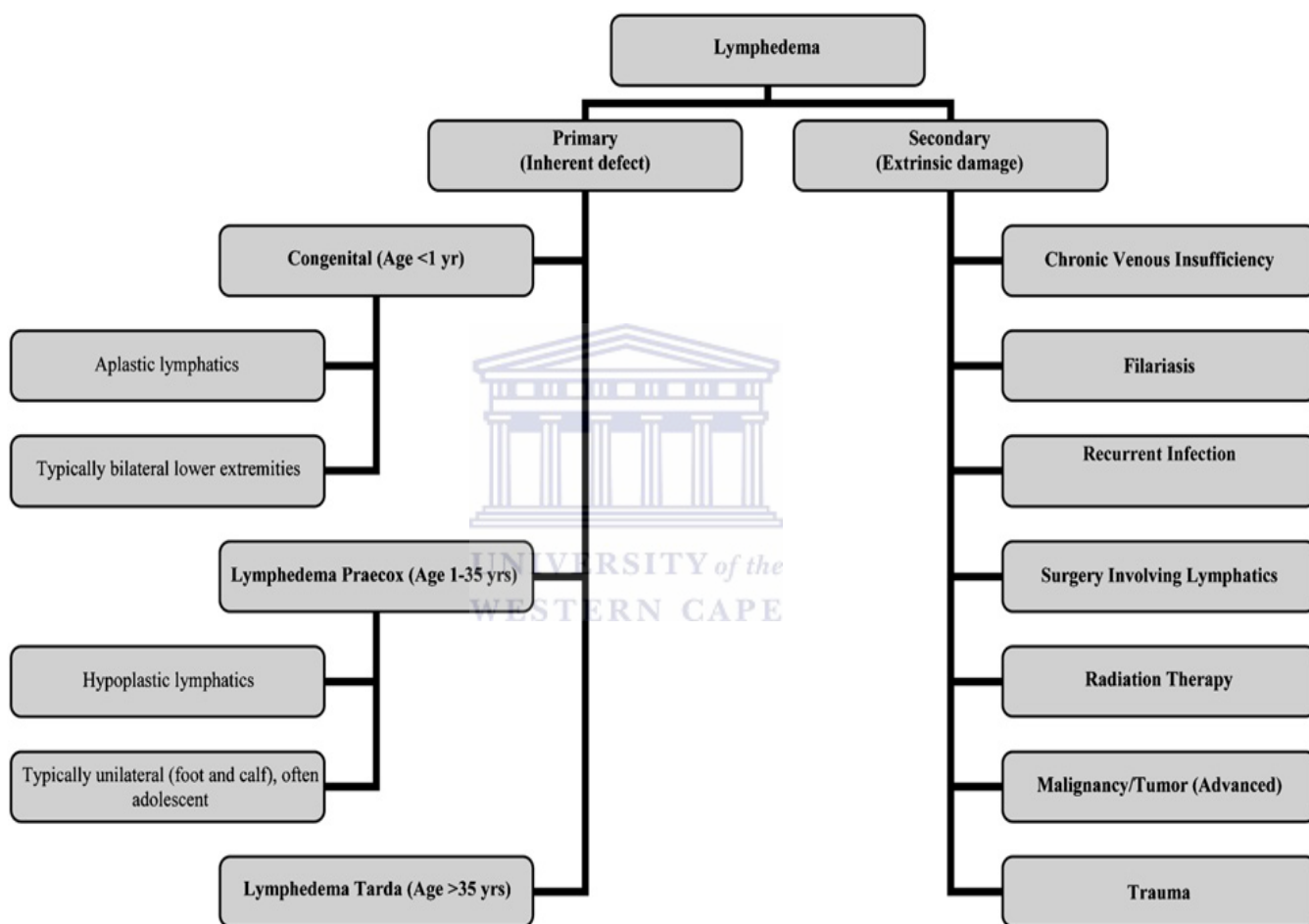


Figure 2.1: Causes of lymphoedema (Kerchner, Fleischer & Yosipovitch, 2008).

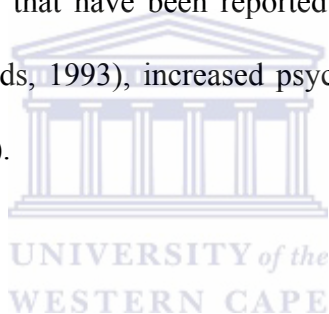
2.8 Predisposing factors associated with lymphoedema

There is divergence regarding the predisposing factors for the development of lymphoedema depending on age, body mass index and weight, infection and pre-existing co-morbid conditions such as cardiovascular conditions (Morrell et al., 2005). In the case of cancer presence: surgical technique used, cancer site, radiotherapy, chemotherapy, experience of the surgeon, skin lesion and/or abnormality of the lymphatic system may all play a role (Hayes, 2008).

It is important to note that there are significant racial differences in breast cancer incidence, mortality, and stage of disease at diagnosis (Taylor, Lamdan, Siegel, Shelby, Hrywna & Moran-Klimi, 2002). In addition to being associated with breast cancer treatment, symptoms occurring post-treatment may be associated with gender and socio-demographic factors like income and ethnicity. These disparities most likely result from a lack of information regarding therapeutic interventions, language barriers, not being able to afford rehabilitative treatment therapies, or lack of information on how to communicate appropriately and effectively with health providers (Eversley, Estrin, Dibble, Wardlaw, Pedrosa & Favila-Penney, 2005).

2.9 Symptoms of lymphoedema

Radina et al., (2004) as well as Marrs (2007) cite various studies that have described the signs and symptoms that women usually notice as a result of lymphoedema. These include swelling in the arm or fingers, which may progress to a pitting oedema or develop into firm, thickened skin; numbness, stiffness, or pain in the affected area; reduced range of motion; heaviness, aching, weakness, warmth or redness; fullness, decreased flexibility of limb, tighter clothing, tightness of rings, and skin changes such as peau d'orange appearance. Psychological symptoms that have been reported include changes in self-image and body image (Woods, 1993), increased psychological distress, anxiety and depression (Carter, 1997).



2.10 Diagnosis of lymphoedema

Diagnosis can be made from the clinical history, physical examination (including inspection and palpation), and volume measurement (can be done using a measuring tape and calculating the volume, water displacement volumetry and/or optoelectronic volumetry) mainly, but other diagnostic tests may be needed or can be used such as lymphoscintigraphy (isotope lymphography), lymphography (direct) (scarcely used as it can cause lymphatic injury), indirect lymphography, fluorescent microlymphography, Doppler ultrasonography, magnetic resonance

imaging (MRI), venous ultrasonography, venography (Ferrell & Coyle, 2001 & Weissleder & Schuchhardt, 2008), and computed tomography (CT) scan (Weissleder & Schuchhardt, 2008).

2.11 Stages of lymphoedema


There are three stages of lymphoedema progression, which differ in terms of the degree of swelling and likelihood of reversal. These are shown in Table 2.1 below:



Table 2.1

Stages of lymphoedema (of all causes)

Stage	Description	Characteristics
I	Reversible lymphoedema	-Pitting. -Swelling reduced with elevation of the swollen extremity.

<p>II</p>	<p>Spontaneously irreversible lymphoedema</p>	<p>-Increased fibrous tissue with progressive skin hardening. -Frequent infections. -No pitting. -No reduction in swelling with elevation of the extremity.</p>
<p>III</p>	<p>Lymphostatic elephantiasis</p> 	<p>-Skin changes (large hanging skin folds, papillomas). -Association with Stewart-Treves syndrome.</p>

(Morrell et al., 2005).

2.12 Treatments for lymphoedema

2.12.1 Treatments overview

There is currently no known cure for lymphoedema, but the condition can be well managed with the suitable treatment. The treatment for lymphoedema typically

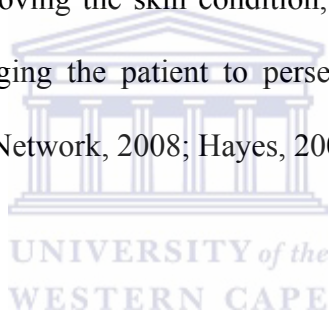
includes combined modality approaches, therapeutic exercises, compression therapy, skin care and pharmacotherapy (Morrell et al., 2005). Lately the use of alternative and complementary medicine has become more popular in many countries (MacLennan, Wilson & Taylor, 2002). Lymphoedema should however not be treated with pharmacotherapy or natural supplements alone (National Lymphedema Network, 2008).

Moseley, Carati and Piller (2007) presented a literature review of conservative therapies used for post-breast cancer including: complete decongestive therapy, manual lymphatic drainage, pneumatic pumps, oral pharmaceuticals, low level laser therapy, compression garments and bandaging, limb exercise, and limb elevation. They concluded that according to the available research and literature complete decongestive therapy, manual lymphatic drainage, pneumatic pump, and laser therapy usually resulted in greater volume reductions.

According to Myoung (2004), currently the most effective therapy used to treat lymphoedema seems to be complete decongestive therapy, if provided by well trained health practitioners.

2.12.2 Complete decongestive therapy (CDT)

Complete decongestive therapy (CDT), sometimes referred to as complex decongestive physiotherapy, has two phases. Phase 1 is a reducing phase where manual lymphatic drainage and compression bandages are applied, and the patient is educated regarding remedial exercises, skin and nail care, compression garments, and lymphoedema in general. This is followed by Phase 2, which is the maintaining phase. The expected outcomes of this therapy include decreasing the oedema, augmenting lymph drainage from the mal-functioning areas, decreasing subdermal fibrosis, improving the skin condition, increasing the functionality of the patient and encouraging the patient to persevere with a self-care program (National Lymphedema Network, 2008; Hayes, 2008).



Liao and colleagues (2004), using CDT with a sample of 30 women with unilateral upper or lower limb chronic lymphoedema after breast or pelvic cancer treatment, found CDT to be effective in reducing 33.2% (mean percentage) volume of the affected limb of all patients receiving this therapy. The authors concluded that there is still a need for further research to be done on the second (maintaining) phase of CDT.

Rinehart-Ayres (1998) reviewed the literature on conservative lymphoedema management approaches, including the compression pump (together with skin

care, exercise and compression garments) and CDT, and found that CDT resulted in a decrease in lymphoedema volume if the participants were compliant with the treatment programme.

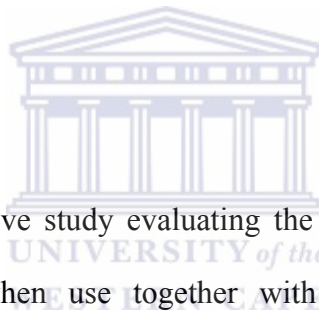
2.12.3 Manual lymphatic drainage (MLD) and Simple lymphatic drainage (SLD)

MLD refers to the manual lymphatic drainage as used as part of CDT where the use of gentle, specific hand movements enhances the pumping of the lymph to areas of the lymphatic system that are not damaged. SLD is a modified version of MLD that is taught to women so that they may help themselves (Williams, Vadgama, Franks & Mortimer, 2002).

A randomized controlled crossover study exploring the effects of MLD and SLD documented a decrease in limb volume and dermal thickness, an improvement in the quality of life of the participants in terms of emotional functioning, dyspnoea, sleep disturbances, and an improvement in sensations such as pain and heaviness that were associated with MLD (Williams, et al., 2002).

2.12.4 Intermittent pneumatic compression (IPC)

This method of treatment can be used as an adjunct to other methods. It entails placing the extremity affected by lymphoedema into an inflatable machine. This machine works together with an air compression pump, inflating and deflating from distal to proximal creating a compression gradient. There are risks when using this treatment, such as developing a fibrosclerotic ring obstructing the lymph flow even more and displacement of the lymphoedema to the proximal limb, nearby trunk or genitalia (National Lymphedema Network, 2008; Hayes, 2008).



A randomized, prospective study evaluating the effectiveness of IPC and CDT concluded that IPC, when use together with CDT, increases the positive therapeutic response (Szuba, Achalu & Rockson, 2002).

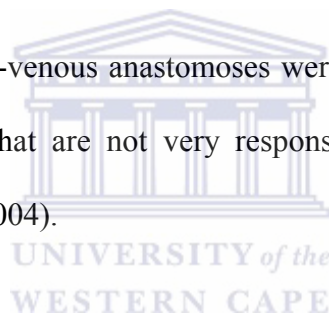
2.12.5 Surgical treatments

Surgical treatments include: debulking, excisional operations, liposuction and lymphatic reconstruction. These surgeries have been “advocated... to reduce the weight of the affected limb, to help minimize the frequency of inflammatory attacks, to improve cosmetics, and to potentially reduce the risk of secondary

angiosarcoma” (National Lymphedema Network, 2008, p. 3). The literature is very ambiguous regarding these treatment modalities.

A number of studies regarding the use of liposuction, sometimes in combination with CDT, resulted in very encouraging results (Brorson & Svensson, 1997; Brorson, 2000; Brorson, Ohlin, Olsson, Langstrom, Wikilund & Svensson, 2006), with Borson (2000) reporting complete reduction of the excess volume at times.

Microsurgical lymphatic-venous anastomoses were suggested to be the treatment of choice for patients that are not very responsive to non-surgical treatments (Campisi & Boccardo, 2004).



Campbell & Harkin (2008) suggested debulking surgical procedures in the case of an intractable case of lower limb lymphoedema in which the patient requested amputation of the limb.

According to the National Lymphedema Network (2008) these surgical treatments are not curative methods, involve great risks, and are not used as a treatment of choice.

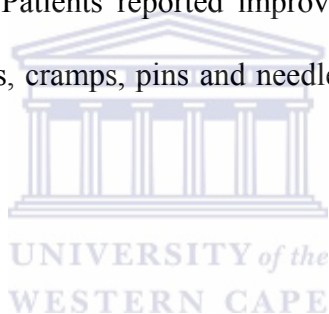
2.12.6 Pharmacotherapy

Diuretics and corticosteroids used solely to treat lymphoedema are harmful and should not be used unless an associated condition requires its use (Bruns, Micke, & Bremer, 2003; National Lymphedema Network, 2008).

Benzopyrones such as coumarin, hydroxyethylrutin, and flavonoid derivatives such as diosmin have been tested in research studies. Coumarin and flavonoids produce long-term problems (Bruns, Micke, & Bremer, 2003). Coumarin was found to produce liver toxicity and so its use has been stopped in some countries. Hydroxyethylrutin has been shown to be of advantage to better skin softening (National Lymphedema Network, 2008). While Daflon 500 (a combination of diosmin and hesperidin), which is used widely in equatorial regions of the world to treat lymphoedema, has only been tested using animal models and “appears to result in a reduction of microvascular permeability and increase thoracic duct pumping” (National Lymphedema Network, 2008, p. 3). A cochrane systematic review of the effectiveness of Benzopyrones in the management of lymphoedema concluded that their effectiveness could not be proven from the current trials thus further research needs to be conducted (Badger, Preston, Seers & Mortimer, 2008).

2.12.7 Low-level laser therapy

Low-level laser therapy is a laser therapy that uses low level milli-watts and seems to have positive results on cells and tissues, such as promoting lymphangiogenesis, motivating lymphatic motoricity, and encouraging the immune system (Carati, Anderson, Gannon & Piller, 2003). Piller and Thelander (1998) studied the effectiveness of low level laser therapy in post-breast cancer lymphoedema patients and followed their outcomes over a period of two and a half years. Their findings showed that this therapy decreases oedema volume, and improves skin texture. Patients reported improved quality of life regarding to pain, tightness, heaviness, cramps, pins and needles, and mobility of the affected arm.



Although there is a paucity of research available on this treatment, the studies that have been conducted show encouraging results related to volume reduction. Further research needs to be conducted (Hayes, 2008; Kaviani, Fateh, Yousefi Nooraie, Alinagi-Zadeh & Ataie-Fashtami, 2006).

2.12.8 Flowave

“Flowave is a machine that uses ...low frequency sound waves like infrasound... (amplitude between 12 and +12 Volts)... to influence interstitial proteins in lymphoedema... It mechanically stimulates the lymphatic ways and it acts in the treated area through means of a molecular activation” resulting in more easily drained interstitial proteins by the lymphatic system (Ricci, 2005, p. 33).

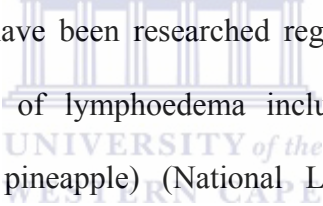
Research suggests that Flowave treatments stimulate the lymphatic fluid movement, activate interconnected limb lymph nodes and decreases derma back flow (Ricci, 2005). Limited evidence based research can be found regarding this treatment modality thus further scientific research needs to be done to continue evaluating the effectiveness of this treatment for the management of lymphoedema.

2.12.9 Other complementary and alternative therapies

Some other complementary and alternative therapies lack research but have been proposed as somewhat aiding the reduction of lymphoedema. These include ultrasound therapy, hyperbaric oxygen therapy, microwave therapy, acupuncture

and moxibustion, magnetic fields, vibration, hyperthermia and natural medicines / therapies.

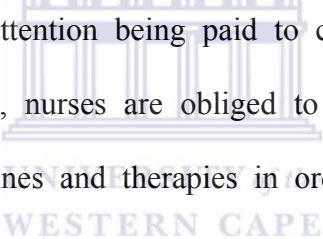
Alem & Gurgel (2008) suggest that acupuncture after breast cancer surgery is related to improvements in movements of the shoulder amplitude, symptoms such as heaviness and tightness and the extent of lymphoedema. Further research needs to be done to clarify if the results were due to the natural evolution and history of lymphoedema or acupuncture itself.



Natural medicines that have been researched regarding their role in alleviating some of the symptoms of lymphoedema include horse chestnut, selenium, bromelain (from fresh pineapple) (National Lymphedema Network, 2008), aromatherapy (Barclay, Vestey, Lambert & Balmer, 2006; Hayes, 2008; Kirshbaum, 1996), vitamin E supplements (Gothard, Cornes, Earl, Hall, MacLaren, Mortimer, Peacock, Peckitt, Woods & Yarnold, 2004 & Hayes, 2008), mulberry leaf (Hayes, 2008), Butcher's broom (*Ruscus Aculeatus*), Hesperidin (from citrus) (Cluzan, Alliot, Ghabboun & Pascot, 1996), and pycnogenol (from pine bark) (Hutson, Love, Cleary, Anderson, Vanummersen, Morgan-Meadows & Doran 2004). The effectiveness of these natural agents will be explored further in section 2.10.

Research suggests that breast cancer patients often make use of alternative or complementary medicines in their treatment of lymphoedema symptoms, especially regarding the treatment of swelling, despite a lack of supporting evidence based literature documenting its effectiveness (Ashikaga et al., 2002; Fouladbakhsh et al., 2005).

2.13 Natural medicine and lymphoedema



Due to the increasing attention being paid to complementary and alternative medicine (Gaskil, 2001), nurses are obliged to become more knowledgeable regarding natural medicines and therapies in order to evaluate their use, and educate patients (Mick, 2008).

Natural medicines / therapies thought to be used complementarily or alternatively for the treatment of lymphoedema include horse chestnut seed extract, which appears to present encouraging benefits (Ody, 1993 & Leung, 2003 cited by National Lymphedema Network, 2008); selenium, which has had mixed benefits in lymphoedema associated with radiation (Ody, 1993, Leung, 2003 & Hoffman, 1997 cited by National Lymphedema Network, 2008; Micke, Bruns, Mucke, Shaffer, Glatzel, DeVries, Schonekaes, Kisters & Buntzel, 2003); bromelain, which is a “natural diuretic found in fresh pineapple” (Cirelli, 1962, Seligman,

1969, Schafer, 1985 & Kelly, 1996 cited by National Lymphedema network, 2008, p. 3.) thought to be beneficial but more research is necessary (National Lymphedema Network, 2008); aromatherapy (Barclay et al., 2006; Kirshbaum, 1996) and vitamin E supplements that have been mentioned in a small number of studies. Mulberry leaf (Hayes, 2008), pycnogenol (from pine bark) has been suggested to be somehow effective for the treatment of lymphoedema (Hutson, Love, Cleary, Anderson, Vanummersen, Morgan-Meadows & Doran 2004) as well as butcher's broom (*Ruscus Aculeatos*) and hesperidin (found in citrus such as orange) (Cluzan, et al., 1996). Some of these natural medicines have been suggested by popular literature, which is often unscientific and ambiguous, and for those that have been scientifically researched, there is a dearth of clinical trials, thus for all of these natural elements further research needs to be done.



2.13.1 Horse chestnut seed extract

Horse chestnut seed extract is assumed to strengthen the tissues of the lymph vessels capillaries (O'Connor, 2008) and decrease venous capillary permeability (Brady, no date & National Lymphedema Network, 2008). Horse chestnut seed extract can be administered as an oral tincture, as tablets (20 mg or 50 mg), or as a topical gel (Suter, Bommer, & Rechner, 2008).

A study evaluating the use of horse chestnut for the treatment of lymphoedema has been completed, but the results are not currently available. Further information regarding their findings and the data itself was requested from the author of this study via email. The response was that the results were not going to be published as the researcher did not find dramatic benefit from horse chestnut seed extract in the treatment of lymphoedema (P. Hutson, personal communication, August 18, 2008).

2.13.2 Selenium



This biological element is believed to act as a toxicity antagonist in chemotherapy and radiation therapy (Hayes, 2008). Selenium has shown encouraging results in radiation-induced lymphoedema, with a recommended dosage ranging between 800 - 1000 μ g daily for the first week, followed by a dosage reduction to about 300 - 500 μ g selenium daily for the remaining weeks (Bruns, Micke & Bremer, 2003; Kasseroller, 1997). It is commonly administered using a sterile solution of sodium selenite in drinking ampules of 100 μ g selenium in 2ml of isotonic solution (Bruns et al., 2003).

2.13.3 Bromelain (from pineapple)

Bromelain is thought to aid in the breaking down of proteins, thus reducing inflammation. It helps antibiotics to treat infections such as cellulites (O'Connor, 2008), and has diuretic effects (National Lymphedema Network, 2008).

2.13.4 Aromatherapy

Aromatherapy, involving the use of essential oils, is believed to improve the functioning of the immune system and thus the lymphatic system. Complementing CDT, aromatherapy is thought to improve the quality of life of patients suffering with lymphoedema (Sims, 2006). The essential oils used in aromatherapy, such as fennel, sage, geranium, black pepper and juniper, are often administered using a self-massage cream.

2.13.5 Vitamin E supplement

Vitamin E (dl-alpha tocopheryl acetate) effectiveness to treat, as an alternative medicine, arm lymphoedema was researched in a randomized controlled trial. The

findings suggested that vitamin E does not benefit this condition, failing to demonstrate efficacy. In clinical trials dl-alpha tocopheryl acetate has been administered at a dosage of 500mg twice a day orally (Gothard, Cornes, Earl, Hall, MacLaren, Mortimer, Peacock, Peckitt, Woods, & Yarnold, 2004).

2.13.6 Mulberry leaf

Mulberry leaf is a natural component that seems to have a diuretic property (Andallu et al., 2001). Mulberry leaf has been used as complementary medicine in the treatment of lymphoedema due to filariasis (Wang, Liu, & Chen et al., 1990 cited by Hayes 2008). Mechanisms behind its potential treatment are unclear and thus further research is needed (Hayes, 2008). Administration is often by means of an injection of mulberry leaf extract.

2.13.7 Pycnogenol (from pine bark) and Procyanidins

Pycnogenol is extracted from French maritime pine tree and procyanidins are found in grape seed extracts. Their effectiveness seems to arise due to “either stabilizing the collagenous subendothelial basal membrane or scavenging the free

radicals, or by a combination of these activities” (Brady, no date, p. 4-5). Thus, the possible benefits seem to be reductions in swelling (Cancer.org, 2007).

Two studies evaluating the use of pycnogenol for the treatment of lymphoedema have been completed but the results are not currently available. Further information was requested from the authors of these studies regarding their findings and the data itself. One of the authors responded that the data was not going to be published and that they did not find dramatic benefits from pycnogenol in the treatment of lymphoedema (P. Hutson, personal communication, August 18, 2008). In some instances Pycnogenol has been administered orally over a period of 8 weeks using 50 mg capsules, 3 times daily for a total of 150 mg daily, while it is also common for the dosage to be set at 300mg daily (Cesarone et al., 2006; P. Hutson, personal communication, August 18, 2008).

2.13.8 Butcher’s broom (*Ruscus aculeatus*)

Butcher’s broom is an aromatic, diuretic, mildly laxative herb that is taken orally and is believed to reduce inflammation, increase perspiration, and constrict the veins (Ageless, 2008). A double-blind, placebo-controlled trial of butcher’s broom extract (*Ruscus aculeatus*) in combination with manual lymphatic drainage demonstrated a significant reduction of the limb volume (Bone, 2008).

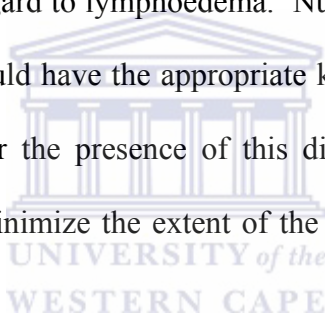
2.14 Post-breast cancer lymphoedema lack of information / education

2.14.1 Patient's lack of information / education

Several studies have shown that many patients at risk of developing lymphoedema after breast cancer treatment report that they did not receive adequate education regarding lymphoedema before and at the time of surgery and did not have enough knowledge about effective treatments (Ridner, 2006; Radina et al., 2004), such as compression decongestive physiotherapy involving manual lymphatic drainage, skin care, compression and exercises which decrease the volume of the limb (Radina et al., 2004). Literature reports that patients suffering from this condition feel discontent towards their health providers, as they believe that their care givers are not well informed and trained about this condition (Ridner, 2006). A South African patient while being interviewed regarding the knowledge of her condition stated: “...*They said the swelling would be there forever. I'm not expecting a bigger arm like this, but they tell me it's going to get bigger, and then it is going to get bigger, then it's going to be like burst... this arm will be so much blood and trickle will start...*” (Ester, personal communication, July 2008). This demonstrates the lack of adequate education regarding lymphoedema hence the need of more awareness of this condition.

2.14.2 Health care providers' lack of information / education

Radina et al., (2004) argue that the lymphoedema incidence is so high in part because most health care providers do not receive appropriate, formal training about the risk of lymphoedema, risk reduction, and treatment. This results in a worldwide lack of education about the symptoms of lymphoedema, leading to late diagnosis and inadequate treatment that is evident because of the lack of treatment centres, certified lymphoedema therapists, and other professionals prepared to treat lymphoedema (Marrs, 2007). Quality nursing care has a big impact on patient's outcomes in regard to lymphoedema. Nurses can be proactive in patient education, thus they should have the appropriate knowledge about this condition. They should monitor for the presence of this disease so that they can rapidly intervene and thereby minimize the extent of the problem (Lomas, 2008; Marrs, 2007).



2.15 Summary

In sum, while there are an abundant variety of treatment methods available for the treatment of lymphoedema, the growing popularity of some natural medicines does not seem to be supported by the available literature, while others such as CDT seem more empirically based. However, in light of the lack of research, and confusion regarding efficacy, more information is needed regarding the

effectiveness of natural medicines in the treatment of post-breast cancer lymphoedema. This systematic review may help to clarify the efficacy of natural medicines in the treatment of post-breast cancer treatment lymphoedema.

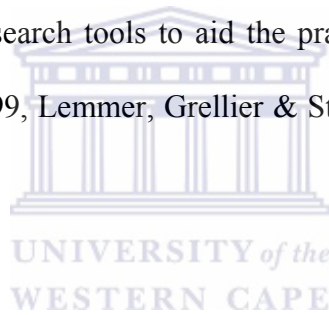


CHAPTER THREE

Research Design & Methodology

3.1 Introduction

Research is essential to promote high quality, up-to-date health care. The research presented here is best described as a systematic review, which involves “an overview of primary studies that used explicit reproducible methods” (Greenhalgh, 1997, p. 672). Systematic reviews are recognized as one of the most valuable and reliable research tools to aid the practice of evidence-based health care (Sleep & Clark, 1999, Lemmer, Grellier & Steven, 1999 cited by Muntanga, 2004).



Systematic reviews are a scientific investigation method or design that follow a research process with a previously prepared methodology (Cook, Mulrow & Heynes, 1997). This method recognizes the vast quantity of existing research and converts the findings of multiple, primary, high quality studies into a complete summary of many studies on the same topic. This helps health practitioners, or anyone interested in a specific topic, to keep up to date with contemporary information and aids them in making informed decisions while circumventing the need to search and read through large amounts of data (Antman et al., 1992; Cook, Mulrow & Heynes, 1997; Greenhalgh, 1997; Lyman & Djulbegovic, 2005).

Some systematic reviews use meta-analysis, considered to be a “building block of evidence-based practice” (Mutanga, 2004, p. 28). Meta-analysis is a statistical or mathematical method that uses combined information from two or more primary studies and summarizes the results (Greenhalgh, 1997; Higgins & Green, 2008; Lyman & Djulbegovic, 2005).

3.2 The Review Manager (RevMan) 5

Review Manager 5 (RevMan 5) is a software tool used to aid in the process of producing a systematic review. This computer programme is provided by the Cochrane Collaboration programme and is intended to help authors prepare and maintain up-to-date Cochrane systematic reviews. This software assists in the development of protocols and full reviews. Furthermore, RevMan 5 may also be used to conduct meta-analyses of the data entered into it, allowing for easy viewing of the results in a graphical format (The Cochrane Collaboration, 2008).

3.3 Systematic reviews

“Systematic reviews attempt to collate all evidence that fits pre-specified eligibility criteria in order to answer a specific research question” (Antman, 1992

cited by Higgins & Green, 2008, p. 4). A systematic review is a collection and selection of data from primary studies, in which these primary studies are analysed and their results presented in either narrative form, quantitative form (using meta-analysis), or both.

Researchers generally prefer to include randomized controlled trials in their reviews as these are considered to be of higher quality (Higgins & Green, 2008; Jadad & McQuay, 1996).

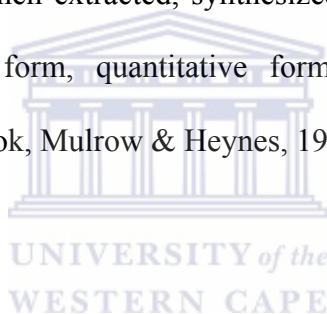


3.4 Rationale for systematic reviews

More than two million articles in over 20,000 biomedical journals get published every year, which makes it impossible to keep up to date even within a specialized area. This is why systematic reviews are so important – they provide a complete summary of many studies on the same topic, helping health practitioners or anyone interested in keeping up to date, or making informed decisions regarding a specific topic, to avoid having to sift through large amounts of data, while accessing contemporary high quality literature about the relevant topic from one source (Antman et al., 1992; Cook, Mulrow & Heynes, 1997; Greenhalgh, 1997).

3.5 Systematic reviews as scientific research

A systematic review is a scientific investigation method in itself that follows a research process with a previously prepared methodology. This method of research, instead of using a sample of participants as a source of data, makes use of a sample of primary studies as a source of data. Selection criteria of inclusion and exclusion of possible studies is delineated prior searching and collecting all possible relevant data. After collecting the data the studies are evaluated for inclusion and exclusion using the selection criteria tool. Following this, the relevant information is then extracted, synthesized, analysed, and the results are presented in narrative form, quantitative form (using meta-analysis), or a combination of both (Cook, Mulrow & Heynes, 1997).



In order to ensure the quantitative rigidity and quality of the results obtained, randomized controlled trials are preferred over other study designs for inclusion in systematic reviews (Higgins & Green, 2008; Jadad & McQuay, 1996).

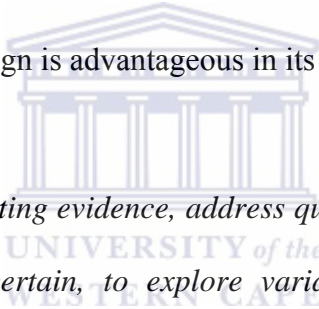
3.6 Main features of systematic reviews

According to Higgins & Green (2008), the main features of a systematic review include: the objectives of the study; selection criteria for the inclusion and

exclusion of studies; a precise and clear methodology that can be reproduced; a vast systematic search locating all the possible studies that could meet the selection criteria; included studies have to be assessed with regards to the validity and reliability of their findings; and a summary, in a systematic arrangement, presenting the characteristics and findings of included studies.

3.7 Advantages of systematic reviews

This type of research design is advantageous in its ability to:



“resolve conflicting evidence, address questions where clinical practice is uncertain, to explore variations in practice, to confirm the appropriateness of current practice or to highlight a need for future research... to summarize and help people to understand the evidence... [and to] help people make practical decisions about health care” (Higgins & Green, 2008, p. 5).

Furthermore systematic reviews limit bias in identification and exclusion of studies due to their explicit methods of selection criteria. Meta-analysis increases the accuracy of the overall result, and different studies’ results can be combined to

establish generalisability of the findings and reliability of results (Greenhalgh, 1997).

3.8 Limitations of systematic reviews

Systematic reviews are limited by the quality of the primary studies from which conclusions are drawn. The results of studies may be limited by factors such as small sample sizes, insufficient statistical power, moderate or weak effect sizes and other such factors, so identification of good quality studies by using selection criteria for inclusion or exclusion of studies is key to ensure valid and reliable results of the systematic review. Sometimes this might not be possible as editors, due to publication bias, do not publish specific findings (Muntanga, 2004).

Systematic reviews are also limited to the experience of the authors in measuring risk of bias in inclusion of studies, collecting studies and data, hunting omitted or unpublished data, analysing data and interpreting the results (Higgins & Green, 2008).

3.9 Ensuring quality of systematic reviews

It is very important to ensure that authors of systematic reviews have appropriate training and experience. This can be achieved by attending relevant training courses. Consultation and involvement with other reviewers regarding the inclusion or exclusion of studies is strongly advised and sometimes required as well as consultation and involvement with relevant practitioners and consumers for input in other areas of the review. Furthermore, to ensure a good quality systematic review it is important to formulate a research question that is answerable, well-structured and focused, as this will aid in the crucial aspect of systematic reviews - being the preparation of the selection criteria for inclusion and exclusion of studies, which in turn will guide the study and show how and what results to present. It is also important to seek for further assistance regarding missing or unpublished data or any other doubts to clarify the quality of the primary studies (Higgins & Green, 2008).

3.10 Criteria for selection of studies for this review

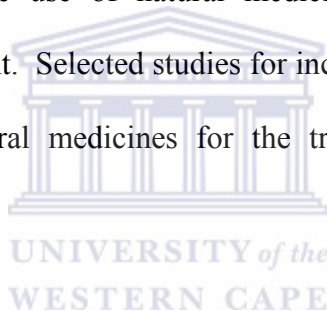
The selection criteria for inclusion of prospect studies in the present systematic review were guided by the research question, namely: What are the effects of natural medicines/therapies on quality of life (signs and symptoms), changes in

arm volume (of the affected limb), adverse effects, modification or cessation of treatment in post-breast cancer lymphedema women?

The following aspects were considered in this study:

Types of studies

All randomized controlled trials, quasi-randomized controlled trials or clinical trials that compared the use of natural medicine versus placebo or routine treatment or not treatment. Selected studies for inclusion should report benefits or adverse effects of natural medicines for the treatment of post-breast cancer lymphoedema.



Types of participants

The types of participants included in the studies forming part of this systematic review were women of any age diagnosed with any stage of post-breast cancer lymphoedema who were using natural medicine to treat the existing signs and symptoms of secondary lymphoedema.

Types of intervention

Any intervention that made use of natural medicine versus placebo or routine treatment or no additional treatment, were included in the review. A list of possible natural medicine interventions include:

Horse chestnut seed extract

Pycnogenol (from French maritime pine bark three) & Proacyanidins

Bromelain (from fresh pineapple)

Butcher's broom (*Ruscus Aculeatos*)

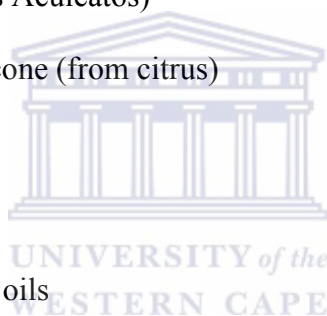
Hesperidin Methyl Chalcone (from citrus)

Selenium

Mulberry leaf

Aromatherapy creams or oils

Vitamin E supplement



Types of outcomes measures

The primary outcomes are:


- 1 Perceived improvements in the domain of life style (this includes any physical signs and symptoms related to the condition such as heaviness, tightness, pain, ache, itch, mobility of affected arm, and skin texture, as well as psychological symptoms like distress)
- 2 Perceptible changes in arm volume (of the affected limb)

- 3 Adverse effects
- 4 Modification or cessation of treatment

A summary of the above in graphic form including the search strategy are show in Table 3.1 below.

Table 3.1

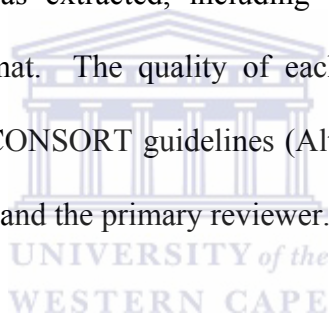
Selection criteria for post-breast cancer lymphedema and its treatment with natural medicine

 Selection criteria				
Question	What are the effects of natural medicines/therapies on quality of life (signs and symptoms), changes in arm volume (of the affected limb), adverse effects, modification or cessation of treatment in post-breast cancer lymphoedema women?			
Eligibility	Interventions	Outcomes	Participants	Study type
	Natural medicines / therapies vs. placebo or conventional treatment, or no treatment.	Life style improvement, adverse effects, modification or cessation of treatment.	Post-breast cancer lymphoedema women.	Randomized controlled trials, quasi-randomized controlled trials and clinical trials.

<p>Search Strategy</p>	<p>Natural medicine Natural therapy Naturopathy Botanic medicine Aromatherapy Nutritional sup. Vitamin/s Herb/s Homeopathy Allopathy/ Allopathic Medicine/ Therapy Alternative Medicine/ Therapy Specific names such as: ginger tea, sweet clover ointment, horse chestnut, Butcher's broom, Heperidin, bromelain, selenium, pycnogenol, pine bark, mulberry leaf.</p>	<p>Index and free text search for: Secondary LE Post breast cancer LE</p>	<p>Same as above.</p>
-------------------------------	--	---	-----------------------

3.11 Search strategy

The databases Blackwell Synergy, CINAHL, Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, EBSCOhost, InfoTrac, JSTOR, PubMed, Medline, ProQuest, ScienceDirect, LILACS, Wiley InterScience and Google Scholar were searched for articles that contain the term lymphoedema, lymphedema, limb swelling and “linfedema” (Spanish and Portuguese); thereby including all possible spellings in English, Spanish and Portuguese. Articles between the years 1988 and 2008 were included for analysis. Relevant information was extracted, including the quality of the study, and recorded in tabular format. The quality of each study was analysed using a checklist, based on the CONSORT guidelines (Altman, 1996) that was drawn up by the review supervisor and the primary reviewer.



3.12 Methodology quality, validity and reliability

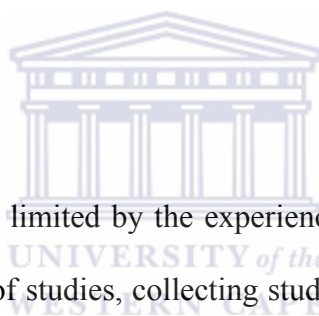
In order to ensure competence the reviewer received training in the Cochrane Review method for developing a systematic review, Review Manager 5 (RevMan5), and attended a two week lymphoedema training course. The Cochrane and RevMan courses were beneficial for developing familiarity with the approach and methods of systematic review, while the lymphoedema course gave

the researcher a better understanding of the contemporary treatment methods being used to manage this little known condition.

Randomized controlled trials, quasi-randomized controlled trials and clinical trials were rigorously searched, based on all obtainable studies from databases that were available to the reviewer. Other studies that seemed to be adequate for this thesis but that were not available in the databases were requested through the inter-library loan division at the University of the Western Cape library so that they could be obtained either locally or from international sources. The studies had to meet the selection criteria and were concerned with herbal and natural or homoeopathic compounds to treat secondary lymphoedema post-breast cancer. The studies were selected by the reviewer and overseen for exclusion and inclusion by the supervisor and co-supervisor; these were also checked to ensure accuracy, consistency and reliability. The information was then entered into the Review Manager 5 (Revman 5) software package to systematically meta-analyze the information. The studies that were not included in this study were captured into a table and the reasons for exclusion were provided.

3.13 Limitations of this systematic review

As for all systematic reviews, this review is limited by the quality of the primary studies from which conclusions are drawn. The results of studies may be limited by factors such as small sample sizes, insufficient statistical power, moderate or weak effect sizes and other such factors, so identification of good quality studies by using selection criteria for inclusion or exclusion of studies is key to ensure valid and reliable results of the systematic review. Sometimes this might not be possible as editors, due to publication bias, do not publish specific findings (Muntanga, 2004).



This review may also be limited by the experience of the reviewer in measuring risk of bias in inclusion of studies, collecting studies and data, hunting omitted or unpublished data, analysing data and interpreting the results (Higgins & Green, 2008).

3.14 Data collection

An extensive search was conducted based on all obtainable literature from databases that were available to the reviewer. If potential studies were not available in the databases they were requested through inter-library loan to be

sourced either locally or internationally. The outcome of this rigorous search was to find primary studies that would meet the selection criteria for inclusion. Once the primary studies were selected, relevant data from each study was taken separately and entered into a specially designed data collection sheet. Finally appropriate data was entered into the Review Manager 5 for analysis.

3.15 Data analysis

The RevMan 5 software package was used in this systematic review for statistical analysis. Data was extracted from studies that met the selection criteria and put into a specially designed collection sheet. From here the appropriate data was entered into the RevMan 5 software to undergo statistical analysis. This software is designed to process the data and present the results in a chart using both graphical and a tabular format. Where it was inappropriate to enter the information into RevMan 5, results were presented in a narrative form.

RevMan 5 produces the results of the analysis in a standard format that makes use of columns of text for nominal data, as well as in the form of a forest plot and blobograms. The first column always displays the study identifier/s. The information represented in the next few columns is determined by the type of data used. Where dichotomous data were used one format for analysis and results

were used, and where continuous data another. These are described, in turn, in sections 3.15.1 and 3.15.2 respectively. The foot of the chart produced provides the same data for both data types. First a summary of the events that occurred in each column, or event are given, and then the heterogeneity test is stated. For this review tests for heterogeneity were not applicable. Finally, the last row of the summary chart presents the test for overall effect, Z statistic, and its associated p-value (Boltman, 2005).

3.15.1 Dichotomous data



For dichotomous data the Mantel-Haenszel statistical method using a fixed effect model and relative Risk Ratio (RR) effect measure were used. In this case, the second and third columns display the number of events of a particular outcome (e.g. adverse effects) with the total sample size for the associated group. This data is presented for both the intervention / experimental group (natural medicine) and control group (placebo). The next column presents the weight that each study (in percentage form) contributed to the overall analysis. Thereafter, the next column contains the RR and confidence interval. The confidence limits are presented in square brackets and represent the range that the RR values can be inferred, or expected, to take in the population. The level used in this systematic review was 95%, meaning that there is a 95% chance that a RR collected from the population

would fall within this range. The RR ratio is presented first and represents the ratio of the risk of the outcome occurring in the experimental group divided by the risk of the outcome occurring in the control group. If the RR is approximately equal to one, or if the confidence interval includes one, then there is no significant difference in outcome between those groups who received natural medicine and those who received placebo as part of their treatment. If the RR is greater than one, and the CI is positive and does not include one, then the outcome event is more likely to occur among patients in the natural medicine group compared to those in the control group. Finally, if the RR is less than one, and the CI lies below one and does not include one, then the outcome events are significantly less likely to occur in the natural medicine group than they are in the control group. The RR is comparable to odds ratios when control intervention risks are low and effects are small, but differ considerably as these increase (Higgins & Green, 2008). This information is presented graphically in the last column that takes the form of a forest plot. A forest plot looks like a series of horizontal lines, with different sizes of 'blocks' intersecting the line. The horizontal lines either intersect, or do not touch a solid vertical line that represents the 'null effect'. A plot is presented for the effect estimates and confidence intervals for each study, and then in the final row for the meta-analysis. The CI is depicted by the horizontal line, and the point estimate of intervention effect is represented by the block on the line. The size of the area of the square block is commonly referred to as the 'size of the trial', and indicates the weight of that specific study in the meta-analysis, with a larger block representing a bigger weight. Generally, studies with

a smaller CI will carry more weight. In the final row of this column a diamond is used to represent the CI for the totals of the meta-analyses.

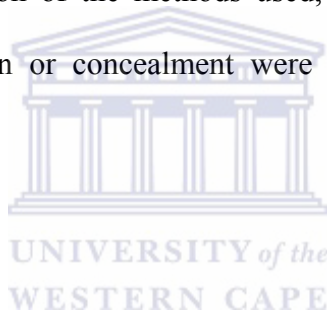
3.15.2 Continuous data

For continuous data the inverse variance statistical method with fixed effect analysis model and mean difference effect measure were used. The fixed effect model is based on the assumptions that all studies are measuring the same underlying effect and that any variability between studies is due to chance. The limitation of this approach is that it may over-estimate precision (SA Cochrane Centre, 2008). In the case of continuous data the second and third columns display the mean, standard deviation, and sample size for the natural medicine and placebo groups respectively. The next column presents the weight that each study (in percentage form) contributed to the overall analysis. Thereafter, the difference between the means of each group is presented, as well as the confidence limits. A positive difference indicates that the natural medicine group tended to score higher on the outcome variable than the placebo group, a negative score indicates that the natural medicine group tended to score lower than the control, and a score of approximately zero indicates that there is no significant difference between the natural medicine and placebo groups in regard to the measured outcome. These results are then represented in the next column in the form of forest plots as

described earlier (Fahey, Griffiths & Peters, 1995, Guyatt, et al., 1995 cited by Boltman, 2005).

3.16 Characteristics of included studies

The characteristics of the included studies were divided into the following subtitles: identifiers of the study (including author/s, title and year the article was published), an explanation of the methods used, the participants, interventions, outcomes, and allocation or concealment were stated, followed by additional notes.



Included studies were divided into two groups:

Comparison 01: Post-breast cancer group (only studies that their sample consisted on post-breast cancer patient).

Comparison 02: Post-cancer group (only studies that included post-breast cancer participants as part of their sample).

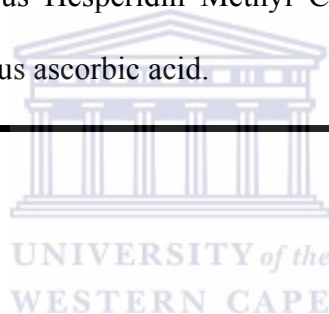
Table 3.2

Comparison 01: Post-breast cancer group (Cluzan et al., 1996)

Study ID	Cluzan (1996). Treatment of secondary lymphedema of the upper limb with CYCLO 3 FORT.
Methods	Double-blind placebo-controlled randomised trial.
Participants	Fifty seven adult women (>18 years of age) with secondary lymphedema of the upper limb after radiotherapy or surgery for breast cancer were included in this study. Patients who had more than 2cm but less than 8 cm on at least one measuring point were eligible for this study. Lymphoedema was classified as mild (between 2cm to 5 cm) or moderate (between 5cm to 8cm). Each of those groups were randomized. Patients who present with any of the following were excluded: recurrent cancer, systemic or cutaneous infection, diabetes mellitus or heart, renal or hepatic failure, morbidity obese. No additional drugs intakes were allowed to be taken by the patients during the period of this study.
Interventions	Each patient received 3 capsules of CYCLO 3 FORT (each capsule containing 150mg of Methyl Hesperidin Chalcone plus 150mg Ruscus Aculeatus extract plus 100mg of ascorbic acid), or placebo, 3 times a day.
Outcomes	The main outcome was swelling reduction in terms of the volume of oedema. Secondary outcome consisted of subjective improvement

	(recorded on a visual analogue scale, taking into account the mobility of the affected limb, feeling of heaviness and softness), as assessed by both the patient and investigator. These outcomes were evaluated on day zero, day 30, day 60, and day 90.
Notes	<p>CYCLO 3 FORT and placebo presented with an identical appearance. The patients were asked to return surplus capsules at each visit in order to assess compliance with treatment.</p> <p>CYCLO 3 FORT is composed of an extract of Ruscus (Butcher's broom) plus Hesperidin Methyl Chalcone (found in citrus such as orange) plus ascorbic acid.</p>

Table 3.3



Comparison 01: Post-breast cancer group (Gothard et al., 2004)

Study ID	Gothard (2004). Double-blind placebo-controlled randomised trial of vitamin E and pentoxifylline in patients with chronic arm lymphoedema and fibrosis after surgery and radiotherapy for breast cancer.
Methods	Randomized, double-blind controlled study.
Participants	Sixty eight volunteers (67 women and one man) between the ages of 37 and 87, presenting with ipsilateral arm lymphoedema following the treatment for breast cancer, having a 20% or more increase in arm

	<p>volume, previous radiotherapy treatment to the breast/chest wall as well as axilla and/or supraclavicular fossa, without cancer recurrence. Out of the 68 volunteers, 33 participants had wide local excision as part of their primary treatment for breast cancer, 24 had some form of axillary surgery as well. Thirty three underwent mastectomy and two had no primary surgery.</p>
Interventions	<p>Thirty five participants were allocated as the treatment group and received 500mg of dl-alpha tocopheryl acetate (vitamin E) twice a day orally as well as 400mg of pentoxifylline twice a day orally for 6 months. Thirty three participants were allocated into the placebo group and received a placebo as treatment. Both groups were assessed at the beginning of the trial, at six months, and then at 12 months.</p>
Outcomes	<p>Changes in volume of the affected upper limb, function and quality of life.</p>
Notes	<p>Pre-treatment baseline assessments included measurement of arm volume using a perometer, clinical assessment of subcutaneous induration within the radiotherapy volume, clinical photographs and patient self-assessments using the EORTC Quality of Life Questionnaires QLC-C30 and BR23 and were repeated at six and 12 months. Blood samples were collected at baseline and 1-2 weeks before the end of six months therapy. Sixty three volunteers</p>

	completed their trial.
--	------------------------

Table 3.4

Comparison 02: post-cancer group (Barclay et al., 2006)

Study ID	Barclay (2006). Reducing the symptoms of lymphoedema: is there a role for aromatherapy?
Methods	Randomized trial.
Participants	<p>The sample used was composed of 81 adult patients (25-80 years old). The sample consisted of seventy seven women and four men. Of the women, sixty one presented with arm lymphoedema and twenty with lower limb lymphoedema. The participants had at least one year's history of symptomology, were clinically diagnosed with bilateral or unilateral stable lymphoedema of the limbs with no evidence of acute inflammation, thrombosis or recurrence. They had to be able to self-massage their affected limbs and avoid any other aromatherapy or other treatment products during the length of the study. The participants were in the maintenance phase of their lymphoedema treatment and did not receive therapy throughout this trial treatment. Forty patients were allocated to the aromatherapy intervention, there was one withdrawal so 39 received the intervention and one discontinued thereafter. Forty one were allocated the placebo cream but 40 received the cream, four discontinued thereafter. These</p>

	<p>patients had been referred to the Dorset Cancer Centre lymphoedema service.</p>
Interventions	<p>Randomized participants received one of two creams immediately after randomization concluded. The intervention cream contained wheat-germ oil with fennel, sage, geranium, black pepper and juniper essential oils in a base cream. The placebo cream consisted of a simple base cream containing wheat-germ oil. All patients performed daily simple lymphatic drainage and limb massage instructed by a lymphoedema specialist. Exercise and skin care were advised for all patients and to continue the use of compression garments if indicated.</p>
Outcomes	<p>To assess the effectiveness, in terms of an objective reduction in limb volume and patient-reported symptom improvement and well-being, of simple lymphatic drainage and skin care/hydration by self-limb massage using a base cream containing aromatherapy oils versus a base cream alone.</p>
Notes	<p>Limb volume circumferences was measured from a standardized start point measured at 4cm segments using a self-tensioning tape measure and recorded as an absolute volume (ml). Measurements were recorded monthly for three months. Symptom improvement, activity and well-being were measured using the 'Measure Yourself Medical Outcome Profile 2' (MYMOP2). This took place at the same time as limb volume measurement.</p>

Table 3.5

Comparison 02: post-cancer group (Micke et al., 2003)

Study ID	Micke (2003). Selenium in the treatment of radiation-associated secondary lymphedema.
Methods	Clinical trial.
Participants	A total of 48 patients (17 females and 31 males) with persistent, extensive or progressive lymphoedema between the ages of 34 to 93 years old (median of 54 years) participated in this study. Twelve of the patients presented with arm lymphedema and 36 with lymphoedema of the head and neck. Of the 12 patients with arm lymphoedema, seven had oedema of the upper extremities after mastectomy plus axillary dissection and five due to breast conserving therapy plus axillary dissection. All patients had radiotherapy previously.
Interventions	All patients received 350 ug/m ² body surface of sodium selenite (Selenase, biosyn Arzneimittel GmbH Fellbach, Germany) p.o. daily (generally giving a total dose of 500ug per day) over 4 to 6 weeks.
Outcomes	To evaluate the impact of selenium in the treatment of lymphoedema after radiotherapy.
Notes	No patient received additional anti-oedematous medication such as steroids or benzopyrones.

3.17 Excluded studies

Four studies were excluded. The reason for their exclusion for each study is given under their notes section.

Table 3.6

Excluded studies (Hutson et al., 2004)

Study ID	Hutson (2004a). Horse chestnut seed extract for the treatment of arm lymphedema.
Methods	Double-blind, randomized, and placebo-controlled study.
Participants	Twenty five participants. Eligible participants had stable arm lymphoedema and have affected: unaffected arm oedema ratios of > 1.1 to 1 by bioelectric impedance, and significant response was empirically set as a 15% decrease in arm ratios.
Interventions	Placebo or horse chestnut seed extract (50mg escins) twice daily orally for three months, followed by a one month washout.
Outcomes	Reduction of arm volume.
Notes	Reason for exclusion: A full text article has not been published up to date, only an abstract is available. According to a personal communication with the corresponding author, an article will not be published and they did not find dramatic benefits using horse chestnut

	seed extract.
--	---------------

Table 3.7

Excluded studies (Kirshbaum, 1996)

Study ID	Kirshbaum. (1996). Using massage in the relief of lymphoedema.
Methods	Case study (semi-structure interviews).
Participants	Eight women who had attended at least six sessions of aromatherapy massage using lavender oil in the breast unit.
Interventions	Interviews post- aromatherapy massage using lavender oil.
Outcomes	To find out the benefits that a patient receive from the lymphoedema massage and to discover out if nursing time spent on massage is justified.
Notes	Reason for exclusion: The research method of this study did not meet the selection criteria.

Table 3.8

Excluded studies (Hutson, 2004)

Study ID	Hutson (2004b). Pycnogenol for the treatment of lymphedema of the arm in breast cancer survivors.
-----------------	--

Methods	Double-blind, placebo-controlled trial
Participants	Post-breast cancer lymphoedema patients.
Interventions	Pycnogenol (an extract of the bark of the French maritime pine tree) or corresponding placebo.
Outcomes	Arm volume reduction and improvement of symptoms.
Notes	Reason for exclusion: data has not been published up to date and according to a personal communication with the corresponding author, will not be published and they did not find dramatic benefits using pycnogenol.

Table 3.9

Excluded studies (Kasseroller, 1997)

Study ID	Kasseroller (1997). Administration of selenium in lymphedema.
Methods	Randomized, double-blind placebo-controlled trial.
Participants	Post-breast cancer patients that developed lymphoedema after a mastectomy or Wertheim-operation.
Interventions	Sodium selenium given orally combined with decongestive physical therapy. The length of the intervention was three months and three weeks.
Outcomes	Reduction of arm volume of the affected limb and improvement of

	symptoms such as increase mobility and heat.
Notes	Reason for exclusion: article was not available through inter-library loan and could not be found available to the reviewer.

3.18 Summary

As systematic reviews are recognized as one of the most valuable and reliable research tools to aid the practice of evidence-based health care (Sleep & Clark, 1999; Lemmer, Grellier & Steven, 1999 cited by Muntanga, 2004), this chapter explored the design and methodology for this systematic review. Furthermore, this chapter also describes how primary studies were chosen to form part of this systematic review. Four studies were selected for inclusion and were divided into two comparison groups; 1. post-breast cancer patients and 2. post-cancer patients. These studies were the only studies available in the field at this moment in time.

CHAPTER FOUR

Results

4.1 Introduction

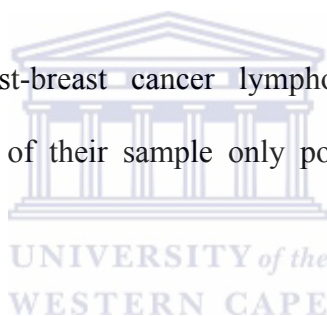
Four research articles met the inclusion criteria and were meta-analysed for the purpose of this systematic review. Outcomes such as: perceived improvement in the domain of life style (this included any physical signs and symptoms related to the condition such as heaviness, tightness, pain, ache, itch, mobility of affected arm, and skin texture, as well as psychological symptoms like distress), changes in arm volume (of the affected limb), adverse effects, modification or cessation of treatment were analysed as continuous or dichotomous data, depending on the type of data that was used in the studies. For dichotomous data the Mantel-Haenszel statistical method using a fixed effect model and Risk Ratio (RR) effect measure were used. For continuous data the inverse variance statistical method with fixed effect analysis model and mean difference effect measure were used. The perceptible change in limb volume outcome was analyzed as continuous data. The analysis was conducted using the Review Manager 5 (RevMan 5) software and presented in narrative form where RevMan 5 was not appropriate for use.

The four studies that met the selection criteria for this review are the following:

- Gothard (2004)
- Cluzan (1996)
- Barclay (2005)
- Micke (2003)

The analysis was done within two main comparison groups:

Comparison 01: Post-breast cancer lymphoedema group (composed of studies that use as part of their sample only post-breast cancer lymphoedema patients).



Comparison 02: Post-cancer lymphoedema group (composed of studies that use as part of their sample post-breast cancer lymphoedema patients).

The results for individual outcomes are displayed as forest graphs. A narrative summary of relevant data is provided for results whose data were not appropriate to be entered into RevMan 5, lacked some type of numerical data, or that did not compare a treatment with something else such as placebo.

4.2 Life style improvement

Life style improvement involved general symptom improvement, improvement specifically concerning the induration of fibrosis symptoms, well-being, and indicators such as softness, heaviness, mobility, and overall arm quality. Results of life style improvement are presented separately for post-breast cancer patients and post-cancer patients.

4.2.1 Comparison 01: Post-breast cancer group.

The results of the comparison between vitamin E plus pentoxifylline versus placebo in the post-breast cancer comparison group regarding changes in induration of fibrosis, showed favour towards the vitamin E plus pentoxifylline (experimental) group in terms of presenting an improvement of the induration fibrosis of lymphoedema patients. However, this result is not statistically significant ($p = 0.68$). This result is graphically represented in figure 4.1

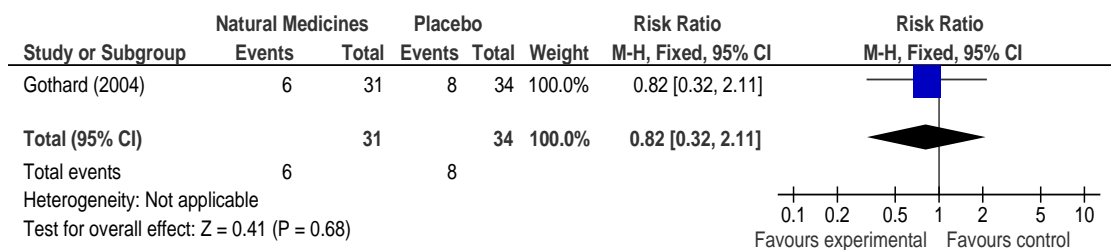


Figure 4.1: Forest plot of comparison 01: changes in induration fibrosis using vitamin E plus pentoxifylline.

Cluzan, et al., (1996), using CYCLO 3 FORT, reported the following symptoms improvement after 3 months of treatment:

Table 4.1

Symptom improvement using CYCLO 3 FORT (Cluzan et al., 1996).

Outcomes	Natural Medicine		Placebo	
	Improvement %	No. participants	Improvement %	No. participants
Softness	11.56%	27	-5.07%	30
Heaviness	32.78%	27	5.26	30
Mobility	33.62%	27	-1.93	30
Overall arm quality (patient)	69.5%	27	32%	30
Overall arm quality (investigator)	73.9%	27	20%	30

4.2.2 Comparison 02: Post-cancer group

The results of the comparison between aromatherapy cream versus placebo cream in the post-cancer comparison group regarding symptom improvement, shows favour towards the aromatherapy (experimental) group in terms of presenting an improvement of symptoms in lymphoedema experienced by the patients. However, this result is not statistically significant ($p = 0.75$). This result is graphically represented in figure 4.2

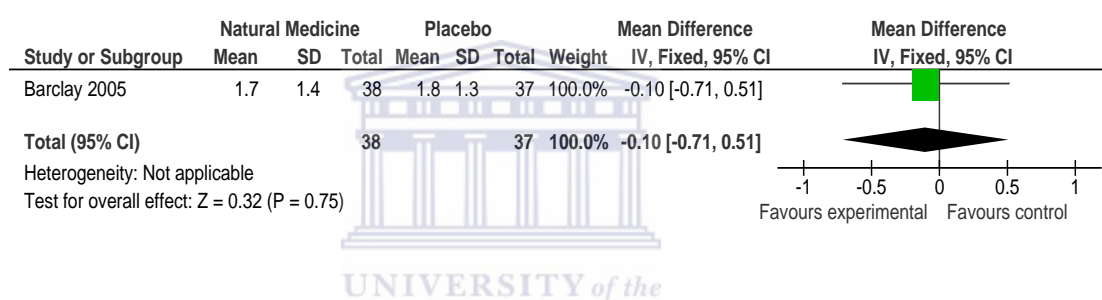


Figure 4.2: Forest plot of comparison 02: symptom improvement using aromatherapy cream.

The results of the comparison between aromatherapy cream versus placebo cream in the post-cancer comparison group regarding well-being, showed favour towards the placebo (control) group implying a worsening in terms of well-being of the patients while using aromatherapy. However, this result was not statistically significant ($p = 0.74$). This result is graphically represented in figure 4.3 below:

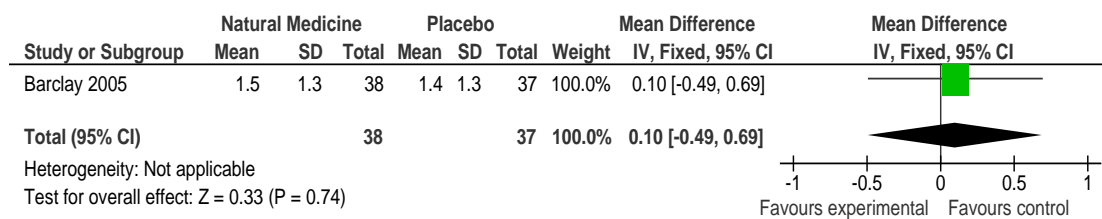


Figure 4.3: Forest plot of comparison 02: well-being using aromatherapy cream.

4.3 Changes in arm volume (of the affected limb).

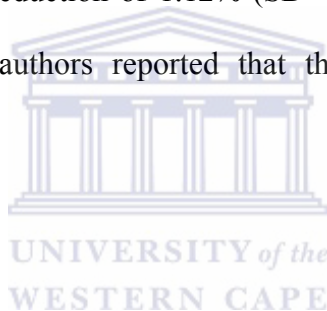
The results that dealt with changes in arm volume are presented separately for post-breast cancer group and post-cancer group, with separate results given for three months, six months, and 12 months where available. None of the data had an appropriate format for analysis in RevMan 5; therefore they are presented in narrative format.

4.3.1 Comparison 01: Post-breast cancer group.

Cluzan, et al., (1996), using CYCLO 3 FORT, recorded a 12.9% significant reduction of arm oedema from baseline to 3 months for the experimental group

compared with a 2.55% increase of arm oedema for the control group. These results were statistically significant ($p = 0.009$).

Gothard, et al., (2004) results of the comparison between vitamin E plus pentoxifylline versus placebo in the post-breast cancer comparison group regarding changes in arm volume after 6 months, showed a slight favour towards the vitamin E plus pentoxifylline in terms of presenting a decreased in arm volume of lymphoedema patients after 6 months of treatment of 2.25% (SD = 15.4) compared with a reduction of 1.12% (SD = 7.74) in the placebo (control) group. However, the authors reported that this result was not statistically significant.



Gothard, et al., (2004) results of the comparison between vitamin E plus pentoxifylline versus placebo in the post-breast cancer comparison group regarding changes in arm volume after 12 months, showed a slight favour towards the vitamin E plus pentoxifylline in terms of presenting a decreased in arm volume of lymphoedema patients after 12 months of treatment of 2.5% (SD = 8.0) compared with a reduction of 1.2% (SD = 10.9) in the placebo (control) group. However, the authors reported that these results were not statistically significant either.

4.3.2 Comparison 02: Post-cancer group

Micke, et al., (2003), in the clinical trial using oral sodium selenite, reported a significant reduction of arm oedema in 83% of their participants.

Barclay et al., (2006), using aromatherapy, reported a reduction of oedema in 69% of their participants compared with 57% from the placebo group. However, results were not statistically significant ($p = 0.38$).



4.4 Adverse effects

The results dealing with the adverse effects of either experimental or control treatments are presented for comparison 01: post-breast cancer group, comparison 02: post-cancer group, and then a combined meta-analysis was provided. Where data were not in an appropriate format for analysis in RevMan 5, the results are presented in narrative format.

4.4.1 Comparison 01: Post-breast cancer group.

The results of the comparison between vitamin E plus pentoxifylline or CYCLO 3 FORT versus placebo in the post-breast cancer comparison group regarding adverse effects showed no favour towards neither the experimental or control group in terms of adverse effects. However, these results are not statistically significant ($p = 0.91$). Results are graphically represented in figure 4.4 below:

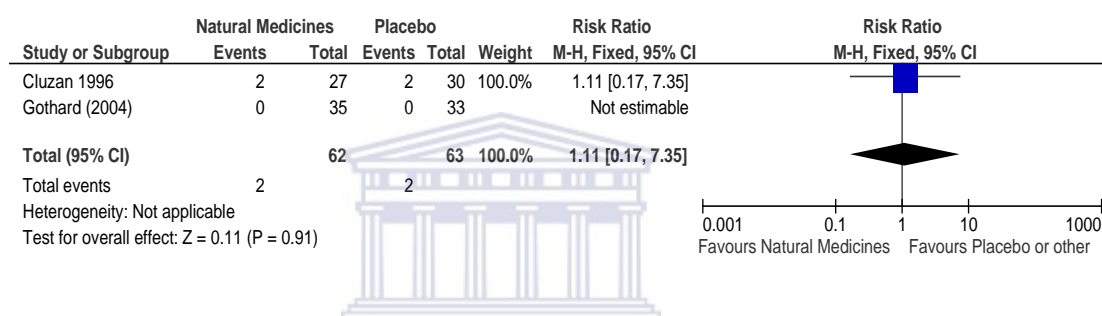


Figure 4.4: Forest plot of comparison 01: Adverse effects using vitamin E plus pentoxifylline or CYCLO 3 FORT.

4.4.2 Comparison 02: Post-cancer group.

The results of the comparison between aromatherapy cream versus placebo in the post-cancer comparison group regarding adverse effects, showed favour towards the placebo (control) group implying an increase of adverse effect in patients using aromatherapy. However, this result was not statistically significant ($p = 0.51$). This result is graphically represented in figure 4.5 below:

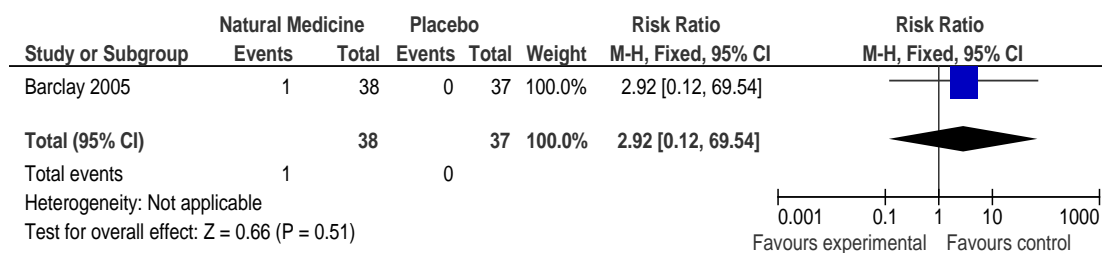


Figure 4.5: Forest plot of comparison 02: Adverse effects using aromatherapy cream.

Micke, et al., (2003), using sodium selenite, reported that none of the participants experienced side effects for this treatment.



4.4.3 Comparison group 01 and 02 combined

The results of the comparison between vitamin E plus pentoxifylline or CYCLO 3 FORT or aromatherapy cream versus placebo in the post-breast cancer comparison group and post-cancer comparison group regarding adverse effects showed a slight favour towards the placebo (control) group implying an increase of adverse effect in patients using aromatherapy or vitamin E plus pentoxifylline (treatment) group. However, these result were not statistically significant ($p = 0.61$). CYCLO 3 FORT presented no side effects for neither of the groups. The results are graphically represented in figure 4.6 below:

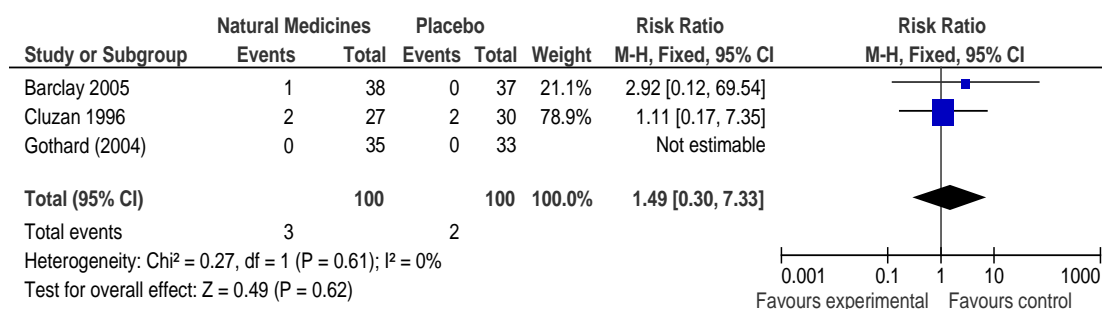


Figure 4.6: Forest plot of both comparison groups: adverse effects using vitamin E plus pentoxifylline or CYCLO 3 FORT or aromatherapy cream.

4.5. Modification or cessation of treatment

The last set of results deal with the modification or cessation of treatment outcome. These results are presented separately for the post-breast cancer group and post-cancer group. Where data were not in an appropriate format for analysis in RevMan 5, the results are presented in narrative format.

4.5.1 Comparison 01: Post-breast cancer group.

The results of the comparison between vitamin E plus pentoxifylline or CYCLO 3 FORT versus placebo in the post-breast cancer comparison group regarding

modification or cessation of treatment showed a slight favour towards the placebo (control) group implying an increase of modification or cessation of treatment in patients using vitamin E plus pentoxifylline or CYCLO 3 FORT. However, the results were not statistically significant ($p = 0.36$). The results are graphically represented in figure 4.7 below:

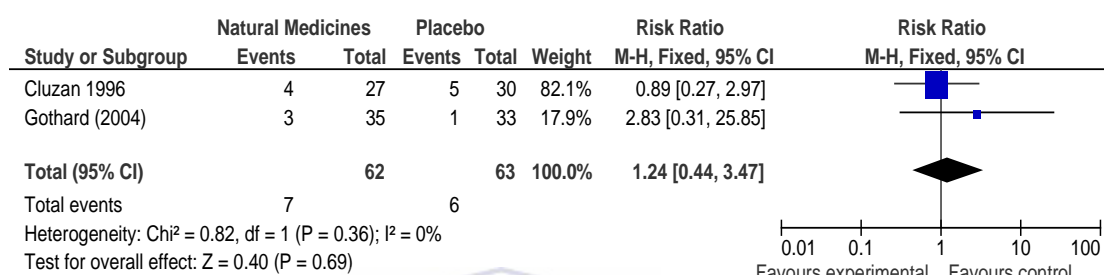
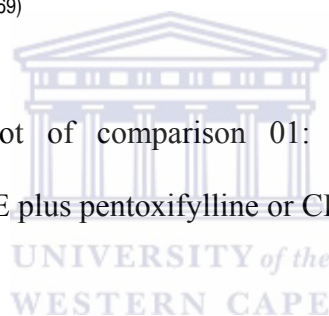


Figure 4.7: Forest plot of comparison 01: modification or cessation of treatment using vitamin E plus pentoxifylline or CLYCLO 3 FORT.



4.5.2 Comparison 02: Post-cancer group.

Barclay et al., (2006), using aromatherapy cream, reported that 5 participants discontinued this trial whereas Micke, et al., (2003), using sodium selenite, did not report any participant discontinuing this treatment.

4.6 Summary results

After the data collection was completed, only four studies met the selection criteria and were included in this systematic review. The sample sizes of these studies were small and the presentation of their data was heterogeneous making it infeasible to enter some of the data into RevMan 5 for meta-analysis. Thus some of the data from these studies was meta-analyzed, while other data had to be presented in a narrative form. Based on the data currently available a definite or conclusive recommendation regarding the efficacy or adverse effects of natural medicines for the treatment of post-breast cancer lymphoedema cannot be drawn. However, it seems that sodium selenite taken orally and CYCLO 3 FORT also taken orally used for post-breast cancer (and post-radiotherapy for sodium selenite) lymphoedema patients had a positive effect on reducing the oedema of the participants. As these are the only two studies meeting the characteristics required for selection for this systematic review, conclusions drawn from their data should be treated as tentative even though their results were statistically significant. Further research needs to be conducted to reinforce the effectiveness of these natural medicines. The results of the other studies regarding life style improvement, changes in limb volume (of the affected limb), adverse effects, and modification or cessation of the treatment were not statistically significant; therefore, no effectiveness or adverse effects conclusions could be drawn from them. The four studies that have been included into this systematic review still need to be replicated, thus their results must be viewed with caution.

CHAPTER FIVE

Discussion

5.1 Introduction

Lymphoedema is a lifelong condition characterised by protein-rich oedema in a part of the body as a result of the accumulation of lymphatic fluid due to obstruction or abnormalities in the lymph nodes of the lymphatic system (Pratt, 1956). This condition may result from treatments for breast cancer, such as lymph node dissection, surgery and/or radiation and can be reduced in severity if detected early and treated. However, it is generally under-reported and under treated (Marrs, 2007). Presently there is no cure for cancer related lymphedema, but it can be effectively managed with the appropriate treatment (Liao et al., 2004).

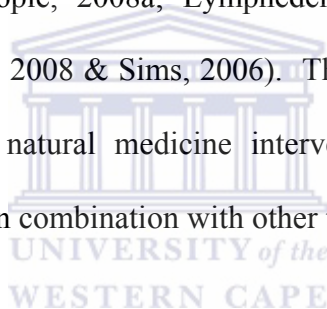
Of all the treatment options currently available, Moseley, Carati and Piller (2006) conclude that complete decongestive therapy, manual lymphatic drainage, pneumatic pump, and laser therapy usually result in greater volume reductions. According to Myoung (2004), the most effective therapy currently used to treat lymphoedema seems to be complete decongestive therapy, if provided by well trained health practitioners.

Despite these options being available, a survey of the literature reveals that patients suffering from lymphoedema often report that their health providers and care givers are not well informed and trained regarding this condition (Ridner, 2006). The worldwide paucity in education and training on the symptoms and treatments of lymphoedema, leads to late diagnosis and inadequate treatment that is evident by the lack of treatment centres and certified lymphoedema therapists, and other professionals prepared to treat lymphoedema (Marrs, 2007).

In the face of limited knowledge and options provided by health care practitioners, patients often turn to popular media for information on lymphoedema and treatment options. Breast cancer patients often make use of alternative or complementary medicines in their treatment of lymphoedema symptoms, especially in cases with heavy swelling, despite a lack of supporting evidence based literature documenting its effectiveness (Ashikaga et al., 2002; Fouladbakhsh et al., 2005). For this reason the present systematic review set out to collect and analyse all available empirical based literature on the effectiveness of natural medicines as part of the treatment of post-breast cancer lymphoedema.

5.2 Discussion

The present study, following a rigorous search for primary studies dealing with natural medicines and their use in post-breast cancer lymphoedema, has confirmed the lack of evidence for the effectiveness of natural medicines. Even though evidence-based research is lacking, patients suffering from this condition are making use of natural medicines, possibly due to the popular literature that is available, which is often unscientific and/or ambiguous (e.g. Bone, 2008; Brady, no date; Brady, 1996a; Brady, 1996b; Dharmananda, 2000; Herbs2000.com, 2008; Lymphedema People, 2008a; Lymphedema People, 2008b; Medifocus Health, 2008; O'Connor, 2008 & Sims, 2006). Thus, further studies are required to address the role of natural medicine interventions for post-breast cancer lymphoedema, alone or in combination with other treatment modalities.



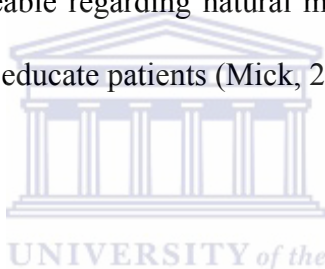
Four research articles met the inclusion criteria and were meta-analysed for the purpose of this systematic review. The primary objective of this systematic review was to assess the effectiveness of natural medicines on post-breast cancer lymphoedema treatment outcomes such as perceived improvement in the domain of life style (this included any physical signs and symptoms related to the condition such as heaviness, tightness, pain, ache, itch, mobility of affected arm, and skin texture, as well as psychological symptoms like distress), changes in arm volume (of the affected limb), adverse effects, and modification or cessation of treatment were analysed. The sample sizes of these studies were small and only

some of the data was meta-analysed as the presentation of their data was heterogeneous, while other data had to be presented in a narrative form.

Concerning the outcomes mentioned above, life style improvement, adverse effects, and modification or cessation of treatment were not significantly impacted by either 1) aromatherapy using an intervention cream containing wheat germ oil and essential oils of fennel, sage, geranium, black pepper and juniper; 2) CYCLO 3 FORT taken orally; 3) sodium selenite ampules taken orally; or 4) vitamin E plus pentoxifylline supplements also taken orally when compared to a placebo. On the other hand, changes in arm volume (of the affected limb) were significantly greater for post-breast cancer patients undergoing sodium selenite post-radiotherapy treatment or CYCLO 3 FORT treatment when compared to patients receiving placebo. As these results are drawn from only two studies that met the characteristics required for selection for this systematic review, conclusions drawn from their data need to be confirmed through replication even though their results were statistically significant. To sum up, although CYCLO 3 FORT taken orally and sodium selenite also taken orally do seem to offer some benefit in reducing arm oedema, further research needs to be conducted to reinforce the effectiveness of these natural medicines.

5.3 Implications for practice

Radina et al., (2004) argue that lymphoedema incidence is so high in part because most health care providers do not receive appropriate, formal training about the risk of lymphoedema, risk reduction, and treatment. Quality nursing care has a big impact on patient's outcomes in regard to lymphoedema. Nurses can be proactive in patient education, thus they should have the appropriate knowledge about lymphoedema. Due to the increasing attention being paid to complementary and alternative medicine (Gaskil, 2001), nurses are obliged to become more knowledgeable regarding natural medicines and therapies in order to evaluate their use, and educate patients (Mick, 2008).



Health care professionals working in wards such as breast cancer units should especially be informed about this condition. They should be encouraged to create awareness and counsel women that have undergone treatment for breast cancer about the risks and possible long-term problems such as lymphoedema that could develop after the intervention. This will allow patients to be more involved in identifying this condition early on, and thereby seeking treatment in the early stages of lymphoedema. Health care providers should be aware that natural medicines are currently popular among patients, and they should for this reason become knowledgeable in this area so that they are able to orientate patients towards evidence-based natural medicines. Patients should be cautioned against self-medicating based on information that they have assimilated from the popular

media as these sources are sometimes misleading in an attempt to make profit. Patients could end up spending large amounts of money on medicines that are unlikely to significantly reduce the symptoms of lymphoedema or prevent it from progressing to the next stage. Patients need to know that once they start to experience signs and symptoms of lymphoedema, they need to seek treatment immediately as the volume of the affected limb is likely to continue to increase and the condition could progress. However, with the appropriate care consisting of manual lymphatic drainage in combination with the application of compression bandages, the condition can be managed and the swelling reduced.



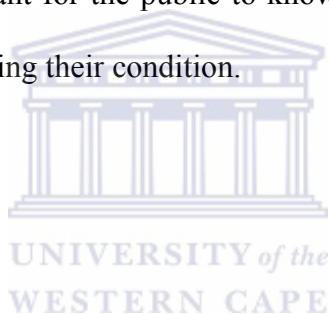
5.4 Implications for future research

In light of the popularity of natural medicines among post-breast cancer lymphoedema patients, it is alarming to find that there are only four randomized controlled trials, quasi-randomized controlled trials, or clinical trials available in all the databases searched by the reviewer. There is an obvious and great need for well-designed, methodologically sound primary studies required to address the role of natural medicine interventions for post-breast cancer lymphoedema, alone or in combination with other treatment modalities. Studies that have been included in this systematic review need to be replicated, and at this time their results may only be viewed as tentative. In addition, some of the proposed natural medicines in this systematic review have not been tested on patients with post-

breast cancer lymphoedema. Current results need to be confirmed and new studies need to be produced regarding natural medicines that could possibly aid in the treatment of lymphoedema.

A number of factors limit the possibility of drawing rigorous conclusions from the available literature, and these limitations need to be addressed and taken into account whenever researchers conduct and report on clinical trials. Firstly, those studies that are available dealing with the treatment of lymphoedema seldom report the various treatment options available, or physiological mechanisms. This kind of information is important not only for the purposes of comparison between one trial and another, but also for health care providers seeking information regarding clinical application. Secondly, the sample sizes of these studies were small and the presentation of their data was heterogeneous making it infeasible to enter some of the data into RevMan 5 for meta-analysis. Even though the included studies represent the best contemporary evidence available on post-breast cancer lymphoedema and its treatment with natural medicines, they tend to fall short of the standards and levels of quality typically sought after for systematic reviews. Either authors need to make raw data available, or consistent standards for analysis and reporting need to be adhered to so that meta-analysis and comparisons can be effectively drawn up. There needs to be consensus on clinically relevant outcomes to be measured, as well as how to define them in the prospective clinical trials. In the future, researchers should take care to benchmark their operationalisation of outcomes such as life style improvements

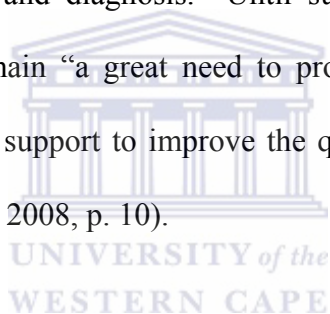
(including signs and symptoms), changes in limb volume, adverse effects, and modification or cessation of treatment against other studies, and ensure there is consensus on how they choose to report their results and other related studies that have already been published. Lastly, the reviewer noticed that research into specific natural medicines has been conducted but that the results of these studies will not be published as the specific treatments were not significant in improving the condition. Failing to publish non-significant results in a biased pool of literature from which one may draw information. It is very important that all research that has been done in this area is published, even if the results are not significant, as it is relevant for the public to know that certain natural medicines are not beneficial in treating their condition.



5.5 Conclusion

Contemporary evidence based research regarding natural medicines for the treatment of lymphoedema and lymphoedema in general is lacking. Of the available randomized controlled trials, quasi-randomized controlled trials, and clinical trials, only four primary studies met the inclusion criteria for this systematic review. The studies generally suffered from small sample sizes and varied somewhat in their operationalisation of outcomes and the format for presenting results, making meta-analysis very difficult. The included studies suggest that sodium selenite taken orally and CYCLO 3 FORT also taken orally

are effective in the reduction of limb volume. On the other hand, based on the studies included in this review, it appears that aromatherapy using an intervention cream containing wheat germ oil and essential oils of fennel, sage, geranium, black pepper and juniper, and vitamin E plus pentoxifylline taken orally are not effective. However, seeing as these results are drawn from single studies with heterogeneous outcome variables, they should be seen as tentative until they are confirmed by replication. Thus, more research is needed to investigate the effectiveness of natural medicines, as well as research on lymphoedema in general to aid in the construction of new policies regarding the characteristics of this condition, its treatment and diagnosis. Until such research is conducted and published there will remain “a great need to produce guidelines regarding the detection, treatment and support to improve the quality of life of patients living with this illness” (Hayes, 2008, p. 10).



BIBLIOGRAPHY

- Ageless (2008). *Butchers broom (box holly) Ruscus aculeatus*. Retrieved September 25, 2008, from <http://www.ageless.co.za/herb-butchers-broom.htm>
- Alem, M., & Gurgel, M.S.C. (2008). Acupuncture in the rehabilitation of women after breast cancer surgery - a case series. *Acupuncture in Medicine*, 26(2), 86-93. Retrieved September 25, 2008, from the Ebscohost database.
- Altman, D.G. (1996). Better reporting of randomised controlled trials: The CONSORT statement. *British Medical Journal*, 313, 570-571.
- Andallu, B., Suryakantham, V., Lakshmi Srikanthi, B., & Reddy, G.K. (2001). *Effect of mulberry (Morus indica L.) therapy on plasma and erythrocyte membrane lipids in patients with type 2 diabetes*. Retrieved September 21, 2008, from the Cochrane Controlled Trials Register database.
- Antman, E., Lau, J., Kupelnik, B., Mosteller, F., & Chalmers, T. (1992). A comparison of results of meta-analysis of randomized controlled trials and recommendations of clinical experts. Treatment for myocardial infarction. *Journal of the American Medical Association*, 268, 240-248.
- Ashikaga, T., Bosompra, K., O'Brien, P., & Nelson, L. (2002). Use of complimentary and alternative medicine by breast cancer patients: prevalence, patterns and communication with physicians. *Support Care Cancer*, 10, 542-548. Retrieved June 23, 2008, from the SpringerLink database.
- Babbie, E., & Mouton, J. (2001). *The practice of social research* (South African ed.). Cape Town: Oxford University Press.
- Badger, C., Preston, N., Seers, K., & Mortimer, P. (Updated July 16, 2008). Benzo-pyrone for reducing and controlling lymphoedema of the limbs. [Cochrane Review]. In *Cochrane Database of Systematic Reviews*, 2003 (4). Retrieved July 29, 2008, from The Cochrane Library, Wiley Interscience.
- Barclay, J., Vestey, J., Lambert, A., & Balmer, C. (2006). Reducing the symptoms of lymphoedema: is there a role for aromatherapy? *European Journal of Oncology Nursing*, 10, 140-149. Retrieved May 23, 2007, from the ScienceDirect database.
- Bicego, D., Brown, K., Ruddick, M., Storey, D., Wong, C., & Harris S.R. (2006). Exercise for women with or at risk for breast cancer-related lymphoedema. *Physical Therapy*, 86(10), 1398-1405. Retrieved May 23, 2007, from the InfoTrac database.

- Boltman, H. (2005). *A systematic review on maternal and neonatal outcomes of ingested herbal and homeopathic remedies used during pregnancy, birth and breastfeeding*. Unpublished master's thesis, University of the Western Cape, Bellville, South Africa.
- Bone, K. (2008). *Butcher's broom, varicose veins, and lymphedema (phytotherapy review & commentary)*. Retrieved September 20, 2008, from the Health & Wellness Resource Center database.
- Brady, D. (no date). *Natural remedies to compliment CDT*. Retrieved September 20, 2008, from <http://www.uhealth.net/NaturalRemedies.htm>
- Brady, D. (1996a). *Complementary holistic remedies for lymphedema treatment*. Retrieved September 20, 2008, from <http://www.uhealth.net/article1.htm>
- Brady, D. (1996b). *Horsechestnut herb in the treatment of lymphedema*. Retrieved September 20, 2008, from <http://www.uhealth.net/article2.htm>
- Breastcancer.org. (2007a). *Breast conserving surgery*. Retrieved August 13, 2007, from <http://www.breastcancer.org/search.jsp?terms=breast+conserving+surgery>
- Breastcancer.org. (2007b). *Axillary lymph node dissection*. Retrieved August 13, 2007, from http://www.breastcancer.org/dictionary/a/axillarylymphnodedissection_t.jsp
- Breastcancer.org. (2007c). *Sentinel lymph node biopsy*. Retrieved August 13, 2007, from <http://www.breastcancer.org/search.jsp?terms=sentinel+lymph+node+biopsy>
- Breastcancer.org. (2007d). *Mastectomy vs lumpectomy*. Retrieved August 13, 2007, from http://www.breastcancer.org/treatment/surgery/mastectomy_vs_lumpectomy/index.jsp
- Brorson, H. (2000). Liposuction gives complete reduction of chronic large arm lymphedema after breast cancer. *Acta Oncologica*, 39(3), 407-420. Retrieved September 25, 2008, from the EbscoHost database.
- Brorson, H., & Svensson, H. (1997). Complete reduction of lymphoedema of the arm by liposuction after breast cancer. *Scandinavian journal of plastic and reconstructive surgery and hand surgery*, 31(2), 137-143. Retrieved September 25, 2008, from the PubMed database.
- Brorson, H., Ohlin, K., Olsson, G., Langstrom, G., Wikilund, I., & Svensson, H. (2006). Quality of life following liposuction and conservative treatment of arm lymphedema. *Lymphology*, 39, 8-25. Retrieved September 25, 2008, from the PubMed database.

- Bruns, F., Micke, O., & Bremer, M. (2003). Current status of selenium and other treatments for secondary lymphedema. *Journal of Supportive Oncology*, 1(2), 121-130. Retrieved September 25, 2008, from the EbscoHost database.
- Bumpers, H.L., Best, I.M., Norman, D., & Weaver, W.L. (2002). Debilitating lymphoedema of the upper extremity after treatment of breast cancer. *American Journal of Clinical Oncology*, 25(4), 365-367. Retrieved May 9, 2007, from the PubMed database.
- Campbell, W., & Harkin, D.W. (2008). Surgical debulking in a case of chronic lymphoedema. *Irish Journal of Medical Science*. [E-publication ahead of print]. Retrieved September 25, 2008, from the PubMed database.
- Campisi, C., & Boccardo, F. (2004). Microsurgical techniques for lymphedema treatment: derivative lymphatic-venous microsurgery. *World Journal of Surgery*, 28(6), 609-613. Retrieved September 25, 2008, from the SpringerLink database.
- Cancer.org. (2007). *Pycnogenol, pine bark extract*. Retrieved June 23, 2008, from http://www.cancer.org/docroot/ETO/content/ETO_5_3X_Pycnogenol.asp.
- Carati, C.J., Anderson, S.N., Gannon, B.J., & Piller, N.B. (2003). Treatment of postmastectomy lymphedema with low-level laser therapy, a double blind, placebo-controlled trial. *Cancer*, 98(6), 1114-1122. Retrieved March, 10, 2008, from the Infotract database.
- Carter, B.J. (1997). Women's experiences of lymphoedema. *Oncology Nursing Forum*, 24(5), 875-882.
- Cesarone, M.R., Belcaro, G., Rohdewald, P., Pellegrini, L., Ledda, A., Vinciguerra, G., Ricci, A., Gizzi, G., Ippolito, E., Fano, F., Dugall, M., Acerbi, G., Cacchio, M., Di Renzo, A., Hosoi, M., Stuard, S., & Corsi, M. (2006). Rapid relief of signs/symptoms in chronic venous microangiopathy with pycnogenol: a prospective, controlled study. *Angiology*, 57(5), 569-576.
- Cherry, P., & Duxbury, A. (Eds.). (1998). *Practical radiotherapy: Physics and equipment*. London: Greenwich Medical Media Ltd.
- ClinicalTrials.org. (2008). Horse chestnut seed extract for lymphedema. Retrieved October 16, 2008, from <http://clinicaltrials.gov/ct2/show/NCT00213928?term=lymphedema&rank=6>
- ClinicalTrials.org. (2008). Pycnogenol for the treatment of lymphedema. Retrieved October 16, 2008, from <http://clinicaltrials.gov/ct2/show/NCT00214032?term=lymphedema&rank=3>

- ClinicalTrials.org. (2008). Pycnogenol for the treatment of lymphedema of the arm in breast cancer survivors. Retrieved October 16, 2008, from <http://clinicaltrials.gov/ct2/show/NCT00064857?term=lymphedema&rank=21>
- Cluzan, R.V., Alliot, F., Ghabboun, S., & Pascot, M. (1996). Treatment of secondary lymphedema of the upper limb with CYCLO 3 FORT. *Lymphology*, 29: 29-35.
- Cook, D.J., Mulrow, C.D., & Haynes, B.R. (1997). Systematic reviews: synthesis of best evidence for clinical decisions. *Academia and Clinic Systematic Review Series*, 126(5), 376-380. Retrieved May 23, 2003, from <http://www.annals.org/cgi/content/full/126/5/376>
- Dharmananda, S. (2000). *Chinese herbs for lymphedema exploring the principles of treating phlegm-damp accumulation*. Retrieved September 20, 2008, from <http://www.itmonline.org/arts/lymphedema.htm>
- Encyclopedia of Surgery. (2007). *Axillary dissection*. Retrieved September 29, 2008, from <http://www.surgeryencyclopedia.com/A-Ce/Axillary-Dissection.html>
- Eversley, R., Estrin, D., Dibble, S., Wardlaw, L., Pedrosa, M., Favila-Penney, W. (2005). Post-treatment symptoms among ethnic minority breast cancer survivors. *Oncology Nursing Forum*, 32(2), 250-256. Retrieved May 23, 2007, from the EBSCOhost database.
- Fahey, T., Griffiths, S., & Peters, T.J. (1995). Evidence based purchasing: understanding results of clinical trials and systematic reviews. *British Medical Journal*, 311, 1056-1059.
- Ferrell, B., & Coyle, N. (Eds.). (2001). *Textbook of palliative nursing* (2nd ed.). USA: Oxford University Press.
- Fisher, B., Jeong, J., Anderson, S., Bryant, J., Fisher, E.R., & Wolmark, N. (2002). Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *New England Journal of Medicine*, 347(8), 567-576.
- Fouladbakhsh, J.M., Stommel, M., Given, B.A., & Given, C.W. (2005). Predictors of use of complementary and alternative therapies among patients with cancer. *Oncology Nursing Forum*, 32(6), 1115-1122. Retrieved June 23, 2008, from the EbscoHost database.
- Gale Encyclopedia of Cancer. (2006). *Oncology Encyclopedia information about mastectomy*. Retrieved May 24, 2007, from <http://www.answers.com/topic/mastectomy>

- Gaskil, M. (2001). *A new attitude: alternative therapies that focus on body, mind, and spirit offer an integrative approach to treatment*. Retrieved January, 2008, from <http://www.nurseweek.com/news/features/01-08/alternative.html>
- Geller, B.M., Vacek, P.M., O'Brian, P., & Secker-Walker, R.H. (2005). Factors associated with arm swelling after breast cancer surgery. *Journal of Women's Health, 12*(9), 921-930. Retrieved May, 23, 2007, from the EBSCOhost database.
- Gothard, L., Cornes, P., Earl, J., Hall, E., MacLaren, J., Mortimer, P., Peacock, J., Peckitt, C., Woods, M., & Yarnold, J. (2004). Double-blind placebo-controlled randomised trial of vitamin E and pentoxifylline in patients with chronic arm lymphoedema and fibrosis after surgery and radiotherapy for breast cancer. *Journal of the European Society for Therapeutic Radiology and Oncology, 73*(2), 133-139. Retrieved September 3, 2008, from the ScienceDirect database.
- Greenhalgh, T. (1997). Papers that summarise other papers: systematic reviews and meta-analyses. *British Medical Journal, 315* (7109), 672-675. Retrieved June 29, 2008 from <http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2127461&blobtype=pdf>
- Hayes, S.C. (2008). *Review of research evidence on secondary lymphoedema: incidence, prevention, risk factors and treatment*. Strawberry Hills: National Breast Cancer and Ovarian Cancer Centre.
- Herbs2000.com (2008). *Lymphedema*. Retrieved September 20, 2008, from <http://www.herbs2000.com/disorders/lymphedema.htm>
- Higgins, J.P.T., Green, S. (Updated February, 2008). *Cochrane handbook for systematic reviews of interventions version 5.0.0*. The Cochrane Collaboration, 2008.
- Hutson, P.R. (2004). Pycnogenol for the treatment of lymphedema of the arm in breast cancer survivors. *Physician Data Query*. Retrieved May 23, 2007, from the Cochrane Controlled Trials Register database.
- Hutson, P.R., Love, R.R., Cleary, J.F., Anderson, S.A., Vanummersen, L., Morgan-Meadows, S.L., & Doran, E.A. (2004). Horse chestnut seed extract for the treatment of arm lymphedema. *Journal of Clinical Oncology, ASCO Annual Meeting Proceedings, 22*(14S), 8095.
- Ingwersen, K.C. (2001). Cell cycle kinetics and antineoplastic agents. In M. Barton-Burke, G.M. Wilkes, & K. Ingwersen (Eds.), *Cancer chemotherapy: A nursing process approach* (3rd ed.). Sandbury, MA: Jones and Bartlett Publishers.

- Jadad, A.R. & McQuay, H.J. (1996). Meta-analysis to evaluate analgesic interventions: A systematic qualitative review of their methodology. *Journal of Clinical Epidemiology*, 49, 235-243.
- Kasseroller, R. (1997). Administration of selenium in lymphedema. *Medizinische Klinik (Munich, Germany:1983)*, 9(3), 50-51. Retrieved June 23, 2008, from the Cochrane Controlled Trials Register database.
- Kaviani, A., Fateh, M., Yousefi Nooraie, R., Alinagi-Zadeh, M.R., & Ataie-Fashtami, L. (2006). Low-level laser therapy in management of postmastectomy lymphedema. *Lasers. Medical Science*, 21(2), 90-94. Retrieved October 3, 2008, from the Cochrane Controlled Trials Register database.
- Kerchner, K., Fleischer, A., & Yosipovitch, G. (2008). Lower extremity lymphedema update: pathophysiology, diagnosis, and treatment guidelines. *Journal of American Academy of Dermatology*, 59(2), 324-331. Retrieved June 29, 2008, from the ScienceDirect database.
- Kirshbaum, M. (1996). Using massage in the relief of lymphoedema. *Professional Nurse*, 11(4), 230-232.
- Kups, K.E. (2008). *A left-over problem from a mastectomy*. Retrieved September 20, 2008, from <http://blog.healthtalk.com/breast-cancer/life-with-breast-cancer/a-left-over-problem-from-a-mastectomy/>
- Leach, M.J. (2004). The clinical feasibility of natural medicine, venotonic therapy and horsechestnut seed extract in the treatment of venous leg ulceration: A descriptive survey. *Complementary Therapies in Nursing & Midwifery*, 10, 97-109. Retrieved August 5, 2008, from the ScienceDirect database.
- Liao, S.F., Huang, M.S., Li, S.H., Chen, I.R., Wei, T.S., Kuo, S.J., Chen, S.T., & Hsu, J.C. (2004). Complex decongestive physiotherapy for patients with chronic cancer-associated lymphedema. *Journal of the Formosan Medical Association*, 103(5), 344-348. Retrieved September 25, 2008, from the BioInfoBank database.
- Lomas, C. (2008). Nurses key to lymphoedema control. *Nursing Times*, 104(21), 7. Retrieved September 24, 2008, from the InfoTrac database.
- Lyman, G.H., & Djulbegovic, B. (2005). The challenge of systematic reviews of diagnostic and staging studies in cancer. *Cancer treatment reviews*, 31, 628-639. Retrieved May 23, 2007, from the EBShost database.
- Lymphedema People. (2008a). *Wholistic treatment*. Retrieved September 20, 2008, from http://www.lymphedemapeople.com/thesite/lymphedema_wholistic_treatment.htm

- Lymphedema People (2008b). *Homeopathic treatment*. Retrieved September 20, 2008, from http://www.lymphedemapeople.com/thesite/lymphedema_and_homeopathy.htm
- Lymphedema Treatment Center.(no date). *What is lymphedema?*. Retrieved September 20, 2008, from <http://www.lymphedematreatmentcenter.com/WhatIsLymphedema08.html>
- MacLennan, A.H., Wilson, D.H., & Taylor, A.W. (2002). The escalating cost and prevalence of alternative medicine. *Preventive Medicine, 35*, 166-173. Retrieved May 23, 2007, from the ScienceDirect database.
- McCallin, M., Johnston, J., & Bassett, S. (2005). How effective are physiotherapy to treat established secondary lymphoedema following surgery for cancer? A critical analysis of the literature. *New Zealand Journal of Physiotherapy, 33*(3), 101-113. Retrieved May 23, 2007, from the Infrotract database.
- Marrs, J. (2007). Lymphedema and implications for oncology nursing practice. *Oncology nursing, 11*(1), 19-21. Retrieved May 23, 2007, from the EBSCOhost database.
- Medifocus Health. (2008). *Complementary medicine for lymphedema*. Retrieved September 21, 2008, from http://www.medifocushealth.com/OC030/Understanding-Lymphedema_Complementary-Medicine-for-Lymphedema.php
- Mick, J. (2008). Factors affecting the evolution on oncology nursing care. *Clinical Journal of Oncology Nursing, 12*(2), 307-313. Retrieved September 20, 2008, from the Medline database.
- Micke, O., Bruns, F., Mucke, R., Schaffer, U., Glatzel, M., DeVries, A.F., Schonekaes, K., Kisters, K., & Buntzel, J. (2003). Selenium in the treatment of radiation-associated secondary lymphedema. *International Journal of Radiation Oncology Biology Physics, 56*, 40-49.
- Morrell, R.M., Halyard, M.Y., Schild, S.E., Ali, M.S., Gunderson, L.L., & Pockaj, B.A. (2005). Breast cancer-related lymphedema. *Mayo Clinic Proceedings, 80*(11), 1480-1484. Retrieved May 23, 2007, from the EBSCOhost database.
- Moseley, A.L., Carati, C.J., & Piller, N.B. (2007). A systematic review of common conservative therapies for arm lymphoedema secondary to breast cancer treatment. *Annals of Oncology, 18*(4), 639-649. Retrieved June 23, 2008, from the BioInfoBank database.
- Muntanga, V.L. (2004). *A systematic review evaluating the effects of bilateral*

tubal ligation on menorrhagia and dysmenorrhoea, post-tubal ligation syndrome. Unpublished master's thesis, University of the Western Cape, Bellville, South Africa.

Myoung, O.C. (2004). Health care seeking behavior of Korean women with lymphedema. *Nursing and Health Sciences*, 6, 149-159. Retrieved June 29, 2008, from the InterScience database.

National Cancer Institute. (2008). *Breast cancer: treatment - patient information [NCI PDQ]*. Retrieved September 20, 2008, from <http://www.medicare.com/kbase/nci/ncicdr0000062955.htm>

National Lymphedema Network (2008). *Position statement of the National Lymphedema Network, topic: treatment.* Retrieved June 29, 2008 from <http://www.lymphnet.org/pdfDocs/nlntreatment.pdf>

Norton School of Lymphatic Therapy. (2008). *Course Manual: Manual lymph drainage / complete decongestive therapy certification training.* Matawan, NJ: Norton School of Lymphatic Therapy.

O'Connor, P. (2008). *Lymphedema and herbal supplements.* Retrieved September 20, 2008, from http://www.lymphedemapeople.com/thesite/lymphedema_herbal_supplements.htm

Olson, G.L. (2001). When pregnant patients use nutritional and herbal supplements. *Contemporary Ob/Gyn*, 10, 63-81. Retrieved September 29, 2008, from <http://nanmt.mediwire.com/main/Default.aspx?P=Content&ArticleID=139521>

Pasket, E.D. & Stark, N. (2000). Lymphedema: knowledge, treatment, and impact among breast cancer survivors. *The Breast Journal*, 6(6), 373-378. Retrieved May 23, 2007, from the EBSCOhost database.

Petrek, J.A., Pressman, P.I., & Smith, R.A. (2000). Lymphedema: current issues in research and management. *Cancer Journal for Clinicians*, 50, 292-307. Retrieved September 21, 2008, from <http://caonline.amcancersoc.org/cgi/reprint/50/5/292.pdf>

Piller, N.B., & Thelander, A. (1998). Treatment of chronic postmastectomy lymphedema with low level laser therapy: a 2.5 year follow-up. *Lymphology*, 31(2), 74-86. Retrieved September, 25, 2008, from the PubMed database.

Pratt, G.H. (1956). Lymphoedema. *The American Journal of Nursing*, 56(12), 1548-1552. Retrieved May 7, 2007, from the JSTOR database.

Radina, M.E., Armer, J.M., Culbertson, S.D., & Dusold, J.M. (2004). Post-breast

- cancer lymphoedema: Understanding women's knowledge of their condition. *Oncology Nursing Forum*, 31(1), 97-104. Retrieved May 23, 2007, from the EBSCO database.
- Revis, D.R. (2005). *Lymphoedema*. Retrieved March 7, 2007, from <http://www.emedicine.com/med/topic2722.htm>
- Ricci, M. (2005). Demonstration of Flowave's effectiveness through lymphoscintigraphy. *European Journal of Lymphology*, 15(44), 33-42.
- Ridner, S.H. (2006). Pretreatment lymphedema education and identified educational resources in breast cancer patients. *Patient Education and Counselling*, 61, 72-79. Retrieved October 16, 2008, from the ScienceDirect database.
- Rinehart-Ayres, M.E. (1998). Conservative approaches to lymphedema treatment. *Cancer*, 83(12), 2828-2832. Retrieved March 3, 2008, from the InterScience database.
- SA Cochrane Centre. (2008, May 2008). Data analysis. Unpublished lecture notes, SA Cochrane Centre, Tygerberg, South Africa.
- Sims, J. (2006). *Lymphedema*. The Gale Encyclopedia of Medicine (3rd ed.). Detroit: Gale.
- Schachter, K., & Neuhauser, D. (1981). *Surgery for breast cancer*. Washington DC: Congress of the United States, Office of Technology Assessment.
- Schnaubelt, K. (1999). *Medical aromatherapy: Healing with essential oils*. Berkely, CA: Frog, Ltd.
- Schuchhardt, C., Weissleder, H., & Zöltzer, H. (2008). Physiology. In H. Weissleder & C. Schuchhardt (Eds.), *Lymphedema: Diagnosis and therapy* (pp. 31-43). Essen: Viavital Verlag GmbH.
- Sleep, J., & Clark, E. (1999). Weighing up the evidence: the contribution of critical literature reviews to the development of practice. *NT Research*, 4(4), 306-314.
- Stein, J.H. (Ed.). (1998). *Internal medicine*. New York: Mosby.
- Storer, A. (2006). *Lymph notes*. Retrieved September 21, 2008, from <http://www.therapytimes.com/content=6201J64E48BE5A841>
- Suter, A., Bommer, S., & Rechner, J. (2008). Treatment of patients with venous insufficiency with fresh plant horse chestnut seed extract: A review of 5 clinical studies. *Advances in Therapy*, 23(1), 179-190.

- Szuba, A., Achalu, R., & Rockson, S. (2002). Decongestive lymphatic therapy for patients with breast carcinoma-associated lymphedema. *Cancer*, 95(11), 2260-2267. Retrieved March 11, 2008, from the Wiley InterScience database.
- Taylor, K.L., Lamdan, R.M., Siegel, J.E., Shelby, R., Hrywna, M., & Moran-Klimi, K. (2002). Treatment regimen, sexual attractiveness concerns and psychological adjustment among African American breast cancer patients. *Psycho-Oncology*, 11, 505-517. Retrieved May 23, 2007, from the ScienceDirect database.
- The Cochrane Collaboration. (2008). *RevMan 5 user guide*. Cochrane Collaboration, 2008.
- The Jacksonville Lymphedema Clinic. (2005). *What is lymphedema?*. Retrieved September 21, 2008, from <http://www.jaxlymph.com/information.html>
- The START Trialists' Group. (2008). The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncology*, 9, 331-341.
- Torgerson, C. (2003). *Systematic Reviews*. New York: Continuum.
- Ulla. (2006). *Lymphedema help: natural treatment & management on lymphedema therapy options to help relieve or possible heal swelling symptoms in arm or leg*. Retrieved September 20, 2008, from <http://www.healingcancernaturally.com/lymphedema-treatment-therapy.html>
- Webb, P., Bain, C., & Pirozzo, S. (2005). *Essential epidemiology: an introduction for students and health professionals*. Cambridge University Press: New York.
- Weissleder, H., & Schuchhardt, C.(Eds.). (2008). *Lymphedema diagnosis and therapy*. Baden-Baden: Viavital Verlag.
- Weissleder, H., & Schuchhardt, C. (2008). Lymphedema of the arm following breast cancer therapy. In H. Weissleder & C. Schuchhardt (Eds.), *Lymphedema: Diagnosis and therapy* (pp. 218-254). Essen: Viavital Verlag GmbH.
- Weller, B.F. (2001). *Bailliere's nurses' dictionary* (23rd ed.). London: Bailliere Tindall.
- Williams, A., Vadgama, A., Franks, P.J., & Mortimer, P.S. (2002). A randomized controlled crossover study of manual lymphatic drainage therapy in women with breast cancer-related lymphoedema. *European Journal of Cancer Care*, 11(4), 254-261. Retrieved September 25, 2008, from the European Journal of Cancer Care database.

- Woods, M. (1993). Patients' perceptions of breast cancer related lymphoedema. *European Journal of Cancer*, 2, 125-128. Retrieved May 23, 2007, from the Wiley InterScience database.
- Woods, M., Tobin, M., & Mortimer, P. (1995). The psychosocial morbidity of breast cancer patients with lymphoedema. *Cancer Nursing*, 18(6), 467-71. Retrieved May 23, 2007, from the PubMed database.
- Zöltzer, H., Weissleder, H., & Schuchhardt, C. (2008). Anatomy of the lymphatic system. In H. Weissleder & C. Schuchhardt (Eds.), *Lymphedema: Diagnosis and therapy* (pp. 15-31). Essen: Viavital Verlag GmbH.
- Zuther, J.E. (1999). *Understanding lymphedema pathophysiology and treatment*. Retrieved September 21, 2008, from <http://www.naturalhealthweb.com/articles/Zuther.html>
- Zuther, J.E. (2004). *Lymphedema management: the comprehensive guide for practitioners*. New York: Thieme.



APPENDICES

Appendix 1:

Data collection sheets**DATA EXTRACTION FORM****Study Identifier:****Comparison group:****Participants:**Ages:Control group No.:Experimental No.:Loss to follow up:Discontinued:Total analyzed:**Length of Treatment:****Intervention:**Experimental:Control:Both:**Method:**

Outcomes:

1

2

3

4

5

Tool of assessment:**Inclusion criteria:****Exclusion criteria:****Other:**

CONTINUOUS OUTCOMES

Continuous outcome measures		Experimental Group		Control Group Placebo or routine	
		Mean (SD)	Total (N)	Mean (SD)	Total (N)
1					
2					
3					

DICHOTOMOUS OUTCOMES

Dichotomous outcome measures		Experimental Group Natural Medicines		Control Group Placebo or routine	
		Events (n)	Total (N)	Events (n)	Total (N)
1					
2					
3					
4					
5					
6					
7					