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 - 1000µg daily for the first week, followed by a dosage reduction to about 300 - 500µg 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 100µg 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 the 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 Cholcone (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.

Search Strategy	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.	Index and free text search for: Secondary LE Post breast cancer LE	Same as above.

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 blobbograms. 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	CYCLO 3 FORT and placebo presented with an identical appearance. The patients were asked to returned surplus capsules at each visit in order to assess compliance with treatment. CLYCLO 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.

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, doubled-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

	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.
Interventions	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.
Outcomes	Changes in volume of the affected upper limb, function and quality of life.
Notes	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

	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	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 discontinue thereafter. Forty one were allocated the placebo cream but 40 received the cream, four discontinued thereafter. These

	patients had been referred to the Dorset Cancer Centre lymphoedema service.
Interventions	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.
Outcomes	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.
Notes	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.

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 Arzeimittel 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 Ration (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

	Natural Medicines		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Gothard (2004)	6	31	8	34	100.0%	0.82 [0.32, 2.11]	
Total (95% CI)		**31**		**34**	**100.0%**	**0.82 [0.32, 2.11]**	
Total events	6		8				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)

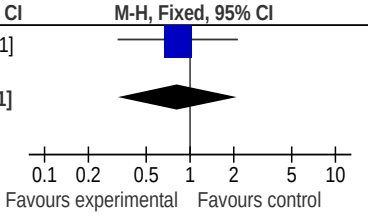

Figure 4.1: Forest plot of comparison 01: changes in induration fibrosis using vitamin E plus pentoxifylline.

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

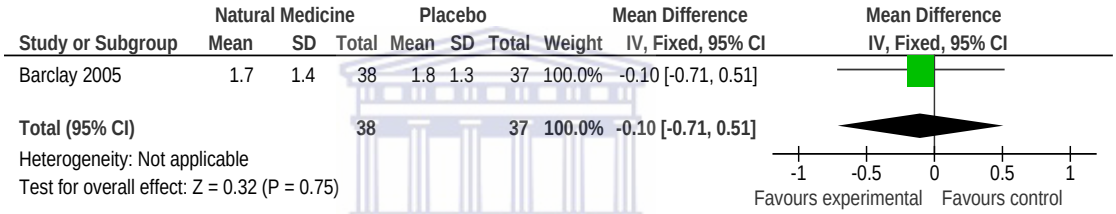

Figure 4.2: Forest plot of comparison 02: symptom improvement using aromatherapy cream.

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:

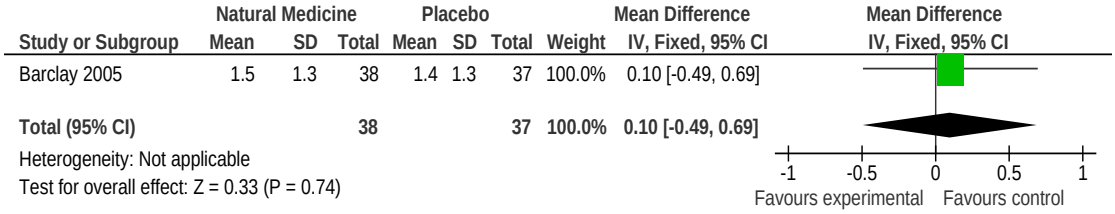

Figure 4.3: Forest plot of comparison 02: well-being using aromatherapy cream.

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:

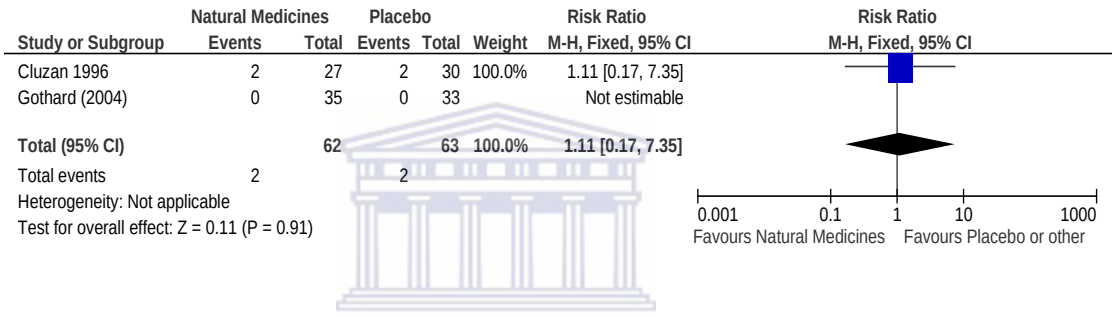

Figure 4.4: Forest plot of comparison 01: Adverse effects using vitamin E plus pentoxifylline or CYCLO 3 FORT.

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:

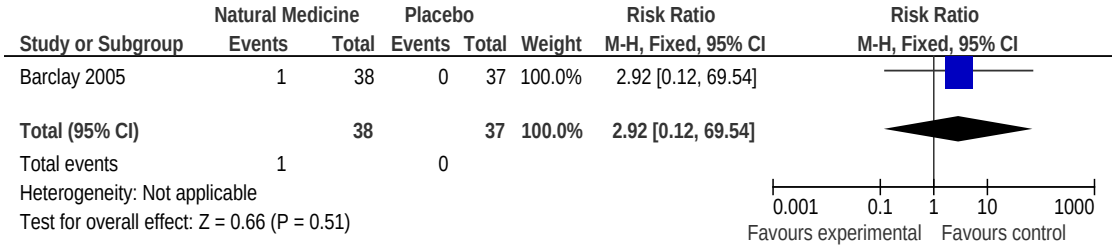

Figure 4.5: Forest plot of comparison 02: Adverse effects using aromatherapy cream.

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:

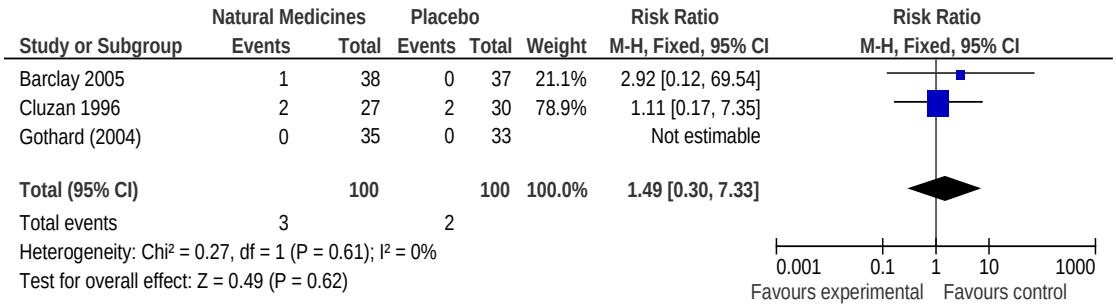

Figure 4.6: Forest plot of both comparison groups: adverse effects using vitamin E plus pentoxifylline or CYCLO 3 FORT or aromatherapy cream.

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:

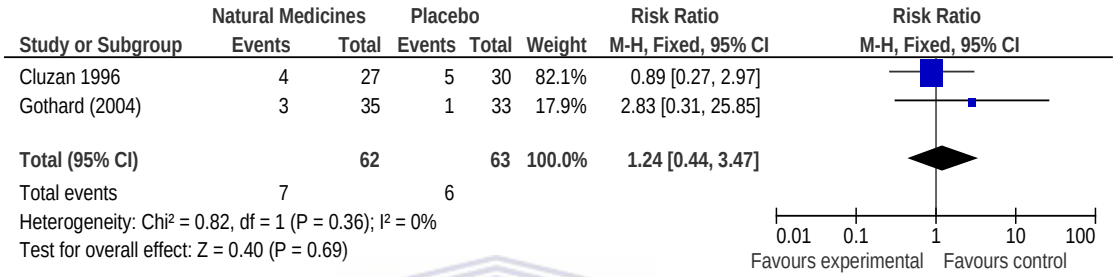

Figure 4.7: Forest plot of comparison 01: modification or cessation of treatment using vitamin E plus pentoxifylline or CLYCLO 3 FORT.

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 orraly; 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).

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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					