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AN INVESTIGATION INTO THE USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE FOR ATOPIC ECZEMA

By

Yasmeen Thandar

Submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in the School of Pharmacy and Pharmacology, University of KwaZulu-Natal

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Yasmeen Thandar

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A thesis submitted to the School of Pharmacy and Pharmacology, Faculty of Health Sciences, University of KwaZulu-Natal, Westville, for the degree of Doctor of Philosophy.

This is a thesis in which the chapters are written as a set of discrete research publications and manuscripts submitted for publication, with an overall introduction and final synthesis. Three of these research papers have been published in local and international accredited and peer-reviewed journals. Another has been submitted for publication and is currently under review in an accredited and peer-reviewed journal.

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    - Writing of all manuscripts
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    - Professor Anisa Mosam was involved in study conception, co-supervision, independent reviewer for manucript 2, reading and editing of all manuscripts.
    - Professor Julia Botha was involved in study conception, supervision, independent reviewer for manuscript 2, reading and editing of all manuscripts.
    - Mr Andy Gray was involved as an independent reviewer for manuscript 2.
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DEDICATION

To my children,
You will always be my greatest achievement

"Whoever teaches some knowledge (that brings goodness to others) will have the reward of the one who acts upon it,
without that detracting from his reward (who acted on it) in the slightest."
— Muhammad Ibn Abdullah (Peace be upon him),
Last Prophet and Messenger to Humanity, (570-633CE)

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LIST OF ACRONYMS

AD	Atopic Dermatitis
ADR	Adverse Drug Reaction
AE	Atopic Eczema
AIDS	Acquired Immunodeficiency Virus
AUD	Australian Dollars
BO	Borage Oil
CAM/CAMs	Complementary and Alternative Medicine/s
CHM	Chinese Herbal Medicines
EPO	Evening Primrose Oil
GP	General Practitioner
HCP	Healthcare Professional / Healthcare Practitioner
HIV	Human Immunodeficiency Virus
HPA	Health Product Association
IDQoL	The Infant's Dermatitis Quality of Life Index
DFI	The Dermatitis Family Impact Questionnaire
ISAAC	International Study of Asthma and Allergies in Childhood
ITT	Intention to Treat
KEH	King Edward VIII Hospital
KZN	KwaZulu-Natal
NCCAM	National Centre of Complementary and Alternative Medicine
NHIS	National Health Interview Survey
O-SSI	SCORAD Severity Index
QoL	Quality of Life
RCT	Randomised Controlled Trial
ROB	Risk of Bias
S/E	Side Effects
SA	South Africa / South African
SA	Staphylococcus Aureus
SCORAD	SCORing Atopic Dermatitis (clinical tool used to assess the extent and severity of eczema
SR	Systematic Review
TCAM	Traditional, Complementary and Alternative Medicines
TM	Traditional Medicine
UFCAM	European Federation of Complementary and Alternative Medicine

LIST OF ACRONYMS (continued)

UK	United Kingdom
US	United States
VCO	Virgin Coconut Oil
VOO	Virgin Olive Oil

ABSTRACT

Background

Atopic eczema (AE) is one of the most common skin diseases that patients frequently present with to dermatological practices in South Africa (SA). It has shown to impact negatively on the quality of life of many patients suffering from it. Epidemiological studies have shown high rates of AE prevalence, ranging from 2-7% in adults and 7-20% in children. Over the last decade, the lifetime prevalence of physician-diagnosed AE has almost doubled in SA. This rise continues despite accessible effective treatments. Due to AE's chronic and relapsing nature and the unattainability of complete clinical cure, patients are progressively exploring complementary and alternative medicines (CAM) in search of a solution. Although the global popularity of CAM for AE is on the rise, a review of the literature demonstrated contradictory evidence with regards to their efficacy with shortcomings in many of the published data thus making it difficult for clinicians to assess their role, if any, in the management of AE.

Objective One

To objectively evaluate the information on the efficacy and safety of CAM in light of the most recent findings, the study entitled "Complementary Therapy in Atopic Eczema: The Latest Systematic Reviews" in Chapter Two of this thesis collectively evaluated all published systematic reviews (SRs) to date on the most popular CAM modalities for AE. These SRs included those of Chinese herbal medicines (CHM), homeopathy, oral herbal remedies (including evening primrose oil and borage oil), probiotics and certain dietary supplements. The study concluded that none of the alternative therapies evaluated demonstrated obvious and indisputable evidence of efficacy due to many limitations in study design, poor methodologies, patient numbers etc. Further studies may be warranted with some therapies (CHM, different probiotic strains and fish oil), whereas homoeopathy failed to show any treatment effect and further studies with evening primrose oil and borage oil may be difficult to justify. This overview was able to provide objective information to enable dermatologists and general practitioners to advise and manage their patients holistically in the light of the most recent findings.

Objective Two

Topical corticosteroids remain the mainstay of treatment for AE. However, many patients are concerned about their long-term safety and thus seek evidence-based safer alternatives. Many published papers have made reference to the wide use of topical herbal creams for AE and many of these been tested, but few in controlled clinical trials. No SRs of these trials could be found,

although SRs of topical herbal extracts have been published for other chronic skin conditions. The study entitled "Topical Herbal Medicines for Atopic Eczema: A Systematic Review of Randomised Controlled Trials" in Chapter Three of this thesis was the first SR to be conducted for topical herbal preparations for AE. Using Cochrane SR methodology, numerous databases were searched from inception until June 2014. All controlled clinical trials of topical herbal medicines for AE in humans of any age and published in English were included regardless of the control intervention or randomisation. Of eight studies that met the inclusion criteria, seven investigated extracts of single plants and one an extract from multiple plants. The study concluded that there is currently insufficient evidence of efficacy for any topical herbal extract in AE with many studies having methodological flaws. Even studies that did show efficacy over placebo were single trials with small patient cohorts. Together with providing clarity to both prescribers and patients, the study was able to identify opportunities for future research in better designed trials with topical extracts that showed a promising effect and had a low risk of bias across all domains. These were randomised controlled trials (RCTs) of *licorice gel* and *Hypericum perforatum*.

Objective Three

The literature has thus far reported on numerous international studies on the widespread use of CAM for AE. These studies not only investigated the prevalence of CAM use but also the modalities used, motivations for use and demographic variables that influence their use. All these factors potentially impact on the treatment of AE. No such studies conducted anywhere in Africa could be found. Given the lack of literature in SA, the study entitled "Complementary and Alternative Medicine Use amongst patients with Atopic Eczema - a South African Perspective" in Chapter Four of this thesis was a cross-sectional study that was conducted amongst AE patients in Durban, KwaZulu-Natal to bridge this gap in knowledge. This study found a 66% current or previous CAM use, which was moderately higher than those reported in other countries. Frequently used CAM were vitamins, aromatherapy oils, herbal creams, traditional African medicines and homeopathy. Non-disclosure to the dermatologist was high and almost half of the patients interviewed said they were not questioned about CAM use. More Indian patients used CAM and Muslims were the most frequent CAM users. Duration of AE was also a predictor of use. Although not statistically significant, the more educated and higher income bracket used CAM more. The study was able to provide detailed trends of CAM use by South Africans for AE which is an important addition to the literature. This information is able to highlight to dermatologists and healthcare professionals treating AE patients, the need to be more conversant with CAM that patients explore, as this could impact overall clinical outcome.

Objective Four

Although evident from the literature that patients have embraced CAM, it is uncertain whether mainstream healthcare professionals are as embracing. Their attitude and knowledge of CAM will influence their pro-activeness in enquiring about CAM and confidently discussing proven/unproven remedies with their patients, thereby influencing an overall positive clinical experience and disease course. Several international studies have explored the knowledge, attitudes and practices amongst general practitioners (GPs), physicians, pharmacists, paediatricians, academic doctors and other healthcare workers towards CAM, but none within the context of a specific disease. No published studies conducted in SA or elsewhere investigating HCPs' knowledge, attitudes and norms of practice with regards to CAM for AE could be found. As a result, and given the extensive use among SA patients with AE as per the study's previous findings, a cross-sectional study entitled "Knowledge, Attitude and Practices of South African Healthcare Professionals towards Complementary and Alternative Medicine Use for Atopic Eczema - A Descriptive Survey" was conducted. Results amongst GPs, dermatologists, paediatricians and pharmacists are reported in Chapter Five of this thesis. GPs and pharmacists were significantly more embracing of CAM compared to dermatologists and paediatricians. The study revealed poor CAM knowledge and communication between HCPs and patients, however there was a strong interest to learn more. It was also found that there is an urgent need for continuing education programmes on CAM and inclusion into undergraduate curriculums as most HCPs were interested in learning more about CAM.

Conclusion

Overall, this thesis was able to fill a gap in the knowledge of CAM use for AE both globally and within the context of SA. The study provided clarity and objective conclusions from the many SRs previously published for popular oral CAM therapies. Furthermore, the study conducted and published the first SR on topical herbal therapies for AE. This SR identified therapies that have demonstrated positive results for AE with low risk of bias and is thus able to provide direction for future research in this regard. Within the SA context, the study described the perspectives and practices of both patients and mainstream healthcare professionals on CAM use for AE, which was lacking in Africa. With this information we were able to ascertain the popular CAM that SA patients are using, the extent of their use as well as establish CAM education needs for local healthcare professionals.

1. CHAPTER ONE

1.1. INTRODUCTION

1.1.1. Background

This chapter consists of the background of the study, the primary and secondary aim/objectives, the problem statement, significance of the study, as well as the structure of the entire dissertation.

1.1.1.1. Atopic Eczema - Its global prevalence and impact on quality of life

Atopic eczema, a chronically relapsing disease, is the commonest inflammatory skin condition; more common in infants and children than in adults. The exact cause of the disease is unknown, but familial/genetic factors are considered to play an important role in the development of the disease and frequency is seen in patients who have a family history of atopy or atopic diseases like asthma, allergic rhinitis and atopic eczema.[1] Symptoms of itch and eczema which appears in episodic exacerbations and remissions are characteristic of the disease.

Recent epidemiological studies have shown high rates of atopic eczema prevalence, ranging from 2-7% in adults and 7-20% in children.[2] The worldwide incidence in children five years and under, is estimated at 3-5%. Literature has revealed that approximately 49% to 75% of children with eczema, develop the disease by 6 months of age and, by the age of 5 years, the percentage increases to 80%-90%.[1] The prevalence of atopic eczema seems to vary across the world in both adults and children. In a systematic review of epidemiological studies investigating the prevalence of atopic eczema between 1990-2010, data from studies done in Africa (Kenya, Morocco and South Africa) showed that the prevalence was increasing. The data was attained mostly from children 13-14 years of age where an approximate doubling of the lifetime prevalence of atopic eczema symptoms was found for South Africa [e.g. flexural rash from 10.2% in 1995 to 16.5% in 2002]. The lifetime prevalence of physician-diagnosed atopic eczema in these children also showed an approximate doubling in South Africa and Kenya.[3]

Skin diseases have been shown to impact negatively on the quality of life of patients affecting physical, social and psychological well-being. This is true for both adults and children. In a questionnaire based study by Finlay, assessing the impact of severe eczema on the quality of life in adults, a number of patients with severe eczema consider that having diabetes or hypertension

would be better than having eczema. The study demonstrated that over the long term, atopic eczema affects family life in 80% of patients and sexual relationships in 57%. Loss of income and days lost at work due to their eczema were also reported in many patients. These findings affirm that severe eczema has a major impact on the quality of life of adults.[4]

Studies using a dermatology-specific quality-of-life instrument have shown that atopic eczema adversely affects a child's quality of life significantly more than many other skin conditions including moles, warts, psoriasis, and alopecia.[5] Furthermore, it has also been shown to affect quality of life more than other common childhood diseases such as asthma and diabetes.[6] This emphasizes the significance of eczema as a major chronic childhood disease.

The symptoms of atopic eczema also have a profound effect on the overall quality of life of parents or primary care-givers who struggle daily, coping with the child's skin disease especially due to its chronic nature with unpredictable flares-ups, itching, lack of sleep and the inconvenience and cost of treatments.[1] Apart from the physical symptoms, there are also psychological and psycho-social factors involved in managing this chronic condition. The physical symptoms of itching and soreness often give rise to sleep deprivation. This has been noted in over 60% of patients, frequently leading to tiredness, mood changes and impaired psychosocial functioning of the child as well as care-givers and family members at school and work. Children often face untoward comments and embarrassment due to teasing and bullying. Factors such as type of clothing, vacations, sleep-overs, swimming and other sporting activities may be limited and thus affect the child's and their family's lifestyle. These may further lead to insecurities, depression and social withdrawal.[6]

Lewis-Jones further reports that other factors that impact on normal family life are adherence to complex, rigid and often unpleasant treatment regimens, increased work in caring for a child with eczema, feelings of hopelessness, exhaustion and guilt when treatments do not work. The hidden costs involved in eczema management may significantly impact on lower income families.[6]

1.1.1.2. Atopic Eczema - Searching for a solution (CAM)

The prevalence of atopic eczema continues to rise despite the increasing number of effective treatments available to dermatologists. Owing to the chronic nature of the disease, finding a cost-effective regimen that will control the disease is imperative.[7] Due to the chronic, persistent and unrelenting nature of the disease, patients are continually exploring complementary and

alternative therapies in search of a cure.[8] Complete clinical cure still remains unattainable and the increased frequency of use of complementary and alternative medicines (CAM) in the management of the disease has been recognised.[9]

A review of the literature has shown that many CAM therapies may impact positively on the relief of symptoms like itching,[8] patient and physician-assessed disease severity[10] and overall health-related quality of life in patients with atopic eczema.[11-13] Other studies have demonstrated less convincing results from specific CAM therapies.[14, 15] Regardless, the awareness and use of CAM is globally prominent. The widespread use of CAM for atopic eczema has made its treatment a matter of extreme controversy between those who favour their use and those who favour the use of rational, conventional medicines with proven efficacy more than any other skin disease. This may result in long term suffering and may be harmful as their use leads to the withholding or delay of effective treatment modalities.[16] Considering the conflicting and inconsistent evidence of efficacy of commonly used alternative therapies in the literature and the shortcomings in available published data, it is difficult for clinicians to assess their role, if any, in management. The potentially serious adverse effects of some alternative therapies as well as drug-herb interactions are also of great concern.[8, 17]

One of the reasons for the persisting nature of atopic eczema is the patients' inability to comply effectively with medical advice. Most studies have reported a non-compliance rate of 30-60% with any given regimen.[18] Non-compliance impacts on the overall cost of treatment, the patient's confidence towards their prescribed medication thus making it more difficult for the practitioner to evaluate their effectiveness and prolonging the illness. Fischer explains that of the reasons cited for non-compliance of treatment for atopic eczema, a significant apprehension about the use of steroids and their potential for danger was noted (40%) together with concern about present and long term side effects of the prescribed medication. More than half of the patients (57%) expressed a preference for natural therapy as a reason for not adhering to the prescribed treatment.[18] The search for more 'natural therapies' presents a problem for practitioners for many reasons which include the unproven effectiveness of many alternative medicines as well as the detraction from funds the patient has to invest in medication with proven reliability and perpetuation of the belief by 'natural' therapists that steroids are dangerous. All of this complicates the overall management of a patient with atopic eczema.

1.1.1.3. CAM and the Patient

Numerous international studies conducted in countries e.g. Ireland[8], United Kingdom[9], Korea, [19] United States [20] and Norway[21] have reported on the widespread use of CAM for AE. These studies have qualified and quantified CAM use in atopic eczema. They not only investigated the prevalence of CAM use but also the modalities used, motivations for use and demographic variables that influence their use; all which potentially impact on the treatment of AE. A few South African studies have also realised the popularity of CAM [22-24], however, these studies were on general CAM use and its use in Human Immunodeficiency Virus (HIV). In Africa, no such studies have been conducted in atopic eczema.

The literature has also demonstrated that patients often do not inform their conventional doctor about their use of CAM and the dermatologists' ability to predict CAM use in their patients has been found to be poor.[25] The doctors' knowledge about a patient's use of CAM may lead to a better understanding of the patient's attitude to the disease and subsequently help to achieve better patient compliance.[17]

1.1.1.4. CAM and the Healthcare Professional

While it is evident in the literature that patients have embraced CAM, the healthcare providers' perspective on CAM and whether they encourage or advocate alternative treatment measures and understand completely their potential benefits or risks, is questionable. Several international studies have explored the knowledge, attitude, practice and factors affecting their recommendation amongst general practitioners, physicians, pharmacists and other health workers towards complementary therapies.[26-33] Given the emphasis necessitating more scientific based evidence in current discussions surrounding CAM, the views and rationales amongst academic doctors with a research orientation have also been investigated.[30] These studies focussed on general use of CAMs and none within a specific disease. The one Durban based study looked at attitude, knowledge and practices of health workers in HIV/AIDs clinics on CAM practitioners[33]. No study has been conducted in South Africa or elsewhere with regards to CAM for eczema and what role mainstream healthcare providers play in terms of their knowledge, awareness and their norms of practice.

1.1.1.5.Problem Statement, Knowledge Gaps and Significance of this Research

Considering the widespread use of CAM for atopic eczema globally, the literature has demonstrated that the current evidence of efficacy of commonly used alternative therapies is inconsistent and conflicting, with some studies reporting efficacy and others not. The literature has also demonstrated that there are shortcomings in the available published data. In view of this, it is difficult for clinicians to assess the role of specific CAMs, if any, in the management of atopic eczema.

Although systematic reviews (SRs) of controlled trials have been undertaken on various CAMs assessing their current evidence of safety and efficacy, these have been found to be varied in their conclusions. There are several SRs undertaken for the most commonly used CAMs reported in the literature, namely, Chinese Herbal Medicines (CHM),[12,13,34] homeopathy,[10] oral herbal remedies including evening primrose oil (EPO) and borage oil (BO),[35] probiotics [36] and certain dietary supplements[37]. However, there is no consolidated overview of these multiple SRs of CAM for AE. It became evident that a thorough scrutiny and analysis of the most recent of these SRs is needed to be able to provide objective information to busy, often sceptical allopathic practitioners regarding the current evidence of CAM in atopic eczema. This study sought to consolidate and critically evaluate all recently published SRs in order to provide evidence-based clarity to all practitioners treating patients for atopic eczema in light of the most current findings.

Although several international cross-sectional studies have analysed the use of CAM and determinants of this use amongst patients, the literature and data in South Africa is lacking. Exploration into the extent of CAM use amongst atopic eczema patients in a local setting would be able to provide valuable insight into the various modalities of CAM employed by patients for atopic eczema and the factors influencing their use. Through this, it would be possible to provide new information beneficial for dermatologists, paediatricians, general practitioners, pharmacists as well as complementary and alternative practitioners. This information may help improve the understanding and manner in which HCPs consult, interact with and advise atopic eczema patients which turn can lead to an overall improved clinical outcome.

Much of the literature to date has shown that a major driving factor for the use of CAM in atopic eczema is the significant apprehension amongst patients towards the use of steroids, both topical and oral. Steroids still remain the mainstay of treatment for atopic eczema but fear of their long term safety has generated a continued search for safer alternative agents. Several published studies

have made reference to the wide use of topical herbal creams e.g. chamomile,[38, 39] licorice gel [40] and St John's wort[41] for atopic eczema. Trials with other types of topicals have also been conducted including hamamelis distillate cream[42] and unani formulation[43] amongst others noted in the literature review. Certain traditional herbal medicines common in Pakistan have been reported to be effective for eczema[44] as well as massage therapy with essential oils, although not in controlled trials.[45] The evidence of efficacy varied amongst the various topical treatments in the literature. Upon sifting through the various SRs of diverse CAM therapies, it became evident that no SRs have been conducted for topical herbal therapies, despite many controlled clinical trials and despite SRs of topical herbal treatments being published for other chronic skin conditions like psoriasis; thus making it difficult to evaluate their efficacy. Conducting a SR on topical herbal extracts for atopic eczema is an imperative tool which would help analyse and ascertain their overall efficacy and safety and thus be able to provide clarity to the prescriber as well as direction steering future research on topical herbal products for AE.

The literature has demonstrated the lack of knowledge amongst most healthcare practitioners on CAM. Details on their attitude and practices have also been clearly highlighted in many papers surrounding CAM use. However, these have been on general CAM use and there have no studies that have demonstrated norms of practice, attitudes and knowledge within the context of a specific disease. The widespread use of CAM in atopic eczema has been confirmed and it can be seen that patients have generally embraced its use, however the role and familiarity of the dermatologist, paediatrician, GP or pharmacist and their viewpoints and recommendations on CAM for eczema are thus far unexplored, both globally as well as in Africa. Investigating the knowledge, attitude and practices of healthcare practitioners that patients consult with for the treatment of atopic eczema would be beneficial in assessing their extent of knowledge of CAM, awareness of its use among patients as well as their ease or proactiveness in communicating with patients regarding CAM when necessary. Findings from this would amongst other aspects, help identify if there is a need for appropriate continuing education programmes or a need for implementation of CAM teaching in undergraduate curricula.

Finding answers through the objectives set out in this study would contribute significantly to what is lacking in the current literature in South Africa, Africa and globally. In meeting the objectives of this thesis, the study aims to generate sufficient new knowledge and information essential in helping both patients and healthcare professionals work together in order to help improve the outcome of atopic eczema.

1.1.1.6. Aim and Objectives

The Aim of this research was to study CAM usage in Durban, KwaZulu-Natal with the following objectives:

- To collectively evaluate all published systematic reviews to date on the most popular CAM modalities for atopic eczema, namely, Chinese herbal medicine, homeopathy, herbal medicines and dietary supplements in order to provide objective information on their efficacy and safety in light of the most recent findings.
- To conduct a systematic review of controlled trials with all topical herbal therapies for atopic eczema.
- To conduct a cross-sectional study amongst atopic eczema patients exploring the demographics of CAM users, extent and determinants of CAM use.
- To conduct a cross-sectional study surveying dermatologists, paediatricians, general practitioners and pharmacists exploring their knowledge, awareness of use, recommendations and attitude on CAM use.

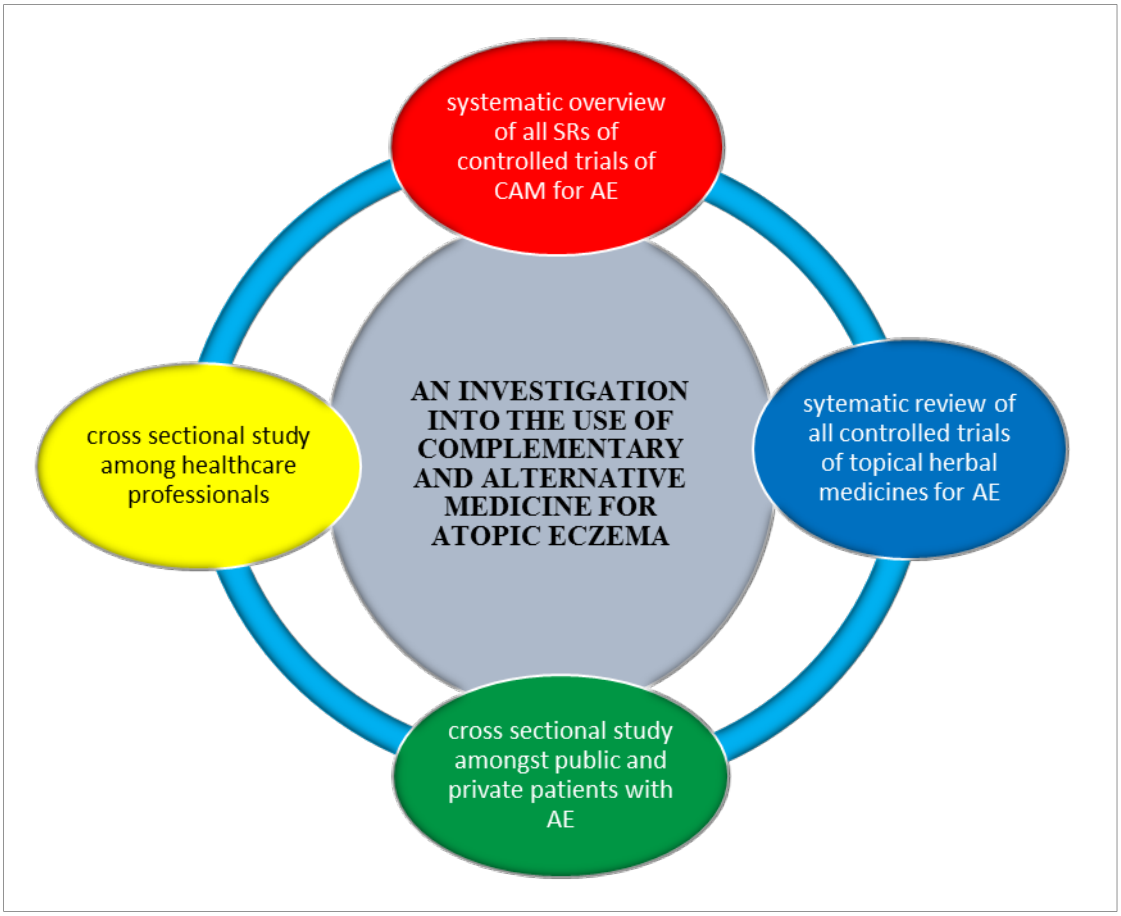

Figure 1 Summary of Aim and Key Objectives of this Research

1.2. METHODOLOGY

1.2.1. Methodology for Objective One

In order to achieve Objective One as detailed in the research description, "An overview of Systematic Reviews", literature searches were carried out using the following databases: Summon, EBSCO, PubMed, Google Scholar and Cochrane Library up to November 2013. The search terms used were 'eczema/dermatitis', 'review', 'systematic review' accompanied by the terms 'Chinese herbal medicines', 'homeopathy',' herbal therapy', 'probiotics', 'evening primrose oil', 'dietary supplements', 'complementary medicine', 'alternative treatment', 'adjunctive therapy'. The bibliographies of all included SRs were scanned for further relevant references. Only SRs of controlled clinical trials with participants of any age with eczema in peer reviewed journals of English origin were reviewed. This overview presents the findings from the most recent of these SRs.

1.2.2. Methodology for Objective Two

As detailed in the research description, Objective Two is a systematic review (SR) based on studies of controlled trials for topical herbal therapies. Although no protocol was registered with the Cochrane Collaboration; the leading source and gold standard for SRs, this SR was conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.[46]

The electronic databases that were searched from inception until June 2014 were: PubMed, Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (via EBSCO), MEDLINE (via EBSCO), Proquest Health and Medical Complete. Bibliographies of retrieved studies were hand-searched for other relevant trials. Subsequent searches were conducted on additional databases, CAM-quest and GREAT.

Varying search terms were used and adjusted according to the suitability for the different databases. Search terms were 'atopic eczema/atopic dermatitis' together with 'topical herbal', 'topical application', 'topical administration', 'plant extract', 'natural', 'cream', 'ointment' and their synonyms.

All controlled clinical trials published in English that tested a topical herbal medicine for AE in human patients of any age, regardless of the control intervention or randomisation, were included. All patients had to be clinically diagnosed with AE. Studies that were excluded were studies on other types of eczema (e.g. hand eczema) and where the type of eczema was not clearly classified (e.g. chronic eczema). Other exclusions were case reports, case series and clinical trials that were not conducted within a controlled environment.

Two independent reviewers (Thandar, Mosam) scrutinized the titles and abstracts of the initial search results. Thereafter a selection of full texts was made. Any discrepancies were clarified by two other independent reviewers (Botha, Gray). Data from included trials were extracted and tabulated by one reviewer (Thandar) and checked independantly by three other reviewers (Mosam, Botha, Gray). Study authors were contacted where clarity was required. The risk of bias (ROB) in each study was assessed by three independent reviewers (Thandar, Mosam, Gray) using the Cochrane domain-based evaluation.

1.2.3. Methodology for Objective Three

1.2.3.1.Study Design

A cross-sectional descriptive study design was used with the aid of interview-assisted questionnaires. Ethical approval for this study was obtained from the Biomedical Research and Ethics Committee of the University of KwaZulu-Natal (BE219/14).

1.2.3.2.Study Population and Study Location

Based on statistics on the number of patients with eczema seen on a monthly basis at King Edward VIII hospital, as well as independent private dermatological practices, the appropriate sample size was calculated. Using an extensively prepared questionnaire, a total of 206 patients were recruited. 106 patients were recruited from the outpatient dermatology clinic at King Edward VIII Hospital (KEH), a tertiary teaching hospital and the largest dermatology clinic in KwaZulu-Natal. The other 100 patients were recruited from five private dermatology practices in central Durban, KwaZulu-Natal. The reason for recruiting patients from both the public and private sector was to provide a broader demographic profile to the study population.

1.2.3.3.Methodology

Using the structured questionnaire, public patients were interviewed face-to-face whereas patients recruited from private practices were interviewed telephonically. In the case where the patient was a child, the parent or primary care-giver was interviewed. A Zulu-speaking translator was present during all interviews with public patients as this is the main language of the Black African population in KwaZulu-Natal and patients attending the outpatient dermatology clinic were predominantly from this population group.

Public patients were recruited over a three-month period (September 2014-November 2014) and private patients over a six-month period (January 2015-July 2015). The study sample included patients of all ages with atopic eczema. Patients all had an existing confirmed diagnosis of atopic eczema by a consulting dermatologist at the outpatient clinic or private practice.

An informed written consent was obtained from public patients whereas a verbal consent was obtained telephonically with private patients.

The questionnaire was initially administered to a pilot group of 10 patients. This enabled us to make necessary changes to questions that were ambiguous, and add appropriate questions that enable the easy lead- on to questions that follow.

1.2.3.4. Statistical analyses

Data was analysed using Stata 13.0 SE (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Relationships between continuous predictors and CAM use were assessed using a standard t-test. One-way analysis of variance (ANOVA) was employed to compare means of continuous predictors across 3 or more groups. Differences in frequencies of categorical explanatory variables by CAM and AE were assessed using Pearson chi-square (χ^2) test or Fishers exact test if an expected cell count contained fewer than 5 observations. A p-value of <0.05 was deemed statistically significant.

1.2.4. Methodology for Objective Four

1.2.4.1.Study Design

A cross-sectional descriptive study design was implemented. Ethical approval for this study was obtained from the Biomedical Research and Ethics Committee of the University of KwaZulu-Natal (BE219/14).

1.2.4.2.Study Participants

Using emailed and hand-delivered questionnaires, participants were recruited to participate in this survey. General practitioners (GPs), dermatologists, paediatricians and pharmacists who were all practicing in private practice in Durban and surrounding areas (within 20km radius of Durban), Kwa-Zulu Natal were randomly selected using a register, professional societies' databases and telephone directory for registered GPs, pharmacies, dermatologists and paediatricians. All HCPs had to be practicing in a private practice where they treat AE patients, however, dermatologists and paediatricians were also considered if they consult in the public sector. Participants were recruited between October 2014 and February 2015. Sample sizes were calculated based on population estimates in Durban and surrounding areas of each type of healthcare professional represented in the study and were confirmed with a biostatistician. A total of 823 healthcare practitioners were recruited. These included 34 dermatologists, 61 paediatricians, 570 general practitioners and 158 retail pharmacists. The percentage response rates are highlighted in Manuscript Four.

1.2.4.3.Data Collection

Participants were sent a direct email with a link to the questionnaire. Questionnaires were also hand-delivered to HCPs practicing nearby. They were asked to complete and return the questionnaire within 10 working days. Three reminders were sent electronically after 10, 15 and 20 working days. Reminder telephone calls were also made to many HCPs. Where accessible, the researcher or research assistant approached participants directly requesting a short time for them to answer the questionnaire.

1.2.4.4.Data analysis

Data was analysed using Stata 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Categorical data were summarised using frequencies and percentages. Association between type of HCP and attitudes, familiarity and practice using CAM variables were assessed using the Pearson chi-square ($\chi 2$) test and Fishers exact test if any cell count contained fewer than 5 expected observations. A p-value <0.05 was considered as being statistically significant.

1.2.5. Data Storage

All data is currently stored in a password protected file on the primary researcher's PC. The data will be kept for a period of 10 years post analyses. Thereafter, it will be electronically deleted. Hard copies of completed surveys are currently stored in a locked cupboard in the primary researcher's office and will be shredded after 10 years.

1.3. STRUCTURE OF THIS DISSERTATION

Chapter One outlines the background and reviews the literature, problem statement, significance of the study, aim and objectives of the study and the structure of the dissertation. It also describes the methodology that was used for data collection and data management. The methods of statistical analyses are also discussed in this chapter.

Chapter Two consists of the first manuscript that addresses **Objective One**. This has been published in the accredited and peer-reviewed journal, *South African Family Practice*. The citation is as follows:

Complementary Therapy in Atopic Eczema: The Latest Systematic Reviews

Thandar Y, Botha J, Mosam A

South African Family Practice 2014; 56(4):216-219

http://dx.doi.org/10.1080/20786190.2014.953864

Chapter Three consists of the second manuscript that addresses **Objective Two**. This has been accepted for publication in the accredited and peer-reviewed *British Journal of Dermatology*. The citation is as follows:

Topical Herbal Medicines for Atopic Eczema: A Systematic Review of Randomised Controlled Trials

Thandar Y, Gray A, Botha J, Mosam A

British Journal of Dermatology 2016 Jul 4; doi: 10.1111/bjd.14840. [Epub ahead of print]

Chapter Four consists of a third manuscript that addresses **Objective Three**. This has been submitted for publication and is currently under review in the accredited and peer-reviewed *Health SA Gesondheid*. The paper is entitled:

Complementary and Alternative Medicine Use amongst patients with Atopic Eczema - a South African Perspective

Thandar Y, Botha J, Sartorius B, Mosam A

Health SA Gesondheid, submitted August 2016, Manuscript number HSAG-D-16-00045 [under review]

Chapter Five consists of a fourth manuscript that addresses **Objective Four**. This has been accepted for publication in the accredited and peer-reviewed journal, *South African Family Practice* and is entitled:

Knowledge, Attitude and Practices of South African Healthcare Professionals towards Complementary and Alternative Medicine Use for Atopic Eczema - A Descriptive Survey

Thandar Y, Botha J, Sartorius B, Mosam A

South African Family Practice, 2016 Sept 26; Manuscript number SAFPJ-2016-0058; doi: 10.1080/20786190.2016.1248146 [in press]

Chapter Six consists of the synthesis of the study and the conclusion. This chapter also includes limitations and recommendations for further studies.

1.4. LITERATURE REVIEW

1.4.1. CAM and its Global Prevalence

A uniform or consistent definition of complementary and alternative medicine does not exist across the literature. However, according to the National Centre of Complementary and Alternative Medicine (NCCAM), complementary and alternative medicine (CAM) is defined as "a group of diverse medical and healthcare systems, practices, and products that are not generally considered part of conventional medicine". "Complementary medicine" refers to use of CAM together with conventional medicine and "Alternative medicine" refers to use of CAM in place of conventional medicine.[47] Many of the techniques used as CAM therapy are the subject of controversy and have not been validated by controlled studies. They are also regarded as having no scientific basis for which no effective or diagnostic reliability has been demonstrated by scientific methods.[48] The use of CAM however, is recognised as abundant around the world and is shown to be increasing. The World Health Organization estimates that 65%-80% of the World's population uses Complementary and Traditional Medicine as their primary form of healthcare.[49, 50]

According to the 2007 National Health and Statistics report in the United States, 4 out of 10 adults had used CAM therapy in the past 12 months. In this report, data from a 2007 National Health Interview Survey (NHIS) revealed that approximately one in nine children used CAM therapy in the last 12 months preceding the survey. Some of the reasons for choosing CAM include the relief of symptoms associated with chronic, even terminal illnesses and the side effects of conventional medicines. Other reasons included were a holistic health philosophy and wanting greater control of one's own health[51].

According to the European Federation of Complementary and Alternative Medicine (UFCAM), CAM is being increasingly used by citizens across Europe as a means of maintaining their health and for treating ill-health.[52] In 2012, Zuzak et al. published data which revealed that 56% of the European population had used CAM in the last year and the prevalence of CAM use by children in Europe was 52%.[53] An Australian survey in 1992/1993 found that 48,5% of the population used at least one non-medically prescribed alternative therapy modality and in a 2006 study it was estimated that Australians spent 1.31 billion AUD on complementary medicines.[54, 55]

A South African study conducted by Peltzer in 2009 reviewing all published and unpublished research investigating the prevalence of traditional medicine (TM) and complementary and alternative medicine (CAM) in the general population, showed a decline in TM use but an increase in the range of CAM use over the past 13 years. Local population-based and health facility-based surveys seem to indicate that TM and CAM use still plays an important role in healthcare delivery in South Africa, covering a wide range of conditions from chronic conditions, acute conditions, complex supernatural or psychosocial problems, generalised pain, HIV and other sexually transmitted infections. A lack of data about CAM use in the varying conditions was reported.[24]

1.4.2. CAM use in Dermatology

An extensive literature search revealed a number of studies on the growing prevalence of CAM amongst patients with dermatological conditions. In a study showing trends of CAM use in the United States, 6.7% of patients who reported having skin problems over the last 12 months, used alternative therapy for their condition and 2.2% visited an alternative practitioner for their skin condition.[56] Another study showing an overview on the use of CAM for skin diseases in the United States reported that, in a 2009 study, 49.4% of patients with skin problems have used CAM within the previous year and 6% had used it specifically for their skin disease.[57]

According to a 2007 review on the use of CAM in skin diseases by Magin and Adams, 14% of patients attending a UK National Health Service CAM clinic, did so for skin conditions and 16% of British dermatological outpatients used CAM for their skin disease.[58] Another UK based study conducted in Leeds and South Wales and published in 2005, investigated CAM in a large population of outpatients with general dermatological conditions and found that of the 39% of patients that used CAM in Leeds, 45% of them used it for dermatological conditions and of the 34% using CAM in South Wales, 50% was for dermatological conditions. This study also revealed that the majority of CAM use was for treatment of eczema and psoriasis, and herbal medicine and homeopathy were the most popular complementary therapies used.[59] In an Israeli study, 6.9% of the 19% of general practice patients who used CAM, did so for their skin disease.[58]

The types of skin diseases where CAM use has been documented are vast and include acne, psoriasis, certain skin malignancies and atopic eczema.[60] In a cross-sectional South African-based study conducted in 2000-2001 in an Indian community in Chatsworth which explored the prevalence and patterns of CAM usage for general ailments, the prevalence was 38.5%. Of this,

16.9% of usage was for skin disorders.[22] From the literature, there have been no studies done in South Africa investigating the use of CAM in skin diseases in particular.

1.4.3. CAM use by Patients with Atopic Eczema

Several international studies have explored the use of CAM in dermatitis, both allergic contact as well as atopic dermatitis/eczema. Once such study in Denmark conducted between 2000 and 2003 reviewed the use of CAM in patients with allergic contact dermatitis. In this particular study it was found that 40% of patients used CAM (predominantly in combination with conventional treatment), 29% had visited an alternate practitioner, women were more frequent users of CAM and patients from urban/rural districts were more frequent users than patients from the capital city area. It was also noted that frequent eczema eruptions, hand eczema, long duration of the disease and work-related problems were positively associated with the use of CAM.[17] This is in keeping with other studies that have also positively related the use of CAM with disease severity and duration, rather than the type of dermatological condition.[61] The study by Noiesen et al. concluded that the use of CAM was not an alternative to conventional medicine, but a supplement, or complementary.[17]

In a European study describing the epidemiological characteristics and determinants of the use of CAM, it was reported that 30-50% of patients with allergies have had experiences with CAM. Users of CAM tend to be younger women with a higher educational background. Users and non-users of CAM differed in their psychomedical characteristics, such as health locus of control or health-related quality of life. Although a large number of different CAM modalities are provided, the techniques which account for the majority of use were acupuncture, homoeopathy, herbalism, bioresonance and autologous blood injection. In Germany, the use of CAM was associated with considerable costs despite its limited evidence of efficacy.[62] Although this study focussed on allergies in general, it provides a good overview of the demographic profile of CAM users.

Of the studies qualifying and quantifying the use of CAM in children with atopic eczema, a 2002 study conducted in a teaching hospital in Leicester in the United Kingdom found that 63% of the subjects had used or intended to use CAM for their eczema. There was a strong association between the use of CAM and ethnicity, the majority of patients being from the Indian subcontinent. The most popular CAM modalities used were Chinese herbal medicine (41%), followed by herbal medicines (41%) and homoeopathy (35%). Half of the CAM users used it on the recommendation of family and friends with skin disease, 37% from family or friends without

skin disease and 6% each from health professionals, the media and the internet. 54% used CAM because conventional medicine was not working and 17% used CAM because they were concerned about the side effects of conventional medicines. While 39% of all patients felt that CAM was safer than conventional medicines, only 14% felt it was more efficacious. More than half of the patients were happy to combine CAM treatments with their conventional treatment and 66% of patients felt that CAM should be available from the National Health Service. 35% of patients using CAM felt that their eczema had improved while 53% reported that it remained unchanged [9]. The results regarding the use of the CAM modality adopted and its impact on the eczema was based on patients' responses and no validated assessment on disease severity or health-related quality of life over time was assessed. Hence, the overall impact of CAM on the disease could not be assessed.

Another cross-sectional study carried out amongst paediatric patients with atopic eczema within a university teaching hospital in Dublin, Ireland was published in 2007. This study assessed the prevalence of CAM and the varying factors associated with its use. Duration of treatment, reasons for trying CAM, approximate cost and success of treatment, duration of childhood eczema, and hospital admission due to eczema were assessed. Of the patients' assessed, 42.5% had used either one type or more than one type of CAM modality. Herbal remedies (41%) and homoeopathy (23.5%) were most frequently used. The most commonly cited reasons for trying alternative therapies were a recommendation from others (47%), a fear of steroid side effects (26.4%) and dissatisfaction of conventional treatment (17.6%). Most treatments were reported to show no improvement (57.7%) and 44.1% reported some improvement with CAM use, mostly a reduction in itching. In almost 10% of patients, deterioration was reported. An average cost of treatment with CAM was estimated around 322 Euros. The study also demonstrated that the overall severity of eczema in both users and non-users were similar.[8]

Other studies investigating the extent of CAM use amongst atopic eczema patients were conducted in Korea where it was found that 69% of patients used CAM,[19] Norway (51%)[21] and the US (50%).[20]

Many of the findings in the study in Dublin were similar to the study carried out in Leicester however, the majority of CAM users in Dublin were indigenous Irish which is a contrast to the majority ethnic origin (and of Indian decent) in the Leicester study. In both studies, a disease severity score was not performed and severity was estimated based on the patients' response on the questionnaire and in the number of admissions to hospital, as in the latter study; thus making

the evidence of CAM's efficacy subjective. Both studies were also unable to determine whether those with more severe disease were more likely to experiment with CAM. The population in these studies were predominantly of low socio-economic status (as in the Dublin study) or from an ethnic minority (as in the Leicester study). Other research has demonstrated that children with higher socio-economic status are more affected with atopic eczema than children from poorer families.[63]

Considering that no South African studies have been conducted in this field, we are thus unaware if differences lie between users of CAM from different socio-economic backgrounds and different racial groups. The South African environment, with its multiracial, multi-ethnic and diverse socio-economic backgrounds provides an ideal backdrop to determine whether such variables influence the use of CAM. Furthermore, no South African based studies have been conducted describing trends of use of CAM within the country's demographic context. There are also no published data providing evidence of the varying types of alternative medicines patients are currently employing for their eczema.

1.4.4. The Most Common CAM modalities used by Patients with Atopic Eczema

From the literature, it was found that the most commonly reported CAM modalities used for atopic eczema were Chinese herbal medicine (41%), followed by herbal medicines (41%) and homoeopathy (35%) which was reported in the Leicester study[9] and herbal medicines (41%) and homoeopathy (23.5%) in a study in Dublin, Ireland.[8] A study in Korea reported frequent use of Oriental medicines (26%), and bath therapy (21%)[19]. Vitamins and herbal creams were commonly used in a US based study.[20] Among patients in Norway, herbal medicines (19%) and homeopathy (34%) were reportedly commonly used.[21] This study, together with the Korean based study also documented a fairly high usage of health food preparations, 18% and 17% respectively.

As homeopathy was commonly reported to be favoured amongst patients exploring CAM in several studies, a literature review of this modality was undertaken in interest of determining its evidence-based effect for atopic eczema. It was found that the literature demonstrated a conflicting evidence of efficacy from the trials that were reported in homeopathy.

Witt *et al*. have reported that one in five children visiting a homoeopathic physician is suffering from atopic eczema.[14] In a multicentre cohort study in Germany and Switzerland investigating homoepathic practices, it was identified that atopic eczema in children was amongst the most

frequent diagnoses together with other chronic diseases. This study assessed disease severity and quality of life at intervals during a 2 year period and the results showed that patient and physician assessment of disease severity and quality of life demonstrated marked and sustained improvements following a homoeopathic treatment period. This improvement was more pronounced in younger patients and those with greater disease severity. In this study, patients were allowed to use conventional therapies in addition to homoeopathic treatment during the study period and thus the observed improvement cannot be attributed to homoeopathic treatment alone.[11] As the results of this study was not only demonstrative of atopic eczema but included other chronic illnesses like allergic rhinitis and headache in adults and children, a further study conducted by Witt et al. which had a clear disease-specific and children-specific approach, focussed on the comparison of homoeopathic versus conventional treatment in children with atopic eczema. The outcome measures was the Scoring Atopic Dermatitis (SCORAD), at 6 and 12 months respectively as well as quality of life in parents and children, use of conventional medicine, disease-related costs, response rates and safety of treatment at 6 and 12 months. There were no significant differences as shown between the groups for the SCORAD at 6 and 12 months and quality of life was also comparable between the groups. However, costs were higher in the homoeopathic group than in the conventional group.[14]

For homeopathy as an example, the two studies by Witt et al. have shown conflicting results thus making any conclusions about efficacy impossible.[11, 14] Reports of efficacy of many of the other popular alternative therapies are also contradictory[64] and the vast available literature and published data are filled with shortcomings making it difficult for doctors to evaluate whether or not there is any role for them in the management of eczema.[65]

To assess their evidence, systematic reviews (SR) of controlled clinical trials, which are critical to any evidence based practice of medicine, have been undertaken for CHM,[12, 13, 34] homeopathy,[10] oral herbal remedies including evening primrose oil (EPO), borage oil (BO),[35] probiotics [36] and certain dietary supplements.[37] On assessing these SRs, many of them were varied in their conclusions. It became evident that a thorough scrutiny and analysis of these SRs is needed and is imperative to be able to provide objective information to busy, often sceptical allopathic practitioners regarding the current evidence of CAM in AE.

Several published studies have made reference to the wide use of topical herbal creams e.g. chamomile [38, 39], licorice gel [40] and St John's wort [41] for atopic eczema. Trials with other types of topicals have also been conducted including hamamelis distillate cream[42] and unani formulation.[43]

Although not tested in clinical trials, some traditional herbal medicines common in the Pakistan have also been reported to be effective for eczema.[44] Massage therapy with essential oils have also been explored for atopic eczema.[45] Evidence of efficacy varies amongst the topical treatments and only few have been tested in controlled trials. Upon sifting through the various SRs of the diverse CAM therapies, it became evident that no SRs have been conducted for topical herbal therapies thus making it difficult to evaluate their efficacy. A SR on all controlled trials with topical CAM treatments will undoubtedly provide conclusions which are currently lacking in the literature with regards to their efficacy and safety in atopic eczema.

1.4.5. Patients and the Determinants for the Use of CAM

It is imperative from both academic and applied perspectives to understand why such substantial numbers of people use CAM. Many reasons have already been cited in the literature. Frequently cited reasons was the dissatisfaction with the therapeutic results from conventional medicines, the concern about the side effects of conventional medicines particularly the steroids, and the perceived safety of CAM compared to conventional medicines. [8, 9] Some used CAM mainly on a recommendation from others.[8, 9, 19]

A systematic review of beliefs involved in the use of CAM was collated and synthesised in 2007 by Bishop *et al*. The evidence suggests that CAM users want to participate in treatment decisions, are likely to have active coping styles and might believe that they can control their health. They value non-toxic, holistic approaches to health and hold 'postmodern belief systems' while viewing themselves as unconventional and spiritual. CAM users also tend to believe that psychological and lifestyle factors are important in the development of illness. There is evidence that different variables are associated with CAM use in groups of CAM users that differ according to different illness groups.[66] It is however difficult to determine with any confidence whether pro-CAM beliefs are held prior to and influence CAM use or are actually a result of CAM experiences.

There is no literature available within the South African context that has investigated patients motivations for CAM use. Considering that local studies in this field are lacking and given the popularity of CAM, a South African based study would help to understand why people use CAM and may generate factors that can predict CAM use. Such information is of interest to dermatologists and other practitioners, helping them to understand better their patients' use and motivations for using CAM and possibly to improve practitioner-patient communication concerning both conventional medicine and CAM. Also, certain aspects of CAM use that are

valued by patients such as holistic and patient-centred care may be incorporated when treating with conventional medicine. An understanding of patients' beliefs may help to guide practitioners in educating their patients with regards to their perceptions that all CAMs are "natural" and "safe" and steroids are harmful.

1.4.6. CAM and the Healthcare Practitioner

Despite the dramatic increase in the general use of CAM, whether for an existing illness or for the purpose of prevention or maintenance of health, the extent to which patients disclose their use of any alternative therapy to their medical practitioner remains low. This was seen in a follow-up national survey by Eisenberg et al. which revealed that less than 40% of the alternative therapies used were disclosed to a physician in both 1990 and 1997.[56] The literature has also demonstrated that patients often do not inform their dermatologist about their use of CAM and the dermatologists' ability to predict CAM use in their patients has been found to be poor.[25] The doctor's knowledge about a patient's use of CAM may lead to a better understanding of the patient's attitude to the disease and subsequently help to achieve better patient compliance.[17]

According to Zhang et al., there exists barriers in communication between patient and physician which include reluctance to disclose CAM use, physicians not asking about CAM use and patients perceiving that their physicians are unwilling to discuss CAM therapies.[67] In a Netherlands based study amongst paediatricians it was found that 62% of paediatricians seldom ask parents of patients about CAM use.[28] It has also been reported that physicians generally underestimate the prevalence of CAM use among their patients.[68] This confirms a definite discrepancy between the patients' use and the familiarity of the healthcare practitioner with CAM. These practices of the healthcare practitioner relates directly to their attitudes and knowledge of CAM.

A 2010 Qatar based study exploring the attitudes, knowledge and practice of general practitioners towards CAM, revealed that 39.1% of doctors reported poor knowledge about CAM. It is interesting to note that 83.8% described their attitude to CAM as welcoming and 97.5% were interested to learn more about it, fewer (30.1%) had practised it before or asked patients' about their use of CAM (34.8%). Their own lack of knowledge and training in CAM was seen as a barrier to its use by 60.0% of the general practitioners.[26]

Several other studies have also demonstrated a positive attitude from the healthcare practitioner towards CAM. In a study amongst primary care providers at a Family Medicine Clinic in West

Texas, 75% believed that incorporating CAM into general practice would be positive and 70% believed that the institution should offer proven CAM therapies to patients.[31] Saudi Arabian primary healthcare physicians generally showed a positive attitude towards CAM and believed that it would lead to a better patient outcome but demonstrated reluctance to discuss with patients or refer patients. This may be due to a lack of knowledge as 85% agreed that physicians should have knowledge about CAM.[69] This is consistent with many other studies including a Netherlands based study where more than 50% of paediatricians admitted that they had little knowledge of CAM.[28] Also, in a study in Brisbane, Australia, pharmacists have confirmed that although there may be potential benefits for patients, a lack of knowledge about safety were definite barriers to their recommendation. However, despite their lack of knowledge, they often recommend CAM alongside conventional medication as part of their pharmacy protocol.[27] In an exploratory survey in California assessing doctors attitudes towards their patients use of CAM, and their willingness to prescribe and enquire about CAM, 61% did not feel sufficiently knowledgeable about CAMs' efficacy or safety and 81% would like to receive more education.[70]

From the literature review, it can be seen that most healthcare practitioners acknowledge their lack of knowledge on CAM and want to be more informed about safety and efficacy of commonly used CAM products. Many have recommended that CAM should be taught in the undergraduate study and included into medical and pharmacy curricula.[27, 32, 71] These findings raise important issues for medical education and patient care. The scenario between high acceptance levels with regards to CAM and poor knowledge can be viewed as critical, demanding urgent intervention to bridge the gap.[72]

On the contrary, there are some studies that have demonstrated scepticism and uncertainty about the value of CAM. One distinct study conducted in Bristol, UK explored views of academic doctors who have a dual academic and clinical role. The majority were doubtful with the reasons being related to their perspective on the scientific evidence base. Some were more open to it as a result of personal experience shaping their views. Despite this, most acknowledged that better doctor-patient communication and patient disclosure is required. However, their views on educating themselves on CAM were varied.[30]

Only one similar study was found in South Africa. Considering that traditional, complementary and alternative medicines (TCAM) are commonly reported to be used amongst HIV and AIDS patients, the HIV/AIDS clinics in Durban were the selected backdrop. The study involved all categories of healthcare workers in these clinics, including doctors, nurses, counsellors,

psychologists and social workers, and examined their knowledge, attitudes and practices regarding various TCAM professions (and not select medicines). The results demonstrated a lack of basic knowledge amongst the majority on TCAM.[33]

The studies in this literature review have demonstrated attitudes, knowledge and practices of various healthcare professionals on the general use of CAM. This provides a good insight, however, no published work has been found on the knowledge, attitudes and practices of healthcare professionals on CAM use when treating patients with eczema. The widespread use of CAM in atopic eczema has been confirmed, however the role and familiarity of the GP, dermatologist, paediatrician or pharmacist and their viewpoints and recommendations on CAM for atopic eczema are currently unexplored.

Considering that CAM and conventional medicine are often used together,[17, 58] the potential for confusion in attribution of therapeutic benefits, adverse effects and drug interactions is clear as well as the potential for non-compliance with prescribed therapy. An appreciation by physicians of when and why their patients with skin disease may be using CAM therapies is essential.[58] Dermatologists, paediatricians and general practitioners need to be conversant with common CAM therapies and their influence on the overall clinical outcome of the patient. Enquiries with regards to alternative medicine use in dermatology patients is essential given that most alternative therapies are subject to minimal regulation and may give rise to side effects.[8] Since many CAMs are unregulated and easily accessible, pharmacists are often the very first to be consulted on their usage by patients with eczema. Also, information from pharmacists would help assess what CAM products are frequently asked for and sold to patients with eczema.

2. CHAPTER TWO

2.1. MANUSCRIPT ONE (PUBLISHED)

Complementary Therapy in Atopic Eczema: The Latest Systematic Reviews

Thandar Y, Botha J, Mosam A

South African Family Practice 2014; 56(4):216-219
http://dx.doi.org/10.1080/20786190.2014.953864

The contents of this chapter is in the form of a published paper. This paper has met Objective one of this thesis.

From the literature review, it was highlighted that the most frequently explored common modalities for atopic eczema in various international studies were: Chinese herbal medicines, homeopathy, herbal medicines and dietary supplements.

Due to conflicting evidence of efficacy in many papers, this study investigated and collated the findings from the most recently published systematic reviews in order to determine objective information on their efficacy and safety.

In so doing, the results from this study are able to provide practitioners with a comprehensive and succinct report as to the current evidence base of each of these treatments in light of the most recent findings.

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REVIEW

Complementary therapy in atopic eczema: the latest systematic reviews

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Complementary and alternative medicines (CAM) are widely used for atopic eczema (AE) with user estimates as high as 63%. Despite the availability of effective conventional therapies, the chronic nature of AE and concerns about long-term steroid use lead many patients to seek alternative treatment. Evidence of the efficacy of these alternative therapies is inconsistent and available published data have shortcomings, making it difficult for clinicians to assess their role, if any, in management. To assess the evidence, systematic reviews of controlled studies have been undertaken for Chinese herbal medicines, homeopathy, evening primrose oil, borage oil, probiotics and certain dietary supplements. This overview summarises the findings from the most recent systematic reviews. Taken together, none of the alternative therapies evaluated demonstrated obvious and indisputable evidence of efficacy. Further studies are warranted with some therapies (Chinese herbal medicines, certain probiotic strains and fish oil), whereas homeopathy failed to show any treatment effect. Further studies on homeopathy, or evening primrose oil and borage oil, are difficult to justify. It must also be remembered that CAM products are currently under-regulated and may not meet the stringent quality standards of conventional medicines.

Keywords: alternative medicine, atopic eczema, complementary, dermatitis

Introduction

Atopic eczema (AE) is the most common skin condition with a prevalence of 2–7% in adults and 7–20% in children, with an approximate doubling of the lifetime prevalence in South Africa over the last decade.[1] Numerous studies have demonstrated the popularity of complementary and alternative medicines (CAM) for AE.[2–5] Although effective conventional therapies exist, the nature of the disease, with remissions and relapses, its chronicity and the fear of long-term steroid use, especially in children, encourages patients to seek out CAM which they perceive to be safe. Despite limited evidence of efficacy, CAM is associated with considerable expense, and some patients spend more on certain alternative therapies than they do on conventional medicines.[6,7] Besides complicating overall management, this reduces funds that patients would otherwise invest in medication with proven reliability, thus delaying a positive clinical outcome.

Studies have indicated that CAM modalities, which are particularly popular for AE, include Chinese herbal medicines, herbal medicines and homeopathy.[2,4] Reports of the efficacy of these alternative therapies are contradictory,[8] and the vast literature is filled with shortcomings. This makes it difficult for clinicians to evaluate whether or not there is any role for them in management.[9] Systematic reviews of randomised controlled studies (RCTs) are central to any evidence-based practice of medicine. Systematic reviews have been undertaken for Chinese herbal medicines, homeopathy, oral herbal remedies, including evening primrose oil and borage oil, probiotics and certain dietary supplements.

This overview aims to summarise the findings from the most recently published systematic reviews in order to provide objective information to busy, often sceptical allopathic practitioners regarding the evidence of CAM in AE.

Method

Literature searches were carried out using the following databases: Summon, EBSCO, PubMed, Google Scholar and Cochrane Library up to November 2013. Search terms were "eczema", "dermatitis", "review", and "systematic review", in combination with "Chinese herbal medicines", "homeopathy", "herbal therapy" "probiotics", "evening primrose oil", "dietary supplements", "complementary medicine", "alternative treatment" and "adjunctive therapy". Only English systematic reviews in peer-reviewed journals, involving controlled clinical trials with eczema patients of any age, were reviewed. This overview presents the findings from the most recent of these systematic reviews.

Chinese herbal medicines

Three systematic reviews were identified, one of which, from 1999,[10] included only two RCTs that were dealt with in both subsequent systematic reviews. In 2010, the Cochrane Collaboration reviewed four RCTs of Zermaphyte® and concluded that it may be effective in AE, although the studies were small and heterogenous. Interestingly, this product is no longer manufactured.[11] The most recent systematic review, published in 2013 by Tan et al, included RCTs of Zermaphyte®, as well as other Chinese herbal medicines. Among the inclusion criteria were studies published in English or Chinese, patients of all ages diagnosed with AE, and "placebo", "pharmacotherapy" or "no treatment" as the control intervention. Outcome measures were disease or symptom severity scoring, quality of life, concurrent therapy use and adverse events. Other forms of Chinese herbal medicines, e.g. acupuncture, topical Chinese herbal medicines and other types of dermatitis were excluded.[12] Seven RCTs were selected, but as there were insufficient data for one, the authors included only six. The individual results of these are summarised in Table 1.

A meta-analysis was attempted and although it favoured Chinese herbal medicines in three placebo-controlled trials, two of these

Table 1: Summary of randomised controlled trials of Chinese herbal medicines for atopic eczema.

Publication	Participants	Study rationale and design	Results
Sheehan MP & Atherton DJ. Br J Dermatol. 1992 126:179-84.	Children	*Double-blind crossover RCT:* Chinese herbal medicines (Zermaphyte®) ($n = 47$) versus placebo ($n = 47$)	Chinese herbal medicines more effective than placebo
Sheehan MP et al. Lancet. 1992 340: 13-7.	Adults (16–65 years)	*Double-blind crossover RCT:* Chinese herbal medicines (Zermaphyte®) ($n = 40$) versus placebo ($n = 40$)	Chinese herbal medicines more effective than placebo
Huang YQ et al. Shan Xi Zhong Yi. 2004 5:396-8.	Children (3–11 years)	*Single-blind RCT:* Chinese herbal medicines (*Jian Pi Shen Shi*) ($n = 49$) versus Western medicine ($n = 49$)	Chinese herbal medicines and Western medicine are more effective than Western medicine alone
Hon KLE et al. Br J Dermatol. 2007 157:357-63.	Children and adults (5–21 years)	*Double-blind RCT:* Chinese herbal medicines (pentaherbs) ($n = 42$) versus placebo ($n = 43$)	Chinese herbal medicines have significantly improved quality of life No significant difference in clinical scores
Kobayashi H et al. Evid Based Complement Alternat Med. 2010 7:367-73.	Adults (20–40 years)	*Double-blind RCT:* Chinese herbal medicines (*Hochu-ekki-to*) ($n = 43$) versus placebo ($n = 48$)	No significant difference in clinical scores
Cheng HM et al. Int Arch Allergy Immunol. 2001 155:141-8.	Age not specified	*Double-blind RCT:* Chinese herbal medicines (*Xiao-Feng-San*) ($n = 47$) versus placebo ($n = 24$)	Chinese herbal medicines more effective than placebo

RCT: randomised controlled trial

showed a high risk of bias. In addition, we noted that these two were crossover studies with short washout periods, which made any certainty about baseline equivalence impossible. There was also a high risk of bias in the WM study. Details on blinding and a lack-of-intention-to-treat analysis led to incomplete outcome data. Overall, the authors suggested that the results should be viewed with caution as there was a low risk of bias in only one study.

Although no severe adverse events were reported in any of the studies, their poor quality and heterogeneity meant that valid conclusions about the safety and effectiveness of Chinese herbal medicines in AE could not be made. The authors proposed that further studies with improved methodology are warranted.[12]

Homeopathy

Homeopathy is based on two main beliefs, namely that "like cures like" and that remedies retain biological activity after repeated dilution and sucussion.[13,14] Despite being of doubtful value, it is still popular for treating eczema.[15] Therefore, we were surprised to find only one systematic review. The author of this systematic review was equally surprised to find only three controlled clinical trials which met his inclusion criteria of testing homeopathic remedies, regardless of the control intervention or randomisation.[15] Table 2 summarises these trials. Only one was a RCT and despite terminating in 2002, was only published in 2009. It contained serious shortcomings, and after dropouts, only 14 patients completed the trial.

It was concluded in the systematic review that the totality of evidence from the three trials failed to show a treatment effect. None of the published trials was rigorous, and selection bias in the two that were not randomised may have resulted in false positive results. Considering the lack of RCTs, with the only one published that was too small to produce reliable findings, Ernst concluded that homeopathy is not supported by sound evidence.[15]

Probiotics

Intestinal microbiota have been shown to be altered in patients with eczema. While it is unknown whether or not this is causative or a result of the eczema, probiotics (live microorganisms) have been proposed to benefit eczematous patients.[16]

We found three recent systematic reviews, the latest published in 2009 by Boyle et al.[16] Being a Cochrane review, this was of high quality and according to the authors, superseded the previous two which had shown marginal and no clinical significance, respectively. This systematic review included 12 studies on live orally ingested bacteria, fungi or yeasts with participants who had doctor-diagnosed eczema. Control groups comprised "placebo", "no treatment" or "another non-microbial intervention", e.g. antibiotics, topical steroids

Table 2: Summary of controlled trials of homeopathy for atopic ezcema

Publication	Participants	Study rationale and design	Results
Keil T, et al. Complement Ther Med. 2008 16:15-21.	118 children (1–16 years)	Homeopathic (n = 54) versus conventional medicines (n = 64) Comparative cohort, open and non-randomised assessment at 0, 6 and 12 months	Similar improvement in perception of symptoms and quality of life (patient and parent) Ratings by physicians favoured homeopathy
Witt CM, et al. Dermatology. 2009 219:329-40.	135 children (1–14 years)	Homeopathic (n = 48) versus conventional medicines (n = 87) Comparative cohort, open and non-randomised assessment at 0, 6 and 12 months	No significant difference at 6 and 12 months Costs higher in the homeopathy group
Siebenwirth J, et al. Forsch Komplementarmed. 2009 16:315-23.	14 adults (18–35 years)	Homeopathic (n = 5) versus placebo (n = 11) *Double-blind RCT:* Treatment and monitoring for 32 weeks	No significant difference in any of the parameters, e.g. clinical score and quality of life

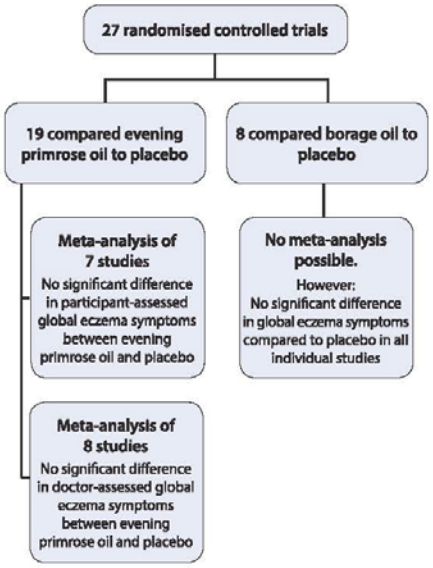

Figure 1: Summary of evening primrose oil and borage oil studies

or exclusion diets. The outcome measures were self-reported symptoms, quality of life, need for other eczema treatment, investigator-rated eczema severity and number of days lost from school or work due to eczema.[16] Seven trials assessed investigator-rated eczema severity at the end of treatment. They were all double-blind RCTs lasting between four and 12 weeks, and included between 48 and 252 children. Pooled data analysis of these showed no benefit for probiotic treatment for this outcome. Data from five of the studies suggested that probiotics do not reduce symptoms, such as itching and sleep disturbance. An analysis of studies in which quality of life or the need for other eczema treatment were reported, also found no benefit with probiotics.

A subgroup analysis comparing three studies using *Lactobacillus rhamnosus* GG with four others using other *Lactobacillus* strains found opposite results in the SCORAD (scoring atopic dermatitis) scores, suggesting a strain-specific effect. As a result, the reviewers concluded that research into as yet unstudied, probiotic strains may be warranted in eczema.[16]

When searching for adverse events, the authors found cases of bowel ischaemia and sepsis. Although these were not in studies on AE, it is clear that probiotics should not be used without a good indication and that AE is not an indication.

Evening primrose oil and borage oil

As natural sources of the essential fatty acid gamma-linoleic acid (GLA), it has been considered likely that evening primrose oil and borage oil improve eczema by favouring the synthesis of relatively non-inflammatory eicosanoids. Because of conflicting results regarding the efficacy and safety of GLA, including the findings of two systematic reviews published in 1989 and 2006, respectively, Bamford et al carried out a Cochrane review in 2013.[17] Twenty-seven RCTs were considered worthy of inclusion. Of parallel or crossover design, they investigated oral evening primrose oil or borage oil for doctor-diagnosed eczema in adults and children. Samples sizes ranged from 12-160 patients, and together involved 1 596 participants from 12 countries. The

Table 3: Summary of included randomised controlled trials of dietary supplements for eczema

Publication	Participants	Intervention and study design	Results
Bjorneboe A, et al. J Intern Med. 1989 225(731):233-6. Soyland E, et al. Br J Dermatol. 1994 130(6):757-64. Gimenez-Arnau A, et al. Adv in Exp Med Biol. 1997 433:285-9.	31 adults 145 adults 48 adults	Fish oil versus placebo Fish oil versus placebo Linoleic acid (sunflower oil) versus fish oil versus placebo	No significant difference for any primary outcomes in all three studies Significant difference in quality of life and area affected at the end of treatment with fish oil (pooled analysis of Bjorneboe and Soyland) Significant difference in improvement of itch with fish oil (Bjorneboe) No significant difference in any outcomes (Soyland) Significant difference in scores in favour of sunflower oil over both fish oil or placebo (but participant numbers in each arm unavailable) (Gimenez-Arnau)
Ewing CI et al. Eur J Clin Nutr. 1991 45(10):507-10.	50 children	Zinc versus placebo	No significant difference in severity at 8 weeks Parental-rated itch better in placebo
Fairris GM, et al. Acta DermVenereol. 1989 69(4):359-62.	60 adults	Selenium versus selenium plus vitamin E versus placebo	No significant difference in global severity scores No benefit for either treatment over placebo
Sidbury R, et al. Br J Dermatol. 2008 159(1): 245-247. Javanbakht MH, et al. J Dermatol. Treatm. 2011 22(3):144-50.	11 children 52 adults	Vitamin D versus placebo Vitamins D plus E versus two placebos versus vitamin D plus placebo versus vitamin E plus placebo	No significant difference of vitamin D over placebo in both studies No significant difference of vitamin E over placebo and significant difference in SCORAD at the end of treatment in favour of vitamin D and vitamin E over placebo (Javanbakht)
Mabin DC, et al. Br J Dermatol. 1995 133(5):764-7.	48 children	Pyridoxine hydrochloride versus placebo	No significant difference in global severity scores
Yang B, et al. J Nutr Biochem. 1999 10(11): 62-630.	78 adults	Sea buckthorn seed oil versus sea buckthorn pulp oil versus placebo	No significant difference in SCORAD at four weeks or four months between either group and placebo
Callaway J, et al. J Dermatol Treatm. 2005 16(2):87-94.	20 adults	Hempseed oil versus placebo (crossover study)	No benefit of hempseed oil over placebo Significant difference in skin dryness and itchiness (although subjective) in favour of hempseed oil
Koch C, et al. Br J Dermatol. 2008 158(4): 786-792.	53 adults	DHA versus isoenergetic control of saturated fatty acids	Significant decrease in SCORAD from baseline to eight weeks for DHA

DHA: docosahexanoic acid, SCORAD: scoring atopic dermatitis
Primary outcomes: symptom improvement at six weeks, decrease conventional treatment or flare ups

studies varied in duration of follow-up and assessed outcomes.[17] Primary outcome measures were firstly, the global degree of improvement in participant or doctor-rated signs and symptoms, and secondly, an improvement in quality of life. The results could be pooled for meta-analysis from studies where these end-points were reported in a similar manner. However, a meta-analysis was not possible in the borage oil studies because the results were reported in different ways. The main findings are summarised in Figure 1. Two studies of evening primrose oil measured quality of life, with only one reporting results, and these did not favour evening primrose oil over placebo.

Although the adverse events were largely minor, with no significant differences between the oils and placebo, long-term safety could not be assessed. The authors cautioned that evening primrose oil was reported in one study to increase bleeding in patients on warfarin. In another case report, prolonged use was associated with potential risk of inflammation, thrombosis and immunosuppression.[17]

The authors concluded that neither evening primrose oil nor borage oil had any benefit in eczema and that more studies would be difficult to justify because the narrow confidence intervals between active and placebo treatments excluded the possibility of any clinically useful difference.[17]

Dietary supplements

Dietary supplements are sometimes chosen by patients who believe that something lacking in their diet is aggravating their eczema.[18] A Cochrane review published by Bath-Hextall et al in 2012 is the most recent systematic review to evaluate the RCTs of an extensive range of dietary supplements for the treatment of doctor-diagnosed atopic eczema. Dietary supplements were compared with "placebo", "no treatment" or "another active intervention" in studies which were of various design, including two-, three- and four-arm parallel studies and one crossover study.[18] Eleven RCTs (596 patients) met the inclusion criteria and their individual results are summarised in Table 3.

The authors were not surprised that most of the studies found no significant differences as they were generally too small. Many of them were of poor methodological quality and some combined various products with possibly opposing, beneficial or harmful effects. Owing to these limitations, it is not possible to conclude that all of the examined supplements are ineffective. However, the absence of evidence means that currently, they cannot be recommended for clinical practice. It is also important to remember that not all supplements are safe and that high doses of certain vitamins can pose serious risks. The positive outcomes seen in the two studies on fish oil, and its theoretical role in suppressing inflammation, mean that further investigationwith a larger placebo-controlled, well-designed study might be justifiable.[18]

Conclusion

None of the discussed alternative therapies have demonstrated evidence of efficacy as assessed by rigorous systematic reviews. Further studies may be warranted with some (Chinese herbal medicines, certain probiotic strains and fish oil), whereas they may be difficult to justify for others, e.g. evening primrose and borage oil. Despite no evidence for homeopathy, long and empathetic consultations with homeopaths may be a possible reason for its popularity. Practitioners also need to remember that CAM products are currently under-regulated and may not meet the stringent quality standards of conventional medicines.

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2.2. LINK BETWEEN MANUSCRIPT ONE AND MANUSCRIPT TWO

On investigating the current status of efficacy and safety of frequently used CAMs for atopic eczema as per **Manuscript One**:

Complementary Therapy in Atopic Eczema: The Latest Systematic Reviews

Thandar Y, Botha J, Mosam A, *South African Family Practice* 2014; 56(4):216-219 http://dx.doi.org/10.1080/20786190.2014.953864; it became evident in the literature that systematic reviews which are critical in providing answers or verdicts on as yet unresolved or variable data, have only been published for oral CAMs.

In studies qualifying and quantifying the use of CAM, topical herbal remedies are continually being sort as 'safer' alternatives to the much feared topical corticosteroids which still remain the gold standard for the management of atopic eczema. An extensive literature search revealed that many topical herbal preparations have been tested for atopic eczema; however not all have been controlled clinical trials. Also, there have been no systematic reviews published on any topical herbal remedies for atopic eczema; despite their popularity and despite the desperate search for suitable safer alternative topicals. Although systematic reviews of topical herbal medicines have previously been published for other common skin diseases like psoriasis, this research had identified a distinct gap in the literature for atopic eczema. The lack of evidence based information to assist clinicians in making informed choices and the ability to highlight areas where further research may be warranted is what spurred on the second objective of this research.

This research in the form of **Manuscript Two** which has been published has bridged the gap in knowledge and has provided the conclusions on the current status of efficacy and safety of topical herbal remedies tested in controlled clinical trials for atopic eczema which were previously lacking. This was done through a critical and thorough reassessment of all relevant trials published, in the form of a systematic review.

The systematic review has been accepted for publication in the *British Journal of Dermatology* in July 2016. It is currently published online and can be accessed as follows:

Topical Herbal Medicines for Atopic Eczema: A Systematic Review of Randomised Controlled Trials

Thandar Y, Gray A, Botha J, Mosam A

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3. CHAPTER THREE

3.1. MANUSCRIPT TWO (PUBLISHED)

Topical Herbal Medicines for Atopic Eczema: A Systematic Review of Randomised Controlled Trials

Thandar Y, Gray A, Botha J, Mosam A

British Journal of Dermatology 2016 Jul 4; doi: 10.1111/bjd.14840. [Epub ahead of print]
http://onlinelibrary.wiley.com/doi/10.1111/bjd.14840/full

The contents of this chapter in the form of a published paper online (print version to follow) has met Objective Two of this thesis. It presents a collation and critical analysis in the form of a systematic review of multiple controlled trials on topical herbal medicines for treating atopic eczema. This research has helped establish conclusions on efficacy of these topical agents and has helped open avenues for future research by identifying investigating agents in trials that have shown promising results.

In addition, an author's video, as was requested by the editor of the *British Journal of Dermatology* (Appendix 15), higlighting the reason for the study, methodology, main findings and its relevence to dermatologists and their patients with atopic eczema, was produced. This video recording can viewed using the following link:
https://drive.google.com/file/d/0BzpWegUfKOmmaThFbGpVSUxBckk/view?usp=drivesdk
(Also available on CD/SD Card attached:
Filename: BJD Video-Topical Herbal Medicines for Atopic Eczema- A Systematic Review of Randomised Controlled Trials-Thandar 2016)

Topical Herbal Medicines for Atopic Eczema: A Systematic Review of Randomised Controlled Trials

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Topical Herbal Medicines for Atopic Eczema: A Systematic Review of Randomised Controlled Trials

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Summary

Despite the availability of medicines with proven efficacy, many patients use complementary or alternative medicines (CAMs) to manage atopic eczema (AE). Due to the lack of objective information on topical CAMs, this systematic review (SR) evaluates current evidence of efficacy and safety of topical herbal preparations in AE. Using Cochrane SR methodology, PubMed, Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (via EBSCO), MEDLINE (via EBSCO), Proquest Health and Medical Complete, GREAT and CAM-QUEST were searched from inception until June 2014. Bibliographies of retrieved studies were hand-searched for further relevant trials. All controlled clinical trials of topical herbal medicines for AE in humans of any age were included regardless of the control intervention or randomisation. Only English publications were considered. Eight studies met the inclusion criteria. Seven investigated extracts of single plants and one an extract from multiple plants. Only two studies that showed a positive effect were considered to have a low risk of bias across all domains (those of

licorice gel and *Hypericum perforatum*). In these two, the test product was reported to be superior to placebo. Despite variations in diagnostic criteria and lack of validated tools for outcome assessments in one of these, the promising results may warrant continued research in better designed studies. No meta-analysis was performed due to heterogeneity in all studies. There is currently insufficient evidence of efficacy for any topical herbal extract in AE. Many studies had methodological flaws and even those showing efficacy were single trials with small patient cohorts.

What's already known about this topic?

- Patients use topical complementary/alternative medicines to manage atopic eczema.
- Objective evidence of efficacy and safety is lacking and is essential for clinicians and patients to make informed choices.

What does this study add?

- Of six studies that displayed superiority to placebo, only two therapies, licorice gel and *Hypericum perforatum* were considered to have a low risk of bias across all domains
- The promising effect of these two therapies for atopic eczema warrants continued research in well-designed studies.

Introduction

Atopic eczema (AE) is a chronic, relapsing and frustrating condition, with marked effects on quality of life (QoL). Despite the availability of medicines with proven efficacy, many patients resort to complementary or alternative medicines (CAMs) to manage flare-ups.[1-3] Many of these CAMs have shown conflicting evidence of efficacy and hence systematic reviews (SRs) have sought to provide clarity on their role for AE. Previous SRs have focussed on oral CAMs[4-8] and an overview of these concluded that there was currently no evidence of efficacy.[9]

Topical corticosteroids remain the mainstay of treatment for AE. Many patients are concerned about their long-term safety and seek evidence-based safer alternatives.[10-12] Many topical herbal preparations have been tested for AE, but few in controlled clinical trials.[13-20] We have found no SRs of these trials, although SRs of topical herbal extracts have been published for other chronic skin conditions, such as psoriasis.[21-23] In 2014, a Cochrane protocol was registered with the aim to review all randomised controlled trials (RCTs) of several forms of CAMs (including phytotherapy) and complementary techniques (including acupuncture).[24] No review based on this protocol has yet been published. Our SR focusses specifically on controlled trials of topical herbal preparations (whether randomised or not),

and on evidence of efficacy and safety. The overall aim is to provide clarity to prescribers and patients, and to identify opportunities for future research.

Methodology

Data Sources

This SR was conducted independently with reference to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (no registered protocol).[25] The electronic databases searched from inception until June 2014 were: PubMed, Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (via EBSCO), MEDLINE (via EBSCO), Proquest Health and Medical Complete. Subsequent searches were conducted in two additional databases (CAM-QUEST and GREAT). Bibliographies of retrieved studies were hand-searched for other relevant trials.

Search terms were 'atopic eczema/atopic dermatitis' together with 'topical herbal', 'topical application', 'topical administration', 'plant extract', 'natural', 'cream', 'ointment' and their synonyms. These were adjusted according to suitability for each database. The corresponding author may be contacted for a list of the search terms per database.

Inclusion and Exclusion Criteria

All controlled clinical trials published in English that tested a topical herbal medicine for AE in human patients of any age were included, regardless of the control intervention or randomisation.

Topical herbal medicines were defined as those containing extracts of multiple or single plants. These could include non-herbal ingredients used in the extraction process or in preparation of the test or vehicle. Preparations described as homeopathic were not excluded. Any preparation incorporating or combined with an active pharmaceutical ingredient, other bioactive ingredients, vitamins or minerals were excluded. Topical Chinese Herbal Medicines were also excluded, as a recent systematic review dealing specifically with these was published in 2014.[26]

All patients had to be clinically diagnosed with AE. Studies on other types of eczema (e.g. hand eczema) and where the type of eczema was not clearly classified (e.g. chronic eczema) were excluded. Case reports, case series and clinical trials not conducted within a controlled environment were also excluded.

Data extraction and analysis

Titles and abstracts of the initial search were scrutinised by two reviewers (YT, AM) and a selection of full texts was made. Discrepancies were clarified by two independent reviewers (JB, AG).

Data from included trials were extracted by one reviewer (YT) and checked by the others. Study authors were contacted where clarity was required. Details of the extracted data and study description are included in Table 1. The risk of bias (ROB) in each study was assessed

by three independent reviewers (YT, AM, AG) according to the Cochrane domain-based evaluation.[27] Table 2 includes this assessment.

Results

Literature Search

Initial searches yielded 3813 potential studies. After removing duplicates, 2451 potential papers remained. Considering inclusion and exclusion criteria, full texts of 42 publications and 3 studies from reference lists were retrieved. Eight publications were finally selected. Subsequent searches of additional databases did not yield any studies that met the inclusion criteria. Figure 1 shows the results of the selection process.

All 8 studies were randomised controlled trials (RCTs) conducted between 1990 -2011. Four were conducted in Germany,[15, 16, 18, 19] the others in Spain,[14] the United Kingdom,[17] Iran[13] and the Philippines.[20] Five were intra-individual paired left/right comparison trials.[15-19] Participants ranged in age from 4 months-65 years. The largest trial included 88 patients[19] and the smallest 12 patients.[17] Treatment duration ranged from 4 weeks[15, 19, 20] to 2 weeks.[13, 16-18] The severity of AE varied. Three studies included patients with mild to moderate AE,[13, 17, 19] 1 with moderate AE,[18] and another with moderately severe AE.[16] One study included patients with low to high moderate objective SCORAD scores, implying a varied degree of AE severity.[20] One study included patients with SCORAD <80 and another, 15-60, hence a wide variation in severity.[14, 15]

Primary outcome measures were a modified SCORAD using a 4 point-scale assessment in 5 studies[13, 15, 16, 18, 19], SCORAD index in one study [14], objective SCORAD[20] and a 10-point self-assessment of symptoms[17] in another. *Staphylococcus aureus* (SA) colonisation was measured in 2 studies[15, 20] and tolerability was assessed secondarily in 4 studies.[15, 16, 18, 19] Only one study assessed health-related quality of life (QoL).[14]

Four studies compared a topical plant extract to a topical placebo.[13, 15, 17, 19] Two trials were 2-arm parallel studies (comparison with placebo and 0.5% hydrocortisone).[16, 18] In another 2, the test was compared to a topical active control; hydrocortisone butyropropionate[14] and virgin olive oil (VOO).[20]

Seven studies investigated single plant extracts and 1, extracts from multiple plants.[19] These were sunflower oleodistillate, *Hypericum perforatum L* (St John's wort), *Hamamelis virginiana* distillate, evening primrose oil (EPO), chamomile, *Glycyrrhiza glabra L* (licorice gel), virgin coconut oil (VCO) and an ointment containing extracts of *Mahonia aquifolium*, *Viola tricolor* and *Centella asiatica*.

Risk of Bias Assessment

The judgement of ROB per domain is summarised in Table 2 and depicted in Figure 2.

Selection bias in terms of sequence generation was unclear in all studies. Only 1 reported randomisation[14] and none stated any method of sequence generation. All studies stated that participants were randomly allocated into treatment groups, hence allocation concealment was considered to be low risk in all but one study.[14] Although 2 did not provide any detail on method of randomisation, they were classified as low risk.[15, 17]

Four studies demonstrated a high risk of performance bias[14, 16, 18, 20] with 2 also having a high risk of detection bias.[14, 18] In the Patzelt-Wenczler study (Kamillosan®), participants and investigators, although blinded to the control, could identify the treatment cream due to its distinct colour and smell.[18] The De Belilovsky study (2% sunflower oleodistillate) was observer-blinded. Participants were unblinded and were given different instructions on application of both creams. Although reported that this was unlikely to influence outcome, it was classified as high risk of performance bias.[14] Unblinding of parents/carers may affect adherence especially if the corticosteroid is known. Also, it was unclear how the commercial test and control products were packaged and supplied to maintain blinding. These generated a study with high risk of detection bias. In the Verallo-Rowell study (VCO), the creams were distinguishable by scent and appearance prior to application.[20] Despite the authors claim that this was unlikely to have influenced results, we considered the performance bias as being high.

In the Korting study (*Hamamelis* distillate), treatment and control creams were dispensed in neutral, coded 50g-tubes; however no mention was made of similarity of texture, colour or smell, thus the claim of double-blinding may have been ineffective.[16] Also, patients had to be actively motivated to complete the trial as they felt uncomfortable with the medication due to delayed onset of desired effect and having received potent glucocorticoids previously. This study was thus regarded as having a high risk of performance bias.

Two studies had incomplete outcome data and was considered to have a high risk of attrition bias.[16, 19] The Korting study (*Hamamelis* distillate) had 7 dropouts, in whom analysis was performed on intention-to-treat numbers and the last value obtained served for analysis.[16] These values were not mentioned, thus the missing data could have resulted in inaccuracies. Conflicting figures exist in this study as an initial report of 7 dropouts was inconsistent with another statement that 4 patients withdrew (3 test and 1 control). Another discrepancy was a statement that 65 patients completed the trial but a later statement that 61 complied with the full trial protocol. Despite the poor quality reporting, results were not in favour of the test product.[16]

Approximately 20% of the sample dropped out in the Klovekorn study (multiple plant extracts) due to lack of efficacy. [19] Analyses were performed on the intention-to-treat data. The missing data could have led to inaccurate results. Attrition bias in other studies were low, due to no dropouts[13, 14, 20], small dropout numbers [15, 17, 18] or clear reasons for dropouts.[15-18]

All 8 studies were considered to be at low risk for selective reporting as all outcomes assessed as part of the trial objectives stated in the paper were reported in the results. One study did not report on additional symptoms investigated as part of the outcomes, however, the risk was low as all major symptoms were reported.[18]

Other potential sources of bias exists in two studies.[14, 17] In the de Belilovsky study (2% sunflower oleodistillate) all children were given Stellatopia® milky bath oil for daily use. Compliance is uncertain and it is possible that its regular use could improve symptoms and bias the results. Also, no mention is made of washout periods with previously used systemic corticosteroids, antibiotics or immunosuppressants.[14] In the Anstey study (EPO), no restrictions were given with any topicals used on other areas of the body.[17] The risk was considered high as systemic absorption of these could potentially produce inaccurate outcomes.

Only 3 studies measured compliance. Two collected and weighed tubes[14, 15] and one collected tubes and documented application frequencies.[19] Follow-up was mentioned only in one study, which ceased after two weeks.[13]

Diagnostic criteria varied among studies.[13, 14, 18] Three reported the use of Hanifin and Rajka criteria (1980).[16, 17, 19] One used the modified Hanifin and Rajka criteria[20] and another, criteria recommended by the European Task Force on Atopic Dermatitis (1993).[15]

Of 5 studies that used a four-point scale to measure outcomes,[13, 15, 16, 18, 19] only 4 used the same scale, of which erythema was the only common symptom assessed. Three were placebo-controlled and 2 included two comparator arms (placebo and 0.5% hydrocortisone cream). Four were half-sided intra-individual comparisons. Due to these differences, a meta-analysis was not considered feasible.

Six studies reported on adverse events;[14-19] of which 3 reported that there were no adverse events,[14, 17, 19] and others reported that none were serious.

Description of studies

Topical single plant extracts compared to placebo (n=4)

Published in 2003, a randomised, placebo-controlled, double-blind trial was conducted by Schempp *et al.* In this intra-individual bilateral comparison, the effects of St John's wort cream, containing *hyperforin* (a major constituent of *Hypericum perforatum*) on AE intensity was compared to placebo using a modified SCORAD of objective variables. Secondary

outcomes were *SA* colonisation and tolerability. The investigators found that St John's wort cream significantly improved the intensity of AE and reduced SA skin colonisation compared to placebo. Tolerability was good with only a few non-serious adverse effects reported.[15]

A randomised, double-blind, placebo-controlled, intra-individual bilateral comparison trial with topical EPO was published in 1990. In this pilot, the effects of topical EPO on eczema severity was assessed by patients and physicians using a 10-point scale. A statistically significant difference only in patient scores (not doctors) was noted, concluding that despite uncertainty of emollient or anti-inflammatory effects; topical EPO has potential to improve eczema.[17] No published main study following this pilot was found.

Published in 2003, Saeedi *et al.* investigated the effect of 1% and 2% licorice gel (extracted from *Glychyrrhiza glabra L* roots). This was a randomised, double-blind, placebo-controlled 3-arm trial. Symptoms were assessed using a 4-point scale. Itching, oedema, erythema and scaling were reduced more effectively with 2% licorice gel compared to 1%. Both were more effective than placebo. The investigators concluded that 2% licorice extract could be considered in AE management.[13]

Topical multiple plant extracts compared to placebo (n=1)

In 2007, Klovekorn *et al.* compared an ointment containing extracts of *Mahonia aquifolium*, *Viola tricolor* and *Centella asiatica* to placebo. This was a bilateral intra-individual comparison. Efficacy was based on a modified SCORAD four-point scale investigator-assessment of objective parameters. Subjective variables were assessed by the patient. A global assessment of effectiveness and tolerability were also assessed. The investigators concluded that this extract was not superior to placebo. Considering the study was conducted over a period of varying climatic conditions, a sub-analysis over similar climatic conditions concluded that the cream might be effective.[19]

Topical single plant extracts compared to topical corticosteroids (n=3)

Three studies compared topicals from single plant extracts to topical corticosteroids.[14, 16, 18] Two were 3-arm studies (comparison to corticosteroid and placebo).[16, 18]

Two percent sunflower oleodistillate (Stelatopia® emollient cream) was compared in an open, single-blind RCT to hydrocortisone butyropropionate by Belilovsky *et al.* in 2011.[14] The SCORAD index as well as individual symptoms improved significantly compared to baseline in both groups but with no differences compared to each other. Xerosis, however, was significantly better with the extract. The lesions decreased to a greater extent and sooner with the topical corticosteroid. Investigator-rated global assessment, flare ups and QoL were similar. The investigators concluded that 2% sunflower oleodistillate cream, is comparative to topical corticosteroid and if used repeatedly on the whole body, is an appropriate first line treatment for children with AE.

Korting *et al.* investigated the effects of *Hamamelis virginiana* distillate cream against 0,5% hydrocortisone cream and placebo in a double-blind RCT in 1995.[16] While all patients received the test cream, the two controls were randomly allocated to the left/right side of the body. *Hamamelis* distillate cream failed to show superiority over the topical corticosteroid and achieved similar results to placebo using the 4-point scale to measure symptoms. Patient and physician-assessed global efficacy and tolerability also failed to show any positive effect.

In 2000, Patzelt-Wenczler *et al.* compared a chamomile extract (Kamillosan®) against 0.5% hydrocortisone cream and placebo.[18] This study was partially double-blinded because the colour and smell of chamomile extract was easily distinguishable from placebo and corticosteroid. A 4-point assessment of symptoms and investigator-global assessment were the main outcomes. A marked superiority of the chamomile extract compared to 0.5% hydrocortisone and a marginal superiority over placebo on assessment of pruritis, erythema and desquamation was reported. No reports were given regarding the other symptoms assessed.[18]

Topical single plant extracts compared to other pharmaceuticals (n=1)

In a 2008 double-blinded RCT by Verallo-Rowell *et al*., the effects of VCO on objective symptoms of SCORAD and SA colonisation was compared against VOO.[20] Both oils improved severity scores but improvement was better with VCO. VCO was also superior in reducing SA colonisation. The investigators concluded that VCO and its key ingredient *monolaurin* may be useful in the proactive treatment of AE.

Discussion

This SR reports on trials conducted over the past 25 years. Despite this lengthy period, evidence regarding the use of topical plant extracts still remains unclear. Objective information rather that complete rejection is essential for any clinician treating patients who may be using or wanting to consider CAMs.

Of 8 RCTs included in this review, 2 reported no efficacy.[16, 19] The Korting study (*Hamamelis* distillate) had a high risk of performance bias possibly leading to inaccurate results.[16] The Klovekorn study (multiple plant extracts), reported a high dropout rate due to lack of efficacy thus having a high risk of attrition bias.[19] The intention-to-treat analysis revealed negative results. It is therefore unlikely that a better designed study would show any positive effect.

Six studies reported that the extracts tested were effective.[13-15, 17, 18, 20] However, there was no common data that was suitable for a meta-analysis. Of these, the Patzelt-Wenczler study (Kamillosan®), which reported that chamomile extract was mildly superior to topical corticosteroid, was considered to be at high risk of performance and detection bias, lending itself towards a positive effect.[18] No statistical analyses or follow up was reported. Considering this, the claim of superiority over a topical corticosteroid cannot be supported

by data in this trial. Following this 2000 publication, we have found no other trials with a chamomile extract for AE. Another better designed study ensuring complete blinding would be useful.

The De Belilovsky study (2% sunflower oleodistillate) had selection, performance and detection biases.[14] Other potential biases were uncertainty of washout periods with prior medicines and the concurrent use of a milky bath oil which may have led to a false positive result. Results of comparability of test cream to a topical corticosteroid and its consideration as first line treatment for mild to moderate AE was reported in this 3-week observer-blinded trial. A longer trial, with double-blinding, addressing flaws in this study may be warranted.

The Anstey study (EPO) did not mention any validated instrument for assessing outcomes. A positive outcome was documented by patients only with no statistical differences in doctors' assessments.[17] This study was considered to be at high risk, as patients were allowed to use other topicals. A study excluding other medicines may be warranted.

Although the Verallo-Rowell study (VCO) showed a positive effect, it had a high risk of detection bias.[20] The reduction in SA colonisation in this study is of limited clinical significance, as it was a cross-sectional study in a small number of patients (unbalanced at baseline) thus posing a high risk of a chance finding.

Only two studies which showed superiority over placebo had low ROB across all domains.[13, 15] Despite variations in diagnostic criteria and a lack of validated tools for outcome assessments in one study,[13] its promising effect in the treatment of mild to moderate AE may warrant continued research using larger patient cohorts, in better designed, longer duration, possibly 3-armed trials (with topical corticosteroids and placebo).

Potential Limitations

Although a thorough literature search was conducted, some studies may have been missed. No information was obtained on unpublished studies. Despite every effort to use a wide array of databases, EMBASE and AMED were inaccessible. Studies published in other languages were not considered.

The heterogeneity among studies in terms of the tested product, age of participants, sample sizes, outcome measures and degree of eczema severity precluded the performance of a meta-analysis. The development of a minimum core outcome set to be used in future studies should be considered, as this would make it easier to compare results across trials and thus establish firm conclusions.

Conclusion

There is currently insufficient evidence of efficacy with any topical herbal extract explored in this review. Many of the included studies were pilot studies, had methodological flaws and even those that did show efficacy were single trials. Further trials with larger patient cohorts and longer follow up to assess efficacy and record adverse effects may be warranted with those topical herbal extracts, like *Hypericum perforatum* extracts, 2% licorice gel and EPO, that did show some promise.

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Table 1 Characteristics of Included Studies

1ST AUTHOR, YEAR, LOCATION	INTERVENTION	CONTROL	NO. & AGE OF PARTICIPANTS DURATION OF STUDY	STUDY DESIGN	OUTCOME MEASURES	DROPOUTS, ADVERSE EFFECTS	OUTCOME	DIAGNOSTIC CRITERIA
De Belilovsky; 2011; Spain[14]	2% sunflower oleodistillate (Stelatopia® emollient cream)	topical corticosteroid (hydrocortisone butyro-propionate)	Treatment:40 Control:40; Children (4mnths-4yrs); 3 weeks	Open, comparative, single-blind, randomised study	1° - SCORAD Days 0,7 & 21) ; 2° - Specific items of SCORAD (extent of AE lesions, erythema, oedema/papulation, oozing/crusting, excoriation/lichenification, dry skin in healthy areas, pruritis, sleep loss; IGA on AE flare-ups at Day 21; QoL at Days 0 & 21 (IDQOL & DFI)	No ADRs or loss to follow-up in either group	2% sunflower oleodistillate demonstrated similar properties to topical steroid; SCORAD was identical at all evaluation points; QOL improved in both groups; tolerance was excellent	Clinical definition was based on presence of acute lesions in the folds of the elbows and/or knees/surfaces of limbs/cheeks. Severity was quantified by initial SCORAD between 15 & 60

1ST AUTHOR, YEAR, LOCATION	INTERVENTION	CONTROL	NO. & AGE OF PARTICIPANTS DURATION OF STUDY	STUDY DESIGN	OUTCOME MEASURES	DROPOUTS, ADVERSE EFFECTS	OUTCOME	DIAGNOSTIC CRITERIA
Schempp; 2003; Germany[15]	Cream containing *hyperforin* - a major constituent of *Hypericum perforatum L* (St. John's Wort)	placebo (colour-matched vehicle) applied on other side (composition of the vehicle identical in the two creams)	21 patients; 12-59yrs; 4 weeks	Prospective, randomised, double-blind, placebo-controlled study; half-side (within patient left/right) comparison	1° - modified SCORAD index based on extent & intensity of erythema, papulation, crust, excoriation,lichenification & scaling (intensity classified using a 4 point scale (excludes subjective variables 2° - skin colonisation with *SA* at Day0 & 28; cosmetic acceptability & skin tolerance of the creams(scored by the patients at visits 2-4)	3 dropouts , 1due to missing efficacy data after 10 days of treatment & 2 because treatment lasted less than 10 days(n=18); 4 S/Es in 3 patients- acute episode of AD leading to withdrawal from study; 1 patient developed contact eczema. None of the S/E were considered serious	*Hypericum* was significantly superior in efficacy & reduction of skin colonisation with *S.aureus* when compared to the vehicle in the topical treatment of mild to moderate AD.	Diagnosis of subacute AD of limited extent (SCORAD<80). Score was calculated using the algorithm recommended by the European Task Force on Atopic Dermatitis (1993).

1ST AUTHOR, YEAR, LOCATION	INTERVENTION	CONTROL	NO. & AGE OF PARTICIPANTS DURATION OF STUDY	STUDY DESIGN	OUTCOME MEASURES	DROPOUTS, ADVERSE EFFECTS	OUTCOME	DIAGNOSTIC CRITERIA
Korting; 1995; Germany[16]	*Hamamelis virginiana* distillate cream	Drug-free vehicle of *Hamamelis* distillate (n=36) OR 0.5% hydrocortisone cream (n=36) applied on other side of the body	Treatment:72 Control: 36 (vehicle) 36 (hydrocortisone cream); 18-62yrs; 14 days	Double-blind, randomised, paired trial	4-point scale rating for itching, erythema & scaling (basic criteria); edema, papules, pustules, exudation, lichenification, excoriation & fissures (minor criteria); basic & minor criteria assessed at Days 0, 7 & 14; GA of therapeutic effect by physician & patient & physician & patient-assessed tolerability at Days 7 & 14	7 dropouts (1 bronchitis, 1 non-compliance & 5 no co-operation) (3 drop-outs from treatment group & 1 from hydrocortisone group)	Low-dose hydrocortisone cream was found to be more superior over *Hamamelis* distillate & the therapeutic outcome with *Hamamelis* distillate was found to be no better than the base preparation	Patients had moderately severe AE, diagnosis was established according to the criteria of Hanifin & Rajka (1980) (at least 3 basic & 3 minor features of AE. Patients also had to present stable or acutely worsening flexural lichenifications on both arms (test areas) with a sum score of 4-7 for the basic criteria (itching, erythema, scaling)

1ST AUTHOR, YEAR, LOCATION	INTERVENTION	CONTROL	NO. & AGE OF PARTICIPANTS DURATION OF STUDY	STUDY DESIGN	OUTCOME MEASURES	DROPOUTS, ADVERSE EFFECTS	OUTCOME	DIAGNOSTIC CRITERIA
Anstey; 1990;United Kingdom[17]	Topical evening primrose oil	placebo (E45 cream)	12 patients; 4-46yrs; 2 weeks	Double-blind; placebo controlled, paired trial (left/right comparison)	A 10-point self-assessment (patient) scoring system for redness, scaling, dryness, itch & overall impression on Days 0,7 & 14 & physician assessments for dryness, scaling, erythema, infiltration/oedema, lichenification & overall impression on Days 0 &14	1 dropout (due to flare in AE); no topical or systemic S/Es effects observed	A statistically significant diff between EPO & E45 cream was seen using patient self-assessments concluding that *topical EPO* has potential for treating AE. No statistically significant diff in doctor-assessed scores	Patients had mild to moderate AE as defined by accepted criteria (Hanifin & Rajka 1980)
Patzelt-Wenczler; 2000; Germany[18]	Chamomile *extract* (Kamillosan®) cream	vehicle cream (placebo) (n=33) OR *0.5%* hydrocortisone cream (n=36) applied on other side of body	72 patients; average age 45.5yrs; 2 weeks	Partially double-blind; randomised; half-side comparison (intra-individual left/right comparison)	All individual symptoms were assessed on a 4 step scale, efficacy was determined with score & sum score consisting of pruritis, erythema & desquamation, edema, vesicles, papules/ pustules, lichenification, excoriation & fissures, investigator-rated GA based on a 4-point scale ; tolerability was also assessed	3 dropouts, intolerability in one patient (from the Kamillosan®/ placebo group)	Kamillosan® cream showed a mild superiority over 0.5% hydrocortisone & a marginal difference as compared to placebo	Patients had to exhibit a moderate degree of AE i.e. a sum score of pruritis, erythema & desquamation of 3-7 (score range 0-9), distal on both arms.

1ST AUTHOR, YEAR, LOCATION	INTERVENTION	CONTROL	NO. & AGE OF PARTICIPANTS DURATION OF STUDY	STUDY DESIGN	OUTCOME MEASURES	DROPOUTS, ADVERSE EFFECTS	OUTCOME	DIAGNOSTIC CRITERIA
Saeedi; 2003; Iran[13]	1% & 2% licorice gel (extracted from *Glycyrrhiza glabra L* roots)	placebo (base gel)	Treatment: 30 (Liqorice *1%*); 30 (Liqorice 2%) Control:30; >15yrs; 2 weeks	Randomised (simple-random sampling), double blind, prospective, placebo-controlled trial	investigator- assessed 4-point scale effect on oedema, itching, erythema & scaling	No dropouts, no S/Es were mentioned in the study	2% licorice gel was more effective than 1% in reducing the scores of erythema, odema & itching over 2 weeks. *Licorice extract* could be considered as an effective agent for treatment of AE.	Patients with clinically diagnosed mild to moderate degrees of AD (1. pruritis & scratching; 2. course marked by exacerbations & remissions; 3. lesions typical of eczematous dermatitis; 4. personal or family history of atopy; 5. clinical course lasting longer than 6 weeks)
Klovekorn; 2007; Germany[19]	Ointment containing alcohol based plant extracts of *Mahonia aquifolium*, *Viola tricolor* & *Centella asiatica* & their ingredients as pharmacological active substances	Vehicle alone (no active ingredients)	88 patients; 18-65 yrs; 4 weeks	Randomised, double-blind, vehicle-controlled, half-side comparison	1°endpoints- 4-point scale summary score for erythema, edema/population, oozing/crusting, excoriation & lichenification; 2° endpoints - assessment of pruritis severity (10 cm VAS) & a GA of effectiveness & tolerablility	1 excluded; 17 dropouts; well-tolerated, no serious adverse events	*Mahonia aquifolium*, *Viola tricolor* & *centella asiatica* ointment could not be proven to be superior to a base cream for treatment of mild to moderate AE. A sub-analysis indicated that the cream might be effective under conditions of cold & dry weather	Patients with mild to moderate AE, diagnosis was based on Hanifin & Rajka (1980) & graded according to Rajka & Langeland (1989)

Table 2 Risk of Bias Assessment

STUDY	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS AND PERSONNEL	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE REPORTING	OTHER POTENTIAL BIASES/CONFOUNDING FACTORS
De Belilovsky 2011 Spain[14] *2% sunflower oleodistillate cream*	Patients were randomly selected (method of randomisation not specified)	Children were randomised into the treatment and control group following a chronological order of inclusion on randomised attribution list. It was unclear how the test packs were packaged & supplied in order to maintain blinding of observers	Observation blinded (package was identified by an individual code); patients (parents) not blinded (different were given instructions as to how to apply the cream)	Observer blinded. As the test and control were both commercial products, it was unclear how the test packs were packaged & supplied in order to maintain blinding of observers.	No dropouts	All outcomes to be evaluated were reported	All children were given a body hygiene product Stelatopia® milky bath oil to use at least once daily. No record mentioned as to which child used this regularly in conjunction with either control or treatment; unclear of washout periods of previously used systemic meds before beginning study; some children could have been on long term antihistamines as these were not excluded
	unclear	high risk	high risk	high risk	low risk	low risk	high risk
Schempp 2003 Germany[15] *Hypericum perforatum L (St John's wort) cream*	Not stated	Treatment was randomnly allocated to the left or right side of the body (detail of randomisation was not specified)	Double-blinded (both treatment and placebo were similar in appearance)	Double-blinded, therefore assessor also blinded colour matching & content of additives were identical in placebo and treatment)	3 dropouts (developed acute AD leading to withdrawal)	All outcomes to be evaluated were reported	

1ST AUTHOR, YEAR, LOCATION	INTERVENTION	CONTROL	NO. & AGE OF PARTICIPANTS DURATION OF STUDY	STUDY DESIGN	OUTCOME MEASURES	DROPOUTS, ADVERSE EFFECTS	OUTCOME	DIAGNOSTIC CRITERIA
Veralio-Rowell; 2008; Phillipines[20]	Virgin coconut oil (VCO)	Virgin olive **oil** (VOO)	Treatment:26 Control: 26 ; 18-40yrs; 4 weeks	Randomised, double-blind, controlled trial	*SA* colonisation, objective SCORAD severity index (O-SSI)	No dropouts, no adverse events were reported	VCO's reduction in OSSI & in-vitro broad spectrum activity against *SA* may be useful in the proactive treatment of AD colonisation	Diagnoses were based on the modified Hanifin major criteria of a history of a chronic & relapsing course; pruritis, a pattern of facial & extensor eczema& xerosis at a younger age, becoming flexural at adult age, frequent association with a family history of AD

SCORAD – Scoring Atopic Dermatitis (Clinical Tool used to assess extent & severity of eczema, **GA** – global assessment, **QoL** – quality of life, **ADRs** – adverse drug effects, **AD/AE** – atopic dermatitis/atopic eczema,

	unclear	low risk	low risk	low risk	low risk	low risk	unclear
Korting 1995 Germany[16] *Hamamelis virginiana distillate cream*	Not stated	To ensure randomised allocation of treatment each patient was given a medication pack with lowest number (from a predetermined randomisation list)	Double-blinded (both treatment / controls were in neutral coded 50g tubes). No mention was made of texture and appearance of meds being the same. It is also stated that patients had to be actively motivated to finish the treatment as they felt uncomfortable with the study medication (due to delayed onset of desired effect and having received more potent glucocorticoids in the past), blinding may not have been effective.	Investigator-blinded	7 dropouts (1 bronchitis, 1 non-compliance & 5 no co-operation) (4 did not comply with protocol- 3 from treatment group & 1 from hydrocortisone group); S/Es of skin irritation seen in control & treatment	All outcomes to be evaluated were reported	
	unclear	low risk	high risk	low risk	high risk	low risk	unclear

Anstey 1990 United Kingdom[17] *Evening primrose oil cream*	Not stated	Randomised (method of randomisation not mentioned)	Double-blind (treatment & control similar in texture, colour and smell	Double-blind (stated in abstract only)	1 dropout (due to flare)	All outcomes to be evaluated were reported	No restriction was imposed on usual topical treatments applied to sites other than test areas. Some systemic absorption of these could influence results
	unclear	low risk	low risk	low risk	low risk	low risk	high risk
Patzelt-Wenczler 2000 Germany[18] *Chamomile (Kamillosan®) cream*	Not stated	Randomised (carried out by Biometrical Dept of AstaMedica balanced after 8 patient numbers each). Ambiguity exists in terms of randomisation (patients allocated in chronological order according to patient number)	Patients partially double-blinded (blinded to control creams as these appeared the same but Kamillosan® appeared different in terms of colour & smell), with reference to Kamillosan® the study had an open study character- Both patients & personnel knew the treatment given	Investigator was aware of the treatment cream. Open study character.	3 dropouts (due to intolerability) these were in the Kamillosan®-placebo group	Main outcomes only were reported on. Incomplete reporting of all symptoms	There were no statistical analyses. Only bold statements were made regarding the effect of placebo. Therefore, the claim that Kamillosan® is superior to hydrocortisone cannot be supported by this data.
	unclear	low risk	high risk	high risk	low risk	low risk	high risk
Saeedi 2003 Iran[13] *Liqorice gel*	Not stated	Randomised (simple-random sampling)	Double-blinded (details of concealment not specified)	Double-blinded (details of concealment not specified)	No dropouts	All outcomes to be evaluated were reported	
	unclear	low risk	low risk	low risk	low risk	low risk	unclear

Klovekorn 2007 Germany[19] *Mahonia aquifolium, Viola tricolor, Centella Asiatica ointment*	Not stated	Randomisation was done using a computer generated randomisation code by a statistician not involved in the study	Double-blinded (Verum & vehicle were similar in appearance & dispensed in identical tubes)	Investigator was blinded	1 excluded (did not provide a valid post-baseline value), 17 dropouts due to lack of efficacy (this is approx 20%)	All outcomes that were to be evaluated were reported	
	unclear	low risk	low risk	low risk	high risk	low risk	unclear
Verallo-Rowell 2008 Phillipines[20] *Virgin coconut oil*	Not stated	Simple concealed random allocation (drawing rolled pieces of paper labelled "A" & "B")	Double-blinded. For preparation of bottles randomisation key & codes were done by a pharmacist &disclosed to investigators at end of study. Upon application of either oil, the scent is notable Appearance of oil is also different when poured onto the hand. Although the authors report that the scent disappears within few minutes, initial application compromises the blinding.	Investigator was blinded Preparation of the bottles Randomisation key & codes were done by a pharmacist and only disclosed to investigators at the end of the study.	no dropouts; no adverse effects reported	All outcomes to be evaluated were reported	Small patient numbers with markedly unbalanced groups at baseline (20 vs 12 positive SA colonies) makes the risk of chance finding high.
	unclear	low risk	high risk	low risk	low risk	low risk	high risk

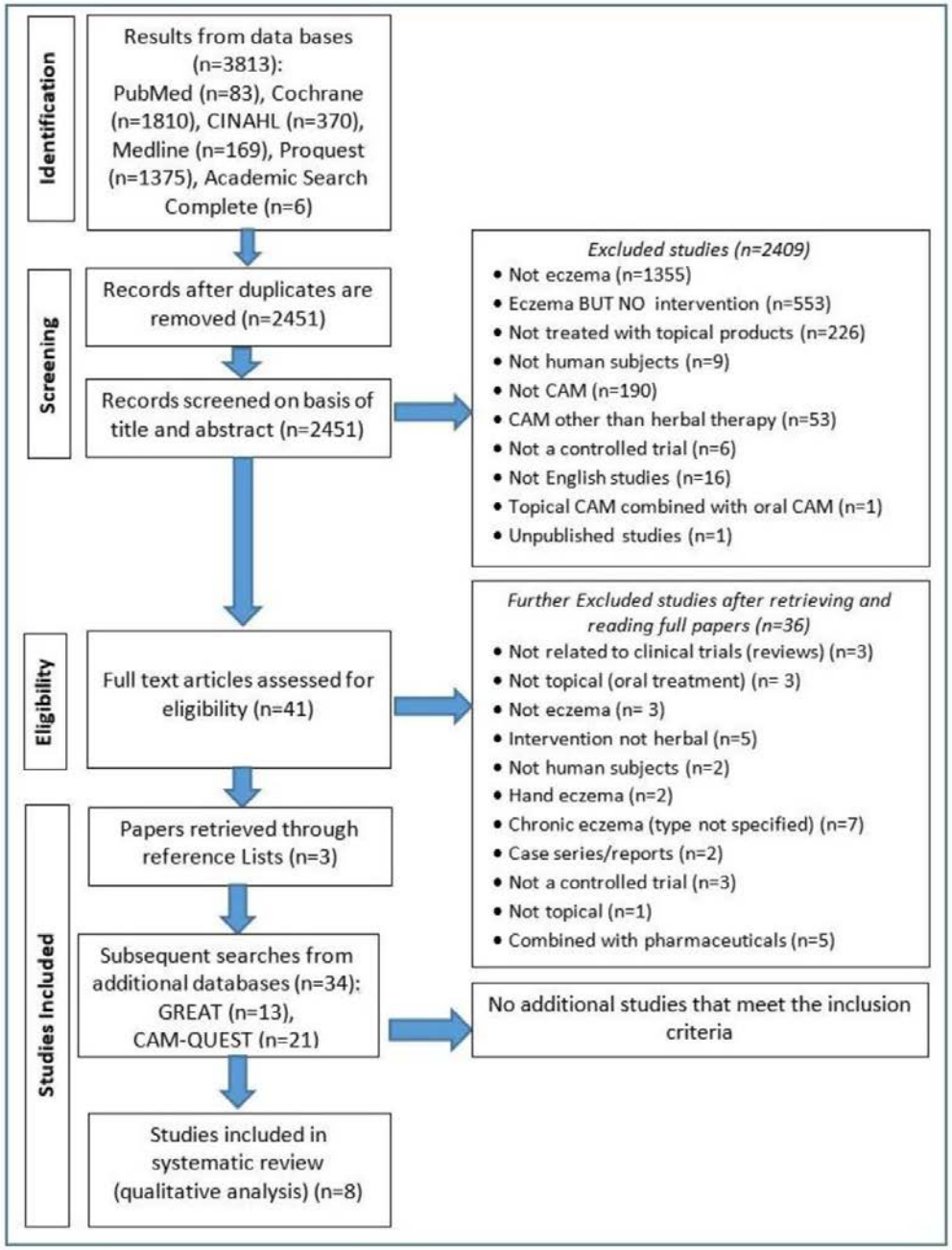

Fig 1 Flow chart showing selection process of controlled clinical trials of topical herbal products for atopic eczema

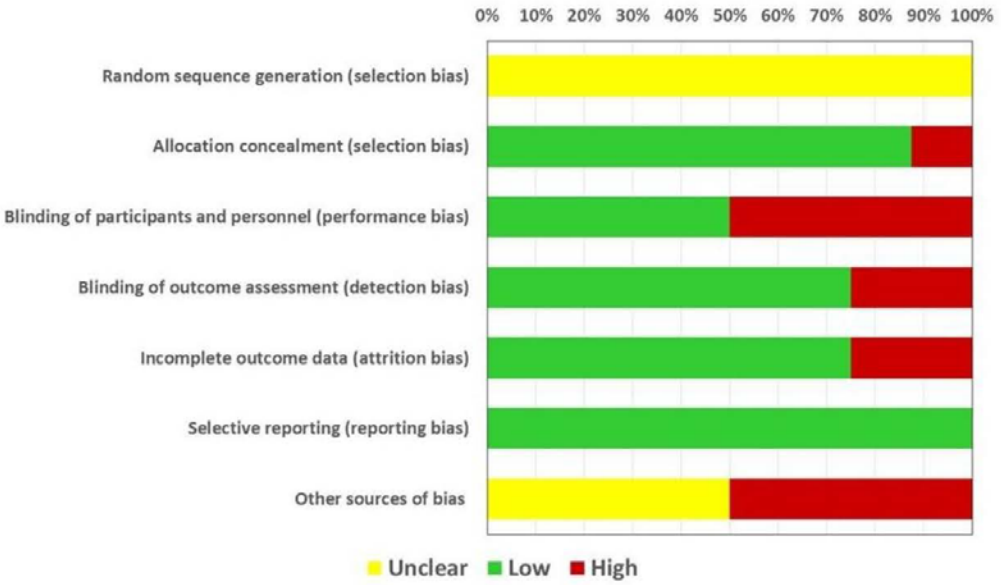

Fig 2 Risk of bias graph, presented as percentages across all included studies

Appendix 1

EXAMPLE OF SEARCH STRATEGY (In Cochrane Library) (1810 hits)

No.	Search Terms (in Title, Abstract, Keywords)	Hits*
1.	"eczema" and "topical" and "herbal" in Trials	3
2.	"dermatitis" and "topical" and "herbal" in Trials	9
3.	"atopic eczema" OR "dermatitis" and "topical" and "herbal" and "randomised controlled trial" in Trials	350
4.	"atopic eczema" OR "dermatitis" and "plant" and "application" and "controlled trial" in Trials	362
5.	"atopic eczema" or "dermatitis" and "cream" and "herbal" and "controlled trial" in Trials	353
6.	"atopic eczema" or "atopic dermatitis" and "phytotherapy" and "application" in Trials	733

***Date of search: 29 June 2014**

3.2. LINK BETWEEN MANUSCRIPTS ONE AND TWO, AND MANUSCRIPT THREE

Stemming from the literature review, this thesis was able to ascertain common CAM modalities used amongst patients for atopic eczema in many countries including Ireland, United Kingdom, Korea, United States and Norway. These common CAM modalities have been critically reviewed in both **Manuscript One:**

Complementary Therapy in Atopic Eczema: The Latest Systematic Reviews

Thandar Y, Botha J, Mosam A, *South African Family Practice* 2014; 56(4):216-219

http://dx.doi.org/10.1080/20786190.2014.953864

and **Manuscript Two:**

Topical Herbal Medicines for Atopic Eczema: A Systematic Review of Randomised Controlled Trials

Thandar Y, Gray A, Botha J, Mosam A

British Journal of Dermatology 2016 Jul 4; doi: 10.1111/bjd.14840. [Epub ahead of print] http://onlinelibrary.wiley.com/doi/10.1111/bjd.14840/full.

Both of these published reviews have provided clarity on the efficacy and safety of these popular identified CAMs, with **Manuscript Two** bridging a gap in knowledge in the literature.

The studies in Ireland, United Kingdom, Korea, United States and Norway have all reported fair and extensive use of CAM ranging from 43%-69% amongst their atopic eczema patients together with reasons and motivations for their use. Very little research has been done in South Africa (SA) regarding the use of CAM. A prevalence study of traditional medicine (TM) and CAM in the general SA population, showed declines in TM-use but increased CAM use over 13 years. Population and health facility-based surveys indicated that both play important roles in SA healthcare delivery, however, lack of data about the extent of CAM use in varying conditions was reported.[14] Other SA studies highlighting CAMs' popularity were amongst an Indian population[15] and in HIV patients.[16]

A systematic review (SR) of epidemiological studies, revealed an increasing prevalence of atopic eczema in Africa with approximate doubling of lifetime prevalence in SA.[2] Despite this, and considering the global hype regarding CAM, the literature revealed no African studies that explored CAM use in atopic eczema. **Manuscript Three** of this research addresses this distinct lack in the literature and explores the extent of CAM use among a large group of South African atopic eczema patients with details about prevalence, extent, types utilized, and the influence of

demographic factors on CAM use in atopic eczema. This manuscript is the first African study to provide such information, yielding new insights beneficial to dermatologists, paediatricians, general practitioners (GPs), pharmacists and CAM practitioners.

Manuscript Three is entitled:

Complementary and Alternative Medicine Use among Patients with Atopic Eczema – A South African Perspective

Thandar Y, Botha J, Sartorius B, Mosam A

Health SA Gesondheid. Submitted 31 August 2016.

Manuscript number HSAG-S-16-00045 ***[under review]***

4. CHAPTER FOUR

4.1. MANUSCRIPT THREE (SUBMITTED FOR PUBLICATION AND UNDER REVIEW)

Complementary and Alternative Medicine Use among Patients with Atopic Eczema – A South African Perspective

Thandar Y, Botha J, Sartorius B, Mosam A
Health SA Gesondheid. Submitted 31 August 2016.
Manuscript number HSAG-S-16-00045 ***[under review]***

The contents of this chapter presented in the form of a manuscript, submitted for publication and currently under review in the accredited *Health SA Gesondheid*, has met Objective Three of this research. Here, the findings from the surveys and interviews amongst patients suffering from atopic eczema and attending both public and private facilities for treatment are presented.

This manuscript provides a detailed analyses of the questions that were asked to patients. This paper has addressed previously unanswered questions regarding the extent of CAM use amongst patients with atopic eczema in Durban, KZN. It has also highlighted the various modalities of CAM that patients in South Africa have tried or are currently using as well as an indication of adherence to treatments prescribed. Reasons, motivations and communication with the healthcare practitioner have also been addressed.

The findings are presented in **Manuscript Three**.

Complementary and Alternative Medicine Use among Patients with Atopic Eczema – A South African Perspective

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Abstract

Background: *Complementary and alternative medicines (CAM) are increasingly popular globally with frequent use amongst patients with atopic eczema (AE). Despite increased AE prevalence in South Africa (SA), no data on CAM-use for this disease exists. We conducted a cross-sectional study qualifying and quantifying CAM use in patients with AE in a SA setting.*

Methods: *We interviewed 206 AE patients; 106 from a public hospital dermatology clinic and 100 from private dermatology practices in central Durban.*

Results: *There were 143 children, 63 adults; 163 females and 43 males. Races represented were Black (56%), Indian (33%), Coloured (6%) and White (4%). 135(66%) reported current or previous CAM use. Common reasons were family/friends' recommendations (42%) and media-influence (23%). Frequently used CAMs were vitamins (35%), aromatherapy oils (27%), herbal creams (26%), traditional African medicines (23%) and homeopathy (19%). Non-disclosure to the dermatologist was high (59%). Almost half (48%) said they were not questioned about CAM use. More Indian patients used CAM ($p=0.001$) and Muslims were most frequent CAM users ($p=0.044$). Duration of AE was also a predictor of use ($p<0.001$). Although not statistically significant, the more educated and higher income bracket used CAM more. 28% felt CAM had fewer side-effects, 28% felt it was safer than conventional medicine and 35% felt CAM was more natural.*

Conclusion: *The detailed trends of CAM use by South Africans for atopic eczema is an important addition to the current literature. Dermatologists and healthcare professionals treating patients with AE need to be conversant with CAMs that their patients explore as this could impact on the overall clinical outcome.*

Introduction

Atopic eczema (AE), a chronic, relapsing disease, is the commonest inflammatory skin condition in children and adults.(Smith Raimer, 2000). A systematic review (SR) of epidemiological studies, revealed an increasing prevalence in Africa with approximate doubling of lifetime prevalence in South Africa (SA) (Deckers et al., 2012).

Numerous studies have demonstrated the increased use of complementary and alternative medicine (CAM) amongst dermatological patients (Baron, Goodwin, Nicolau, Blackford, & Goulden, 2005; Buchar, Katta & Wolf, 2012; Eisenberg et al., 1998; Magin & Adams, 2007). Atopic eczema was reported to be the most frequent dermatological condition where CAM was sought (Baron et al., 2005; Bielory & Lupoli, 1999; Ernst, 2000). Several cross-sectional studies, in Ireland (Hughes, Ward, Tobin, & Keegan, 2007), United Kingdom (Johnston, Bilbao, & Graham-Brown, 2003), Korea, (Kim, Park, Chin, & Ko, 2013) United States (Simpson, Basco, & Hanifin, 2003) and Norway (Jensen, 1990) have qualified and quantified CAM-use in AE.

A prevalence-study of traditional medicine (TM) and CAM in the general SA-population, showed declines in TM-use but increased CAM-use over 13 years. Population and health facility-based surveys indicated that both play important roles in SA healthcare delivery, however, lack of data about the extent of CAM-use in varying conditions was reported (Peltzer, 2009). Other SA studies highlighting CAM's popularity were amongst an Indian population (Singh, Raidoo, & Harries, 2004) and in HIV patients (Peltzer, Friend-du Preez, Ramlagan, & Fomundam, 2008).

We found no African studies that explored CAM-use in AE and thus devised a comprehensive questionnaire to quantify the extent of CAM-use, types utilized, influence of age, gender, race, socio-economic status and education level on CAM-use in AE. We believe ours is the first African study to provide such information, yielding new insights beneficial to dermatologists, paediatricians, general practitioners (GPs), pharmacists and CAM practitioners.

Subjects and Methods

The Ethics Committee of University of KwaZulu-Natal provided approval (BE219/14).This cross-sectional study comprised 206 patients; 106 from King Edward VIII Hospital (KEH), a teaching hospital and KwaZulu-Natal's largest dermatology clinic and 100 from five private dermatology practices in central-Durban. Public and private sector patients provided a broader demographic profile.

Public-patients recruited over 3 months were interviewed face to face, whereas private-patients recruited over 6 months were interviewed telephonically. For children, the parent/primary caregiver was interviewed. isiZulu being the main

language of the predominantly Black population in KwaZulu-Natal, necessitated the presence of a translator. Informed written/verbal consent was obtained from all patients. Patients of all ages, with an existing diagnosis of AE confirmed by a consulting dermatologist at the respective practices, were recruited. A pilot questionnaire among 10 patients enabled us to address ambiguous questions. The main themes of the questionnaire are summarised in Table 1.

[Insert Table 1]

Statistical Analysis

Data was analysed using Stata 13.0 SE (StataCorp.2013.Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Relationships between continuous predictors and CAM-use were assessed using a standard t-test. One way analysis of variance (ANOVA) was employed to compare means of continuous predictors across 3 or more groups. Differences in frequencies of categorical explanatory variables by CAM and AE were assessed using Pearson chi-square (χ^2) test or Fishers exact test if an expected cell count contained fewer than 5 observations. A p-value of <0.05 was deemed statistically significant.

Results

Demographics

All 206 patients approached agreed to participate, yielding a 100% response-rate. There were 143 children and 63 adults. Ages ranged from <3 months to >50 years. Females comprised 79%(163) and males 21%(43). Race was predominantly Black, 116(56%), then 68(33%) Indian, 12(6%) Coloured, 9(4%) White and <1% Chinese. The majority were Christian, 141(68%). Others were Muslim 33(16%) and Hindu 26(12%). Six (3%) were atheist, agnostic or did not respond. Most had secondary schooling as their highest educational level 95(46%), 61(30%) had college education, 20(10%) postgraduate qualifications, 21(10%) up to primary school and 9(4%) no schooling. Average gross monthly household incomes were: 49(24%) <R2000, 45(22%) R2000-R5000, 21(10%) R5000-R10000, 40(19%) R10000-R20000 and 44(21%) >R20000. Students and pensioners (7-3%) did not know their household-income. As anticipated, private patients were more educated with higher household incomes compared to public patients ($p<0.001$). 196(95%) reported currently using topical steroids, 68(33%) systemic immunosuppressants and 27(13%) systemic steroids.

CAM-users

Of 206, 71(35%) had never used any CAM, providing reasons such as "belief that CAM does not work" (30/71-42%), "faith in conventional-medicines only" (23/71-32%), "fear of combining treatment types" (7/71-10%) and 9/71(13%) felt "no reason to as their prescribed conventional medicines worked well". 6%(4/71) said "CAM

was expensive" and 4%(3/71) had "no knowledge of them". This equates to >100% as some provided several reasons.

135(66%) reported using CAM for AE. Forty-five (22%) were currently using CAM and 90(44%) had tried them previously. Ninety-two used CAM for their children and 43 for themselves. However, there was no significant difference in frequency of children CAM-users (92/143-64%) compared to adults (43/63-68%) (p=0.586). No significant difference was noted between male (30/43-70%) or female (105/163-64%) CAM-users (p=0.511) and with respect to ages that explored CAM for themselves or their children (p=0.905). Ages were: <30 years (51/75-68%), >50 years (15/22-68%), 41-50 years (29/45-64%) and 31-40 years (40/64-63%).

More Indian patients used CAM, 53/68(78%) compared to 8/12(67%) Coloured, 68/116(59%) Black and 5/9(56%) White patients. The 1 Chinese patient was currently using CAM. Race (p=0.001) and religion (p=0.044) were both statistically significant predictors of CAM-use. More Muslims explored CAM, 28/33(85%) than 18/26(69%) Hindu and 85/141(60%) Christian.

Although more patients who attended college, 46/61(75%) or had postgraduate qualifications, 14/20(70%) used CAM, this was not statistically significant (p=0.302) compared to CAM-users with no schooling (6/9-67%), primary-school education (13/21-62%) or up to secondary-school (56/95-59%).

Whilst there was no significant difference among monthly household-income levels with respect to CAM-use (p= 0.23), more patients with incomes of R5000-R10000(16/21-76%) and R10000-R20000(30/40-75%) used CAM. Among those with income >R20 000, 30/44(68%) were CAM-users. Fewer in the lower income bracket tried CAM (27/47-57% earning <R2000; 25/45-56% earning R2000-R5000).

Of the 100 private-users, 69% used CAM and among 106 public-users, 62%(66/106) were CAM-users. No significant difference was noted between these (p=0.309).

Results showed that long-time sufferers were more likely to use CAM (p<0.001). Amongst CAM-users, the mean duration of AE was 8.4yrs (SD=9.8) compared to non-users with mean duration of 4.1yrs (SD=4.9).

Demographics and characteristics of CAM-users and non-users are presented in Table 2. Table 3 shows the various CAMs used and patients' familiarity with them.

[Insert Table 2 and Table 3]

Familiarity and CAM choices

Although vitamins were most frequently used, 38(52%) said they were not necessarily for eczema but for overall well-being in the hope that it would also help

their skin. Vitamins specifically for AE were used by 35(48%), mostly products also containing omega-3 and zinc. Aromatherapy, herbal creams, traditional African-medicines and homeopathy were amongst most frequently used CAMs.

Regarding efficacy, 59(45%) CAM-users reported "no improvement", 32(24%) reported "some improvement" and 32(24%) felt "a definite improvement". Nine (7%) were "uncertain of benefit". Three did not respond.

CAM was used together with conventionally-prescribed medicines in 63(52%). Twenty-nine (24%) reported predominantly using CAM over conventionally-prescribed medicines. Seven (6%) were rarely able to use either regularly. Fourteen did not respond.

Familiarity with CAM

Despite extensive CAM-use in this study, a considerable number of people were unfamiliar with CAM. Unfamiliarity was reported with Chinese herbal medicines (CHM) (80%), oral herbal medicines (78%), Reiki (78%) and traditional Indian-medicines (74%). More than half had no knowledge of traditional African-medicines (57%), homeopathy (57%), acupuncture (57%), natural health supplements (63%) and reflexology (64%). Although comparatively smaller, 45% and 41% were unfamiliar with herbal creams and aromatherapy oils respectively. The proportion of patients unfamiliar with vitamins (35%) was equal to those who used vitamins for AE (35%).

Reasons for CAM-use

Patients were questioned as to their reasons for using CAM while prescribed conventional-medicines. Table 4 provides a summary of reasons and attitudes towards CAM.

[Insert Table 4]

Disclosure of CAM-use

On investigating disclosure of CAM-use, 53(41%) said their dermatologist "was aware", 75(59%) said their dermatologist "was unaware" and 7(5%) did not respond. The common reasons for non-disclosure were "the dermatologist did not ask about other medicine usage" (48%); 33% said "it was not necessary for their dermatologist to know".

Discussion

Several studies have demonstrated that among dermatological diseases where patients explore CAM, AE is the most prevalent (Hughes et al., 2007; Jensen, 1990; Johnston et al., 2003; Kim et al., 2013; Simpson et al., 2003). According to the

International Study of Asthma and Allergies in Childhood (ISAAC), a three-year follow-up noted an increased one-year prevalence of AE from 8.3%-13.3% among SA children (Todd, 2014). Despite this, no data on CAM-use in AE was found in Africa. Our study determined prevalence, extent and determinants of CAM-use among AE-patients in Durban.

The 100% response rate is a strength of this study and a reflection of keen interest in CAM amongst AE-sufferers. We found a 66% current/previous use of CAMs which was similar to a Korean study (69%) (Kim et al., 2013) and moderately higher than studies in Europe (51%) (Jensen, 1990), UK (46%) (Johnston et al., 2003), Ireland (43%) (Hughes et al., 2007) and US (50%) (Simpson et al., 2003). Our sample size (n=206) was comparable to the Korean study (n=254) and larger than studies in UK (n=100), US (n=70) and Ireland (n=80).

Demographics

The racial distribution in this study represents the demographics of Durban where Blacks form the largest ethnic group (87%). Although an ethnic minority in SA, the largest Indian population resides in Durban (7.4%), followed by Whites (4.2%), Coloured (1.4%) and 0.3% other races. Indians explored CAM the most (78%), similar to a Leicester-study where Indians, also an ethnic minority, used CAM more frequently, also mostly through recommendations from family/friends (Johnston et al., 2003). A local study among an Indian community also reflected substantial CAM-use (Singh et al., 2004). Indian communities, traditionally close-knit with extended family and strong cultural influences, could be the reason for this. Other studies also reported recommendation by family/friends as the most common reason for trying CAM (Hughes et al., 2007; Johnston et al., 2003; Kim et al., 2013). Other influences were the media (23%) which compared favourably to the Korean study (38%) (Kim et al., 2013). Mass media was also a main information source for CAM in a Norway study (Jensen, 1990). Less media influence was reported in Leicester (6%) and Ireland (3%) (Hughes et al., 2007; Johnston et al., 2003).

Religion was a significant predictor of CAM-use and Muslims were more frequent users than other religions. Many Muslims explored CAMs based on medicine prescribed in Islamic religious texts or stemming from cultural practices e.g. cupping, Unani-Tibb, Ayurveda, Hakim-medicines (traditional remedies from India and Islamic countries).

A higher percentage (17%) of conventional healthcare practitioners (12% GPs, 5% pharmacists) recommended CAM to patients compared to Leicester (6%) and Korea (10%) (Johnston et al., 2003; Kim et al., 2013). None reported recommendations by dermatologists. We found that some GPs also practice complementary therapies e.g. Unani-Tibb and Ayurveda and may hold dual registrations with SA Professional

Councils. In 2000, the Health Product Association (HPA) of manufacturers, importers and distributors of complementary medicines and health products, estimated that 50% turnover in CAM occurred in pharmacies and 2500 pharmacies stocked complementary medicines (Gqaleni, Moodley, Kruger, Ntuli, & McLeod, 2007), making it imperative for pharmacists, often the first treatment source, to know the evidence regarding CAMs' efficacy.

Reasons for CAM-use

Many believed CAMs are "more natural" (35%), "safer than conventional-medicines" (28%), "have less side-effects" (28%) and "part of a holistic healthcare approach" (11%). 12% reported better effect when combined with conventionally-prescribed medicines and 52% said they used CAM this way. None reported exclusive CAM-use which is apparent since patients were recruited while seeking conventional treatment. CAM's role is seen to be mainly complementary and not an alternative for majority. This combined use poses potential for confusion in attribution of therapeutic benefits, side-effects, drug-interactions and non-compliance with prescribed-conventional therapy.

The perception of CAM being natural, safe and without side-effects is important to address amongst the general population. SA legislation was amended in November 2013 providing for the stepwise registration of all complementary medicines based on safety, quality and efficacy. Although full application will take time; new labelling restrictions and their manufacture in a registered facility to progressively meet GMP requirements, have been applied to all unregistered complementary medicines (Medicines Control Council, 2013).

Although not directly questioned about steroid-phobia, open-ended responses showed that it is a dominant driver towards CAM-use. Many demonstrated reservations and reluctance on steroid-use, expressing their need for "something mild", "not wanting to become dependent on steroids" and "concerned about the side-effects of steroids".

Patients with higher monthly-household incomes (R5000-R20000), were more frequent CAM-users; possibly due to high costs making CAM unaffordable to the poorer population who are able to receive free conventional treatment. This is consistent with trends in several countries showing positive association between socio-economic advantage and AE and that children with higher socio-economic backgrounds are more affected with AE than those from poorer families (Medicines Control Council, 2013; Werner, Buser, Kapp, & Werfel, 2002). SA Indians, the more frequent CAM-users in this study, fall within the higher income category compared to Blacks and Coloureds (Medicines Control Council, 2013).

Demographics of age, gender and education level were not significant predictors of CAM-use and were not reported as significant in other studies either (Hughes et al., 2007; Jensen, 1990; Johnston et al., 2003; Kim et al., 2013; Simpson et al., 2003).

CAM Types

Frequently explored CAMs were vitamins (35%), aromatherapy oils (27%), herbal creams (26%), traditional African-Medicines (23%) and homeopathy (19%). Vitamins were mostly used for children for general well-being and less specifically for AE. Vitamins and herbal creams were also most commonly used in a US-study (Simpson et al., 2003). Herbal medicines were frequently used in Europe (19%), UK (26%) and Ireland (41%). These were uncategorised and assumed to incorporate topical and oral (Hughes et al., 2007; Jensen, 1990; Johnston et al., 2003). In ours and the US-study, topical herbal preparations were more frequently used than oral. Homeopathy demonstrated popularity in our study (19%) and in Europe (34%), UK (22%) and Ireland (24%). Compared to 10% in our study, 18% and 17% used health food preparations/health supplements in the European and Korean studies respectively. In 2000, HPA estimated that only 20% of turnover in complementary medicine occurred in health food stores in SA.

CHM (27%) and Oriental-medicines (26%) proved popular in UK and Korea. In contrast, we found only 3% CHM use and 80% reported unfamiliarity with CHM; evidently due to the small Chinese population in KwaZulu-Natal (as reflected in our study sample). Although SA has a large Chinese population compared to other African countries, the majority reside in other cities.

In our study, 27% used aromatherapy oils. Olive oil, coconut oil, tea tree oil and tissue oil were frequently used. Other studies have not reported aromatherapy use. The Korean study mentioned bath therapy use by 21% but with no details. Although many CAM-users were Indian, traditional Indian-medicines were not frequently used in our study (9%) or the Leicester-study (12%).

Traditional African-medicines were used by 23%. We found no studies on traditional African-medicine use in dermatological diseases. A 2008 SA-national household survey revealed low traditional healer use (1,2%), predominantly by the poor, unemployed rural community (Nxumalo, Alaba, Harris, Chersich, & Goudge, 2011). Another SA study which investigated the prevalence of TM and CAM-use in the general population, showed TM decline but increased CAM-use (Peltzer, 2009).

We found that CAM-users were long-time AE-sufferers compared to non-users. This relationship of disease duration and CAM-use is consistent with a European-study (Jensen, 1990), re-affirming the lack of gratification patients experience from conventional medicine driving them to seek alternative treatment.

To date, no CAMs have shown unequivocal evidence of efficacy for AE as confirmed in an overview of SRs of controlled trials including CAMs frequently used in our study e.g. vitamins and homeopathy (Thandar, Botha, Sartorius, & Mosam, 2016). The conclusion from 11 RCTs on vitamins found no benefit. Studies were small and of poor quality. A positive effect in two fish-oil studies suggested that better designed studies might be justified (Bath-Hextall, Jenkinson, Humphreys, & Williams, 2012). The SR reported that although not possible to conclude that all vitamins studied are ineffective, absence of evidence prevents them from being recommended clinically (Bath-Hextall et al., 2012). Considering extensive vitamin use in our study, it is important to remember that some pose serious risks at high doses. Homeopathy remains a popular CAM choice in our study and several others (Ernst, 2000). A recent SR failed to show any treatment effect and concluded that homeopathy is not supported by sound evidence (Ernst, 2012).

Unfamiliarity with most CAMs was evident. A Durban study amongst healthcare workers in HIV/AIDS clinics also reflected poor CAM knowledge including traditional African-medicines, therapeutic aromatherapy, homeopathy, CHM, acupuncture, ayurvedic treatment amongst others (Mbutho, Gqaleni, & Korporaal, 2012); thus not surprising that patients, predominantly the less educated, have limited CAM knowledge. This is likely due to poor information dissemination, lack of education and possible low literacy amongst lower socio-economic patients. Although not investigated, CAMs are considered expensive and most are not covered by SA medical schemes. In this study, the poor with less access to doctors/specialists are not more reliant on CAM and higher income and education are important determinants for CAM-use. CAMs are preferred and more accessible to those with resources to access them.

The majority (59%) did not disclose CAM-use to their dermatologist. Almost half (48%) said they were not asked and 33% thought it was not necessary. Patients are more willing to discuss CAM-use if prompted as seen from this study's overwhelming response with patients eager and comfortable discussing all aspects of CAM-use. In a Taiwan study with high non-disclosure rates (77%) among hospital dermatological patients, more (58%) felt no need to disclose use and fewer (25%) said they were not asked (Chen & Chang, 2003). Similarly, a study assessing patient-provider dialogue about CAM use highlighted barriers in communication between patient and physician including reluctance to disclose CAM-use, physicians not asking about CAM-use and patients perceiving that physicians are unwilling to discuss CAM (Zhang, Peck, Spalding, & Jones, 2012). These issues could be addressed by educating dermatologists and other healthcare professionals regarding the current lack of evidence-based safety and efficacy of frequently used CAMs, enabling them to confidently discuss and advise patients.

Limitations

Patients were recruited consecutively, thus a possible selection bias due to non-randomisation exists. However, considering that all patients were amenable to participating, response and volunteer-bias could be refuted. The majority were open to discussing all aspects of their CAM experience. Patients were ensured of confidentiality, that responses would not be disclosed to their practitioner, documented in their files nor have any impact on their clinical care. Results cannot be generalised to another city or SA as a whole considering differing demographics per city or province. There was a small representation of White patients as fewer attend KEH which predominantly services patients of poor socio-economic backgrounds. Although recruitment also occurred in five private dermatological practices within central Durban, it was found that fewer White patients attend these practices. The dermatologists in these practices were Indian (4) and Black (1). It is likely that White patients frequently consult White dermatologists, practicing outside central Durban.

We could not ascertain any association between severity and CAM-use as a disease severity assessment was not done. For patients attending KEH, a referral hospital, it was assumed that severity was moderate to severe.

Conclusion

We found that 66% of our sample had used CAMs and that race, religion and duration of AE were predictors of use. Vitamins, aromatherapy oils, herbal creams, traditional African-medicines and homeopathy were the most frequently explored CAMs. The majority of patients had not disclosed their CAM-use to their dermatologist. Healthcare professionals treating patients with AE need to be conversant with the various CAMs explored as this may influence the patient's overall clinical outcome.

Conflict of Interest

The authors declare no conflict of interest.

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Table 1 Main Themes addressed in Study Questionnaire

SECTION A **Demographics**	Patient particulars, Practice attending for treatment
	Gender, Religion, Race, Age of Patient/Care-giver, Level of Education, Average gross monthly household income
SECTION B **Treatment Management of Atopic Eczema**	Duration of disease
	Current dermatologist prescribed treatment e.g. steroid creams/tablets/syrup, antihistamines, immunosuppressant creams/tablets, emollients, moisturizers
SECTION C **CAM use and the Patient**	Current or Previous use of CAM
	Patients familiarity and usage of the following CAMs: Herbal creams, Herbal tablets/capsules/powders/pellets, Chinese herbal medicines, Traditional Indian medicines (Ayuverdic) Traditional African medicines (Inyanga/Isangoma), Homeopathy Vitamin supplements, Acupuncture, Natural Health Supplements, Aromatherapy (massage oils), Reflexology, Reiki, Chiropractic, Other
	Duration of CAM use
	Disclosure/Non-disclosure of CAM use to dermatologist with reasons
	CAM use with/without conventional medicines
	Reasons for using CAM
	Patients Satisfaction of CAM use on eczema symptoms
	Reasons for not exploring CAM (where applicable)

Table 2 Demographics and Characteristics of CAM users vs total study population

	Total Study Population	CAM Users	Proportion of CAM-users within the total study population
	n=206 (100%)	n=135/206 (66%)	n=135/206 (66%)
Gender			
Male	43 (21%)	30/135 (22%)	30/43 (70%)
Female	163 (79%)	105/135 (78%)	105/163 (64%)
Age Category			
Adult with AE	63 (31%)	43/135 (32%)	43/63 (68%)
Children with AE	143 (69%)	92/135 (68%)	92/143 (64%)
Highest frequency age range of adults with AE	<30 [n=30(15%)]	<30 [n=22(73%)]	<30 [n=22(73%)]
Highest frequency age range of children with AE	2-5 years [n=39(27%)]	Parents/care-givers are the decision-makers	Parents/care-givers are the decision-makers
Race*			
Black African	116 (56%)	68/135 (50%)	68/116 (59%)
Indian	68 (33%)	53/135 (39%)	53/68 (78%)
Coloured	12 (6%)	8/135 (6%)	8/12 (67%)
White	9 (4%)	5/135 (4%)	5/9 (56%)
Asian	1 (0.5%)	1/135 (0.74%)	1/1 (100%)
Religion*			
Christian	141 (68%)	85/135 (63%)	85/141 (60%)
Islam	33 (16%)	28/135 (21%)	28/33 (85%)
Hinduism	26 (13%)	18/135 (13%)	18/26 (69%)
No religious domination	6 (3%)	4/135 (3%)	4/6 (67%)
Education			
Postgraduate qualification	20 (10%)	14/135 (10%)	14/20 (70%)
College education	61 (30%)	46/135 (34%)	46/61 (75%)
Secondary School	95 (46%)	56/135 (41%)	56/95 (59%)
Primary School	21 (10%)	13/135 (10%)	13/21 (62%)
No school	9 (4%)	6/135 (4%)	6/9 (67%)
Monthly Household Income			
< R2000	49 (24%)	29/49 (59%)	29/49 (59%)
R2000-R5000	45 (22%)	25/45 (56%)	25/45 (56%)
R5000-R10 000	21 (10%)	16/21 (76%)	16/21 (76%)
R10000-R20 000	40 (19%)	30/40 (75%)	30/40 (75%)

>R20 000	44 (21%)	30/44 (68%)	30/44 (68%)
Unknown (student, pensioner)	7 (3%)	Nil	Nil
Type of Facility attended			
Public	106	66/106 (49%)	66/106 (49%)
Private	100	69/100 (69%)	69/100 (69%)
Duration of AE*	4 years (SD=4,87)	8 years (SD=9,75)	8 years (SD=9,75)

*significant difference noted ($p<0.05$)

Table 3 Complementary Therapies Used for Atopic Eczema and Patients' familiarity with them (of a sample of 206 patients)

	Total Number Used	Familiar but have not used	Unfamiliar
Vitamin supplements	73 (35%)	60 (29%)	73 (35%)
Aromatherapy oils	55 (27%)	67 (33%)	84 (41%)
Herbal creams	53 (26%)	61 (30%)	92 (45%)
Traditional African Medicines	47 (23%)	41 (20%)	118 (57%)
Homeopathy	39 (19%)	42 (20%)	118 (57%)
Natural Health Supplements	21 (10%)	55 (27%)	130 (63%)
Traditional Indian Medicines	18 (9%)	35 (17%)	153 (74%)
Oral Herbal Medicines	13 (6%)	32 (16%)	161 (78%)
Acupuncture	8 (4%)	79 (38%)	118 (57%)
Chinese Herbal Medicines	6 (3%)	36 (17%)	164 (80%)
Reflexology	7 (3%)	67 (33%)	132 (64%)
Reiki	2 (1%)	44 (21%)	160 (78%)

Table 4 The reasons and general attitude towards CAM use amongst 135 patients who have reported using/previously using CAM

REASONS FOR USING CAM	Number/Proportion of Patients
It was recommended to me by family/friends	54 (42%)
I read about it in the media	30 (23%)
My GP recommended it to me	15 (12%)
The pharmacist recommended it to me	6 (5%)
The paediatrician recommended it to me	2 (2%)
GENERAL ATTITUDES TOWARDS CAM	
They are more natural	46 (35%)
I find that they are safer than conventional medicines	36 (28%)
They have less side effects	36 (28%)
The effect is better when I combine it with the dermatologist's medicines	15 (12%)
It is a more holistic healthcare	14 (11%)

4.2. LINK BETWEEN MANUSCRIPT THREE AND MANUSCRIPT FOUR

Manuscript Three: Complementary and Alternative Medicine Use among Patients with Atopic Eczema – A South African Perspective,

Thandar Y, Botha J, Sartorius B, Mosam A,

Health SA Gesondheid. Manuscript number HSAG-S-16-00045 [under review];

has identified an extensive (66%) CAM use amongst atopic eczema patients in a South African setting. It is evident from this research that the majority of patients have not disclosed CAM use to their dermatologist (59%). About half (48%) of the patients said they were not questioned about CAM use by their dermatologist.

Given the prevalence of its use in atopic eczema, most healthcare professionals treating patients for atopic eczema would encounter patients using some form of CAM. Previous studies have reported that healthcare professionals underestimate the use of CAM in their patients.[73] This is likely due to lack of communication between the HCP and the patient which is evident in our findings in Manuscript Three in which almost half of those reporting non-disclosure said that they were 'not asked'. The balance of those that reported non-disclosure felt that 'it was not necessary for their dermatologist to know what other medication they are using'.

These findings pose a huge risk as it affects compliance which in turn affects the overall disease course and outcome from prescribed treatment. It also reflects lack of assurance and trust on the part of the patient towards the HCP. As patients are not necessarily informed regarding the efficacy and safety of many of these CAMs, it is the HCP's role to be knowledgeable about the commonly used CAM and be proactive in initiating discussions with patients. It has been reported that the degree to which HCPs are proactive in enquiring about CAM is largely influenced by their attitude toward them.[73] It is clear that patients have generally embraced CAM, but the uncertainty about the level of knowledge that HCPs have to advise patients, their attitudes and standard practices regarding CAM is what prompted the study which is presented in **Manuscript Four**.

Manuscript Four has been accepted for publication in the accredited and peer-reviewed *South African Family Practice* and is entitled:

Knowledge, Attitude and Practices of South African Healthcare Professionals towards Complementary and Alternative Medicine Use for Atopic Eczema - A Descriptive Survey

Thandar Y, Botha J, Sartorius B, Mosam A

South African Family Practice, 2016 Sept 26; Manuscript number SAFPJ-2016-0058; doi: 10.1080/20786190.2016.1248146 *[in press]*

5. CHAPTER FIVE

5.1. MANUSCRIPT FOUR (IN PRESS)

Knowledge, Attitude and Practices of South African Healthcare Professionals towards Complementary and Alternative Medicine Use for Atopic Eczema - A Descriptive Survey.

Thandar Y, Botha J, Sartorius B, Mosam A

South African Family Practice, 2016 Sept 26; Manuscript number SAFPJ-2016-0058; doi: 10.1080/20786190.2016.1248146 [in press]

This chapter which has addressed Objective Four of this thesis, examines the knowledge, attitude and practices of HCPs towards CAM in atopic eczema in a South African context. Several international studies have explored knowledge, attitude and practices amongst general practitioners (GPs), physicians, pharmacists, paediatricians, academic doctors and other healthcare workers towards CAM; [6-11] however these studies focussed on general CAM use and none within the context of a specific disease. There were no published studies conducted in SA or elsewhere investigating HCPs' knowledge, attitudes and norms of practice with regards to CAM for AE.

Given the extensive use among SA patients with AE,[12] the views and rationales among SA HCPs treating patients with AE is what was investigated in this paper. Also, considering that the levels of knowledge, views and attitudes may vary between HCP groups, this research has taken all mainstream HCPs that treat patients for eczema into account, namely; dermatologists, paediatricians, general practitioners and pharmacists.

The findings are presented in **Manuscript Four**.

Knowledge, Attitude and Practices of South African Healthcare Professionals towards Complementary and Alternative Medicine Use for Atopic Eczema – A Descriptive Survey

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Abstract

Background

Complementary and alternative medicines (CAM) are used widely for treating atopic eczema (AE), commonly in conjunction with conventional medicines prescribed by mainstream healthcare professionals (HCPs). This cross-sectional survey evaluated the knowledge, general attitudes and practices regarding CAM among dermatologists, paediatricians, general practitioners(GPs) and pharmacists treating patients with AE in Durban, KwaZulu-Natal.

Methods

Questionnaires were sent via email or hand-delivered to HCPs nearby.

Results

Of the 330 respondents, 220(67%) were males and 110(33%) females. Most(40%) were >50 years. GPs and pharmacists were significantly more embracing of CAM compared to dermatologists and paediatricians. The majority were not familiar with most CAMs for AE. More GPs(29%) and pharmacists(43%) recommend CAM compare to dermatologists(8%) and paediatricians(5%). GPs and pharmacists were also amenable to referring patients to CAM practitioners. The majority do not initiate discussions with their patients regarding CAM use nor enquire when taking a history. Many dermatologists(65%) and pharmacists(51%) reported that their patients ask about CAM. All dermatologists, 95% paediatricians, 87% GPs and 55% pharmacists reported having no training in CAM but believed it should be included in their curriculum. Most are interested in learning about CAM and agreed that it would better prepare them in managing patients.

Conclusion

Our study demonstrated poor CAM knowledge and communication between HCPs and patients however a strong interest amongst HCPs to learn more. There is an urgent need for continuing education programmes and inclusion into undergraduate curriculums which will assist HCPs in influencing better patient outcomes.

Background

Atopic eczema (AE) is one of the most common skin diseases affecting patients who present to dermatological practices in South Africa (SA).[1] Over the last decade, the lifetime prevalence of physician-diagnosed AE has almost doubled in SA.[2] This rise continues despite accessible effective treatments.[3] Due to AE's chronic, relapsing nature and the unattainability of complete clinical cure, patients are continually exploring complementary and alternative medicines (CAM) in search of a cure.[3] CAM's popularity in the management of AE is well established.[4]

Non-compliance with therapy is a major contributor to AE's persistence. Reported non-compliance rates are 30-60% with most regimes.[5] Common reasons cited for non-compliance were apprehension of the danger of steroids, concern about side effects of other prescribed medication and a preference for 'natural' therapy.[5] This presents a dilemma for practitioners for many reasons: unproven effectiveness of many CAMs, less funding for medication with proven reliability, difficulty in evaluating treatment and perpetuation of 'natural' therapists' perspectives that steroids are dangerous, resulting in long-term suffering.[5]

Although evident from the literature that patients have embraced CAM[3], healthcare professionals (HCP) may not be as embracing. Their attitude and knowledge of CAMs will influence their pro-activeness in enquiring about CAM and confidently discussing proven/ unproven remedies with their patients, thereby influencing an overall positive clinical experience and disease course.

Several international studies have explored the knowledge, attitudes and practices amongst general practitioners (GPs), physicians, pharmacists, paediatricians, academic doctors and other healthcare workers towards CAM.[6-11] These studies focussed on general CAM use and none within the context of a specific disease. We found no

published studies conducted in SA or elsewhere investigating HCPs' knowledge, attitudes and norms of practice with regards to CAMs for AE. Given the extensive use among SA patients with AE,[12] the views and rationales among SA HCPs treating patients with AE requires investigation.

Objectives
We conducted a cross-sectional survey among mainstream HCPs treating patients with AE in Durban, KwaZulu-Natal, with the aim of exploring their knowledge, awareness of use, recommendations, practices and attitudes on CAM use amongst their AE patients.

Methods
The Ethics Committee of University of KwaZulu-Natal provided approval (BE219/14).

Study Population
Practicing dermatologists, paediatricians, GPs and pharmacists in Durban were selected randomly using professional societies' databases and the telephone directory. HCPs had to be practicing in a private practice where they treat AE patients, however, dermatologists and paediatricians were also considered if they consult in the public sector. Sample sizes were calculated based on population estimates of each group of HCP represented in this study in Durban and surrounding areas (within 20km).

Participants were recruited between October 2014-February 2015. 330 HCPs responded to the survey:
25/34 dermatologists (74% response rate)
41/61 paediatricians (67% response rate)
182/570 general practitioners (33% response rate)
82/158 retail pharmacists (52% response rate)

Data Collection
Participants were sent an email with a link to the questionnaire. Questionnaires were also hand-delivered to HCPs practicing nearby. Three reminders were sent electronically and via telephone calls.
The questionnaire covered the following sections:

- Practitioner and Practice Particulars
- General and Demographic particulars of the HCP
- Views/Attitudes on CAM for eczema
- Knowledge of CAM for eczema
- Professional Practices with regards to CAM
- Education regarding CAM for eczema

Statistical Analyses
Data was analysed using Stata 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Categorical data were summarised using frequencies and percentages. Association between type of HCP and attitudes, familiarity and practice using CAM variables were assessed using the Pearson chi-square ($\chi 2$) test and Fishers exact test if any cell count contained fewer than 5 expected observations. We considered a p-value<0.05 as being statistically significant.

Results
Demographics
The 330 HCPs respondents comprised 26 dermatologists, 40 paediatricians, 182 GPs and 82 pharmacists. There were 220(67%) males and 110(33%) females. 113(34%) were Muslim practitioners, 104(32%) Hindu, 99(30%) Christian and 1(0.3%) Buddhist. Two were atheist (0.6%), 1 agnostic (0.3%) and 10 did not respond (3%). The majority (132) were >50yrs (40%), 105(32%) were 31-40yrs, 76(23%) were 41-50yrs and 17(5%) were <30yrs. The majority were Indian practitioners (71%), 48(15%) White, 42(13%) Black and 7(2%) Coloured.

Our study demonstrated that there was no statistically significant demographic factor e.g. age, gender, religion or ethnicity that were predictors of HCPs knowledge, attitudes and practices towards CAM.

SA HCPs' Views/Attitude towards CAM
Views/attitudes were assessed by the degree of agreement to general statements regarding CAM. Fewer specialists (8% dermatologists and 13% paediatricians) felt that CAM provides a more holistic healthcare

approach compared to GPs (32%) and pharmacists (29%) ($p=0.002$). Again, fewer specialists (8% dermatologists and 18% paediatricians) felt that CAM can offer benefits over conventional medicines compared to GPs (36%) and pharmacists (35%) ($p=0.001$). Regarding the perception that the results from CAMs are due to a placebo effect, more specialists (45% paediatricians and 27% dermatologists) than GPs (16%) and pharmacists (11%) were of this opinion ($p<0.001$). More GPs (52%) and pharmacists (59%) felt that if physicians were more knowledgeable about CAM practices, their patients would have better clinical outcomes ($p<0,001$). None of the dermatologists and only 3% paediatricians felt that CAM produced a more complete clinical cure than conventional medicines. This was significantly less than the views of GPs (14%) and pharmacists (16%) ($p=0.037$). More dermatologists (35%) and paediatricians (30%) felt that CAM interferes with standard medical care compared to GPs and pharmacists (both 15%) ($p<0.001$).
These results are represented in Table I.

Table I South African Healthcare Professionals' Views/Attitudes towards CAM			
Statement	**Agree**	**Disagree**	**Neutral**
1. CAM provides a more holistic approach to health than conventional medicines. (p=0.002)			
Dermatologists (n=26)	8%	46%	42%
Paediatricians (n=40)	13%	45%	43%
General Practitioners (n=182)	32%	24%	45%
Pharmacists (n=82)	29%	22%	49%
2. Most CAM are safe and have very few side effects. (p=0.013)			
Dermatologists (n=26)	15%	42%	38%
Paediatricians (n=40)	23%	45%	33%
General Practitioners (n=182)	29%	34%	37%
Pharmacists (n=82)	37%	23%	40%
3. CAM can offer patients benefits that conventional medicines cannot. (p=0.001)			
Dermatologists (n=26)	8%	46%	42%
Paediatricians (n=40)	18%	48%	35%
General Practitioners (n=182)	36%	24%	41%
Pharmacists (n=82)	35%	23%	41%
4. The results of complementary therapies are due to the placebo effect. (p<0.001)			
Dermatologists (n=26)	27%	12%	58%
Paediatricians (n=40)	45%	8%	48%
General Practitioners (n=182)	16%	40%	43%
Pharmacists (n=82)	11%	46%	43%
5. Patients whose physicians are knowledgeable about CAM practices, in addition to conventional medicine, have better clinical outcomes. (p<0.001)			
Dermatologists (n=26)	23%	12%	62%
Paediatricians (n=40)	20%	25%	55%
General Practitioners (n=182)	52%	12%	37%
Pharmacists (n=82)	59%	7%	34%
6. Physicians should have knowledge about the most prominent CAM treatments. (p=0.013)			
Dermatologists (n=26)	69%	8%	19%
Paediatricians (n=40)	73%	10%	18%
General Practitioners (n=182)	81%	2%	17%
Pharmacists (n=82)	83%	5%	12%
7. While we need to be cautions in our claims, a number of CAM therapies hold promise for the treatment of symptoms, conditions and/or diseases. (p<0.001)			
Dermatologists (n=26)	31%	19%	46%
Paediatricians (n=40)	25%	10%	65%
General Practitioners (n=182)	55%	4%	41%
Pharmacists (n=82)	0%	0%	0%
8. CAM therapies should be subjected to more scientific testing before being accepted by conventional doctors. (p=0.886)			
Dermatologists (n=26)	96%	0%	4%
Paediatricians (n=40)	88%	3%	10%
General Practitioners (n=182)	87%	2%	11%
Pharmacists (n=82)	87%	1%	12%
9. CAM can produce longer lasting and more complete clinical results than conventional medicines. (p=0.003)			
Dermatologists (n=26)	0%	58%	42%
Paediatricians (n=40)	3%	53%	45%
General Practitioners (n=182)	17%	29%	54%
Pharmacists (n=82)	11%	34%	55%
10. I am annoyed when I find out my patients are using CAM without telling me. (p=0.034)			
Dermatologists (n=26)	35%	31%	31%
Paediatricians (n=40)	28%	33%	40%
General Practitioners (n=182)	14%	55%	31%
Pharmacists (n=82)	16%	50%	34%

11. CAM means quackery and makes fraudulent claims. (p=0.002)			
Dermatologists (n=26)	12%	46%	42%
Paediatricians (n=40)	13%	20%	68%
General Practitioners (n=182)	6%	58%	36%
Pharmacists (n=82)	10%	51%	39%
12. Interferes with standard medical care. (p<0.001)			
Dermatologists (n=26)	35%	19%	46%
Paediatricians (n=40)	30%	13%	58%
General Practitioners (n=182)	15%	48%	37%
Pharmacists (n=82)	15%	49%	37%

SA HCPs' Familiarity regarding CAM

The percentage of HCPs that reported being very familiar with any of the CAMs frequently used for AE were low. Most were slightly familiar with probiotics and dietary supplements. However, it was evident that all HCPs were unfamiliar with the majority of the CAMs listed on Table 2 with higher levels of unfamiliarity regarding Chinese herbal medicines (CHM) and homeopathy. GPs and pharmacists were more familiar with oral and topical herbal products than dermatologists and paediatricians.
HCPs' familiarity is shown in Table II.

Table II South African Healthcare Professionals' Familiarity regarding CAM

CAM Therapy	Unfamiliar	Slightly Familiar	Very Familiar
1. **Homeopathy (p<0.001)**			
Dermatologists (n=26)	69%	15%	12%
Paediatricians (n=40)	83%	15%	3%
General Practitioners (n=182)	60%	34%	7%
Pharmacists (n=82)	41%	48%	11%
2. **Chinese Herbal Medicines (p<0.001)**			
Dermatologists (n=26)	54%	35%	8%
Paediatricians (n=40)	93%	8%	0%
General Practitioners (n=182)	87%	9%	4%
Pharmacists (n=82)	84%	12%	4%
3. **Probiotics (p<0.001)**			
Dermatologists (n=26)	27%	58%	12%
Paediatricians (n=40)	40%	45%	15%
General Practitioners (n=182)	35%	45%	21%
Pharmacists (n=82)	22%	33%	45%
4. **Dietary Supplements (p=0.002)**			
Dermatologists (n=26)	35%	50%	12%
Paediatricians (n=40)	28%	63%	10%
General Practitioners (n=182)	23%	51%	26%
Pharmacists (n=82)	13%	54%	33%
5. **Oral Herbal Products e.g. evening primrose oil, borage oil (p<0.001)**			
Dermatologists (n=26)	50%	23%	23%
Paediatricians (n=40)	68%	28%	5%
General Practitioners (n=182)	38%	48%	13%
Pharmacists (n=82)	17%	57%	26%
6. **Topical Herbal Creams e.g. calendula, chamomile, St John's Wort (p<0.001)**			
Dermatologists (n=26)	46%	42%	8%
Paediatricians (n=40)	58%	40%	3%
General Practitioners (n=182)	41%	46%	14%
Pharmacists (n=82)	17%	61%	22%

SA HCPs' Professional Practices regarding CAM

The majority of HCPs never/rarely initiate discussions regarding CAM for AE (p=0.006) and only sometimes have discussions with patients when a patient requests a CAM (no difference across HCP groups was noted) (p=0.698). Although most reported not being confident in discussing CAM therapies with their patients, the majority reported that they always believe that HCPs treating patients for AE should regularly ask about CAM use. In general, most HCPs were unhappy to refer patients to CAM practitioners. More specialists (54% dematologists and 45% paediatricians) reported never being happy to refer patients to CAM practitioners compared to GPs (25%) and pharmacists (22%).

HCPs' professional practice habits are shown in Table III.

Table III South African Healthcare Professionals' Practices regarding CAM

Statement	Always	Never	Often	Rarely	Sometimes
1. I initiate a discussion with patients regarding CAM for their eczema. (p=0.006)					
Dermatologists (n=26)	0%	65%	4%	12%	19%
Paediatricians (n=40)	0%	55%	5%	28%	13%
General Practitioners (n=182)	4%	29%	12%	31%	24%
Pharmacists (n=82)	7%	31%	9%	23%	29%
2. I have a discussion when a patient requests CAM for their eczema. (p=0.698)					
Dermatologists (n=26)	4%	19%	23%	19%	34%
Paediatricians (n=40)	5%	15%	15%	30%	35%
General Practitioners (n=182)	12%	12%	19%	22%	36%
Pharmacists (n=82)	13%	17%	21%	15%	34%
3. I ask about CAM use when taking a medication history for a new patient. (p=0.110)					
Dermatologists (n=26)	0%	27%	31%	23%	19%
Paediatricians (n=40)	18%	23%	13%	18%	30%
General Practitioners (n=182)	18%	20%	26%	16%	20%
Pharmacists (n=82)	15%	10%	22%	24%	29%
4. I am confident discussing CAM therapies with patients. (p=0.036)	4%	42%	12%	31%	12%
Dermatologists (n=26)	5%	35%	8%	35%	18%
Paediatricians (n=40)	6%	25%	13%	33%	23%
General Practitioners (n=182)	10%	12%	10%	30%	38%
Pharmacists (n=82)					
5. I believe that health practitioners treating patients for their eczema should regularly ask patients if they are using CAM therapies. (p=0.138)					
Dermatologists (n=26)	54%	0%	23%	0%	23%
Paediatricians (n=40)	30%	3%	35%	8%	25%
General Practitioners (n=182)	44%	4%	26%	7%	19%
Pharmacists (n=82)	57%	1%	29%	2%	10%
6. I am happy to refer patients to CAM practitioners e.g. Homeopaths, herbalists etc. for complementary treatment for their eczema. (p=0.002)					
Dermatologists (n=26)	0%	54%	0%	35%	12%
Paediatricians (n=40)	3%	45%	5%	25%	23%
General Practitioners (n=182)	8%	25%	9%	19%	38%
Pharmacists (n=82)	13%	22%	7%	21%	37%

SA HCPs' recommendation of CAM

Most SA HCPs do not recommend CAM for AE. However, in comparison, the majority of specialists (92% dermatologists and 95% paediatricians) do not recommend CAM compare to GPs (71%) and pharmacists(57%)(p<0.001). This reflects a substantial number of GPs and pharmacists that do recommend CAM.

Figure 1 represents these results.

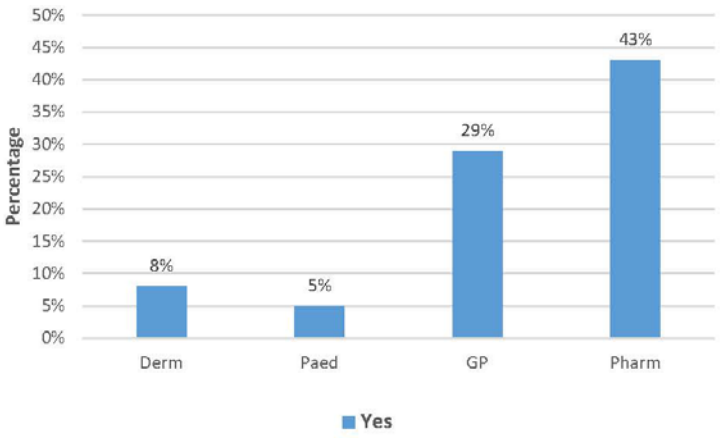

Figure 1 Percentage of Healthcare Professionals that recommend CAM for Eczema (p<0.001)

Patients requesting CAM

More than half of the dermatologists (65%) and pharmacists (51%) reported that their patients ask questions about or request CAMs for AE. Fewer paediatricians (33%) and GPs (36%) reported this (p=0.005).

SA HCPs' Knowledge/Education regarding CAM

All dermatologists and most paediatricians (95%) and GPs (85%) had no training in CAM compared to 55% pharmacists (p<0.001). A larger number of specialists did not access medical journals (p<0.001), internet (p=0.005) or have discussions with other colleagues regarding CAM (p=0.037) compared to GPs and pharmacists. Comparatively, pharmacists were among the HCPs who sourced CAM information the most. The majority of paediatricians (85%), GPs (83%) and pharmacists (82%) reported that CAM is never discussed at meetings whereas more than half of dermatologists reported CAM being discussed in congresses (p<0.001). Table IV reflects these results.

Table IV South African Healthcare Professionals' Education regarding CAM

Statement	No	Yes, but minimal/rarely	Yes, substantial/frequently
1. Did you have any training on CAM? (p<0.001)			
Dermatologists (n=26)	100%	0%	0%
Paediatricians (n=40)	95%	3%	3%
General Practitioners (n=182)	87%	8%	4%
Pharmacists (n=82)	55%	37%	9%
2. Do you access any medical journals to source information on CAMs for eczema? (p<0.001)			
Dermatologists (n=26)	77%	15%	8%
Paediatricians (n=40)	83%	10%	8%
General Practitioners (n=182)	68%	26%	6%
Pharmacists (n=82)	44%	50%	6%
3. Do you access any information on the internet with regards to CAMs for eczema? (p=0.006)			
Dermatologists (n=26)	62%	27%	12%
Paediatricians (n=40)	68%	25%	8%
General Practitioners (n=182)	59%	31%	9%
Pharmacists (n=82)	35%	45%	20%
4. Do you have discussions with other colleagues about CAM use for eczema? (p=0.034)			

Dermatologists (n=26)	62%	38%	0%
Paediatricians (n=40)	78%	23%	0%
General Practitioners (n=182)	64%	30%	5%
Pharmacists (n=82)	48%	43%	9%
5. Is CAM for eczema discussed in congresses you have attended? (p<0.001)			
Dermatologists (n=26)	35%	58%	8%
Paediatricians (n=40)	85%	15%	0%
General Practitioners (n=182)	83%	15%	2%
Pharmacists (n=82)	82%	15%	4%

SA HCPs' Perspectives on CAM Education

On assessing the HCPs perspectives on CAM education, the majority responded positively to universities including CAM as part of the curriculum (p=0.001). Most agreed that learning about CAM would better prepare them for treating patients with AE (p=0.004) and the majority were interested in learning more about CAM for AE (p=0.004). These results are shown in Figure 2.

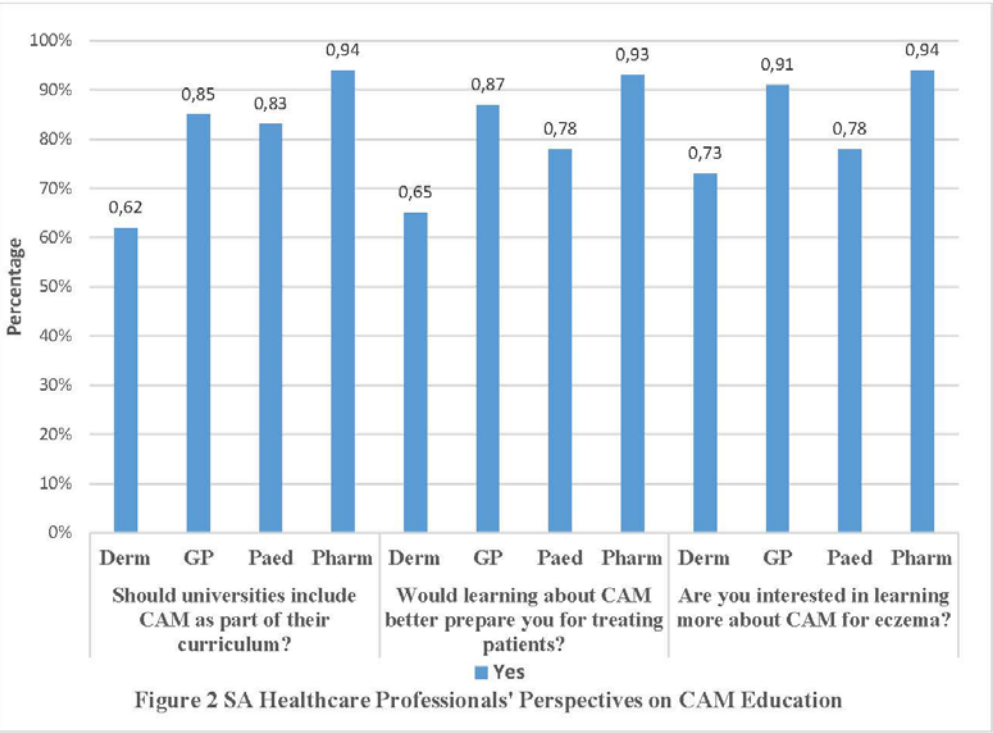

Figure 2 SA Healthcare Professionals' Perspectives on CAM Education

Discussion

Attitudes

The widespread use of CAM for AE among patients worldwide has been documented.[13] Data has also revealed extensive use among SA AE patients.[12] We thus explored the knowledge, attitudes and practices of SA HCPs on CAM for AE.

The attitudes among HCPs in our study varied. Those with specialist training (dermatologists and paediatricians) were more skeptical; uncertain about the value and less receptive towards CAM compared to GPs and pharmacists who were significantly more positive and embracing of CAM.

This positive attitude was seen in several other studies. A Texas-based study reported that a large number of GPs were positive about incorporating CAM into general practice (75%), referring patients to CAM practitioners (>60%) and offering proven CAM therapies to patients (70%).[10] Saudi Arabian primary healthcare physicians also showed a positive attitude and 76% believed that CAM would lead to a better patient outcome.[14] GPs in a Qatar survey reflected support of CAM with 83% agreeing that it is a useful supplement to conventional medicine and included ideas and methods beneficial to the primary care physician.[6] The overall attitudes of Australian GPs and pharmacists towards CAM are positive.[15] In a SA based study among pharmacists, almost half (47%) believed in the benefits of both conventional and herbal medicines and 64% perceived herbs to be therapeutically effective drugs.[16] Our survey shows a similar positive attitude among GPs and pharmacists.

On the contrary, certain studies have demonstrated scepticism and uncertainty about CAM's value. The majority of academic doctors with dual academic and clinical roles in a Bristol, UK study expressed doubt due to the lack of scientific evidence.[9] This scepticism is seen amongst SA specialists (dermatologists and paediatricians) in our survey with many also having dual academic and clinical roles. The Texas-based study among GPs reported that in comparison to another study using the same instrument, a more positive attitude was seen among primary care practitioners compared to non-primary care peers (sub-speciality physicians) at Mayo Clinic.[10] GPs are generally based within the community and are exposed to a variety of diseases for which patients are using CAM. This type of family medical practice seems a more open forum for patients and doctors to discuss CAM choices thus realising a more open approach from GPs. A study among paediatricians in the Netherlands however, found a positive attitude towards CAM, mostly towards probiotics and dietary supplements whose action can be rationalised with those of conventional medicines.

Familiarity

The skepticism among HCPs can be attributed to their lack of knowledge. On assessing knowledge/familiarity, it was evident that the majority were unfamiliar with most CAMs for AE. GPs and pharmacists were more familiar with herbal products (oral and topical) compared to specialists. Higher levels of unfamiliarity was seen with CHM and homeopathy, possibly because the theory behind their action differs vastly from conventional medicine as well as the limited exposure to CHM practitioners in Durban. Another Durban-based study amongst healthcare workers in HIV/AIDS clinics reflected poor CAM knowledge including homeopathy and CHM.[11] Likewise, 81% of Turkish dermatologists reported very little/no knowledge of CAM and more than half of paediatricians surveyed in the Netherlands also had little knowledge of CAM therapies.[17] Studies among GPs in Qatar and Saudi Arabia reported similiar poor CAM knowledge (39% and >63% respectively).[6, 14] On the contrary, several Australian surveys indicate that GPs are familiar with a wide range of CAM therapies.[15] Australian pharmacists reported that while a lack of knowledge about safety was a definite barrier to their recommendation, they still often recommended CAM alongside conventional medicines as part of the pharmacy protocol.[7]

Recommendations and Referrals

Although most HCPs do not recommend CAM to their patients, more GPs (29%) and pharmacists (43%) do compare to dermatologists (8%) and paediatricians (5%). Similiarly more GPs and pharmacists were amenable to referring patients compared to the specialists (Table 3). Both practices are reflective of their general attitudes towards CAM. The concern is that those recommending CAM are doing so without adequate knowledge/training. This lack of knowledge/training was reported among the majority of respondents in our study but did vary depending on CAM type. Recommendations despite knowledge was seen among Turkish dermatologists where 80% reported little/no knowledge, yet more than half have recommended at some stage topical herbal therapies and a significant proportion other herbal therapies.[17] With regards to referrals, 50% of paediatricians in a Michigan, USA study said that they would refer patients to CAM practitioners whereas only 27% of paediatricians in Netherlands occasionally refer patients.[18] In a survey among Durban pharmacists, only 8% considered themselves sufficiently equipped to advise patients, yet 45% indicated that they did counsel patients on herbal medicines and these were recommended by 36% of respondents. In a Texas based study, almost half (42%) of the primary HCPs did refer patients to CAM practitioners and 64% would like to.[10] Referral rates were low among Qatar GPs where 39% stated that they had poor CAM knowledge.[6] A greater number of doctors in Australia (68%) were in favour of referring patients to complementary therapists and most were familiar with various CAM therapies.[15]

Communication

Although fewer HCPs in our survey recommend or refer patients to CAM practitioners, a fair number are doing so. Fewer paediatricians (33%) and GPs (36%) said that their patients ask about CAM compared to a larger number of dermatologists (65%) and pharmacists (51%). It appears that patients frequently ask for CAM for skin diseases. On assessing HCPs' practices when treating patients, our study indicated that the majority of SA

HCPs do not initiate discussions with their patients regarding their CAM use. Even when a patient requests/asks about CAM it is not their practice to always discuss this with patients. Most do not even enquire about the patients' CAM use when taking a medical history. The majority reported a a lack of confidence in discussing CAM therapies. This is undoubtedly due to their lack of knowledge as confirmed through this study.

Despite these practices, most believed that HCPs treating patients for AE should regularly ask patients if they are using CAM and most agreed that it is necessary for practitioners to have knowledge about the most prominent CAM treatments. As pharmacies are the major stockists of CAM products, patients expect pharmacists to have sufficient knowledge to advise them. This is an important aspect of a pharmacist's service. This reluctance is discussing CAM issues with patients is also seen in other studies. In the Netherlands, the majority of paediatricians seldom discuss CAM use with parents and among paediatricians in Michigan, USA, discussions regarding CAM were found to be mostly initiated by parents (85%).[18,19] Even primary healthcare physicians in Saudi Arabia who claimed to be comfortable in counselling patients on certain types of CAMs commonly used in their region were reluctant to initiate discussions regarding their patients' CAM practices.[14] Among GPs in Texas, USA, 84% stated that their patients initiated discussions around CAM.[10] On the other hand, a national Australian survey indicated that a large number of GPs who practice integrative medicine (66%) as well as almost half (47%) of those not practicing integrative medicine do initiate CAM discussions with patients and a similar number also ask about its use when taking a history.[20]

Education

Our survey revealed that most SA HCPs acknowledge their lack of knowledge on CAM and want to be better informed. This lack of knowledge is due to lack of training on CAM both in the undergraduate and continuing education programmes. All dermatologists, 95% paediatricians and 87% GPs reported having no training in CAM. Pharmacists on the other hand have had a little more CAM training (45%). The majority of respondents believed that universities should include CAM as part of their curriculum. A similar number also agreed that learning about CAM would better prepare them for managing patients and are interested in learning more. These views correlate with other studies which have recommended that CAM be included in undergraduate medical and pharmacy curricula.[7,16] Among Saudi Arabian primary healthcare physicians, 85% agreed that they should have knowledge about CAM[14] In Qatar, almost all GPs (98%) were interested to learn more about CAM and most dermatologists in a study in Turkey also claimed that they would like to be better informed about CAM.[17] In a survey amongst paediatricians in Michigan, USA, 54% were keen on continuing medical education courses for CAM.[18] Academic doctors in Bristol, UK acknowledged that better doctor-patient communication and patient disclosure is required, however, their views on educating themselves on CAM were varied.[9] Our survey was comparable to most as the majority of HCPs (>72% specialists, >90% GPs and pharmacists) said that they wanted to learn more about CAM for AE.

Limitations

Although this study has been compared to those in other countries, our study was reflective of CAM practices specifically for AE whereas those of other countries were on general use of CAM. It is presumed that the attitudes, knowledge and practices of CAM for AE would be similiar to CAM use in other contexts. The responses in the study may not represent the views of all SA HCPs as our study sample were majority Indian HCPs within the Durban metropolitan area.

Conclusion

It is clear that CAM is an established therapy for a large part of the population and considering that CAM and conventional medicine are often used together, there is a potential for confusion in attribution of therapeutic benefits, adverse effects and drug interactions. Their concomitant use also creates a potential for non-compliance with prescribed therapy affecting overall clinical outcome. It is imperative that HCPs initiate discussions as well as realise and accept a responsibility in understanding their evidence based role. HCPs need to become more conversant with common CAM therapies in order to influence better patient management and possibly better outcomes. Our study demonstrated poor CAM knowledge and communication between HCP and patient but a strong interest amongst HCPs to learn more.

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6. CHAPTER SIX

6.1. SYNTHESIS AND CONCLUSION

The synthesis consolidates this study's predominant findings. The limitations of the study and recommendations are also discussed at the end of this chapter.

Taking into consideration the increase in prevalence of atopic eczema in South Africa over the last decade[3] and in light of the numerous reports on extensive CAM use for skin conditions, especially atopic eczema, many questions surrounding CAM use amongst local atopic eczema patients were prior to this study, unanswered. This research provides a synopsis on the use of CAM for atopic eczema in Durban, Kwa-Zulu Natal. Apart from providing a perspective on the trends of CAM use amongst patients, the synthesis discusses the predominant findings surrounding the perspectives of healthcare professionals towards CAM for atopic eczema. The current study has further contributed to the literature by adding results from its original systematic review on topical CAM and has provided clarity from findings of previously published systematic reviews on oral CAM. Three papers have been published from this thesis in accredited and peer-reviewed journals and one manuscript is currently under review for publication in another accredited and peer-reviewed journal.

The interest in complementary and alternative medicines has increased dramatically over the past decade. Daily, patients are spending large amounts of money on CAM, usually from their own pockets as most medical aid companies do not cover these treatments. This in itself reflects the general positivity and acceptance of CAM by the public and indicates that some of these treatments may provide benefits which outweigh their costs.[74] The findings from this study is consistent with others in terms of the general embracement of CAM, whereby an overwhelming number of patients (66%) are currently using or have tried CAM for their atopic eczema; and although subjective, almost half (48%) reported "some improvement" to "definite improvement".

Despite this successful and booming commercial market, CAM use still remains controversial among healthcare professionals as the debate surrounding its scientific and clinical evidence base remains unproven in many modalities. The present study reflected that close to 90% of all healthcare professionals interviewed felt that CAM should be subjected to more scientific testing. Regardless of the attraction that CAM has for patients and the attention given to it by the media, information in the literature proving their efficacy and safety was inconclusive. It was thus among

the objectives of this current study to provide clarity on what the current evidence is with regards to popular oral CAMs and topical CAMs studied for atopic eczema. This was accomplished by investigating and critiquing the clinical effectiveness of specific and commonly used oral CAMs for atopic eczema in the form of an overview of the many published systematic reviews. The thesis also contributed to academia globally by bridging a gap in the literature and successfully completing and publishing the very first systematic review on topical herbal medicines for atopic eczema; thereby providing answers to topical herbal remedies for the disease.

As an outcome from Objective One, the research identified inconclusive evidence of efficacy and safety with the selected frequently used oral CAMs. It was found that homeopathy failed to show any treatment effect whereas further studies are warranted with some therapies (Chinese Herbal Medicine, certain probiotic strains and fish oil). It was also noted that further studies of evening primrose oil and borage oil are difficult to justify as the results from these trials did not favour these oils over placebo and the narrow confidence intervals between active and placebo treatments exclude the possibility of any clinical useful difference. These results are presented in Manuscript One and published in *South African Family Practice*. The results from this overview are able to provide evidence-based clarity to all practitioners treating patients for atopic eczema in light of the most current findings in the literature.

Stemming from Objective Two, as presented in Chapter Three of this thesis and published in the *British Journal of Dermatology*, is the first systematic review on topical herbal extracts for atopic eczema. These findings have helped analyse and ascertain the overall efficacy and safety of various topical preparations which was lacking in the literature, thus providing clarity to the prescriber as well as directions for future research on topical herbal products for atopic eczema. The systematic review concluded that there was insufficient evidence of efficacy for all the topical herbal medicines explored in the systemic review. However, with the glimmer of hope in studies with both positive results and a low risk of bias across all domains, the systematic review was able to determine specific CAMs namely, *licorice gel* and *Hypericum perforatum*; where future research is warranted.

The thesis further examined the use and views amongst patients suffering from atopic eczema and also explored the role and practices surrounding CAM of all mainstream healthcare professionals that treat this disease.

Objective Three of this research determined what was lacking in the literature on the prevalence of CAM use amongst atopic eczema patients in a South African setting. This is the only African and South African study which demonstrates the extent of use of CAM for atopic eczema, the types of CAMs utilized, and the influence of demographic factors such as age, gender, race, ethnicity, socio-economic status and level of education on CAM use in atopic eczema. This study identified extensive (66%) CAM usage among atopic eczema patients in Durban, Kwa-Zulu Natal. This usage, which is amongst a larger sample population in comparison to other studies, was significantly higher than studies conducted in Europe, United Kingdom and the US. Race and religion and duration of the disease were significant predictors of CAM. It was found that cultural influences play a significant role in driving people to use CAM, with Indians and Muslims being the most frequent users. Additonally, this study identified the frequently used CAMs for atopic eczema to be vitamins, aromatherapy oils, herbal creams, traditional African medicines and homeopathy. The study further highlighted that CAM is mostly used in combination with conventional therapy and there was a reported poor patient disclosure to the dermatologist with regards to their CAM use. This paper is currently under review for publication in the accredited journal, *Health SA Gesondheid*.

Chapter Five of this thesis, in press in *South African Family Practice*, presented the findings stemming from Objective Four on the knowledge, attitude and practices of healthcare professionals towards CAM for atopic eczema. This research discerned differences among mainstream healthcare professionals' views and attitudes towards the use of CAM with the specialist group being the most sceptical surrounding its use. The findings established that there was poor communication between the healthcare professional and the patient surrounding CAM. The majority healthcare professionals did not initiate discussions nor discuss CAM with patients on request. The healthcare professionals in this study had very little knowledge of CAM, however, all acknowledged their lack of knowledge and indicated that they would like to be further educated with regards to the most recent evidence or lack of evidence of the common CAMs used for atopic eczema. It was found that CAM and conventional medicines are often used together. Considering this, the poor CAM knowledge and lack of communication between healthcare practitioners and patients found in this study have emphasized an urgent need for continuing education programmes on CAM and inclusion into undergraduate curriculums. It also highlights the need for healthcare professionals to communicate better with their patients regarding CAM use in light of the recent findings (as highlighted in Chapters Two and Three).

In conclusion, this work has accomplished its main aim through meeting its individual objectives. The findings from this thesis can be considered a key cornerstone in understanding CAM for atopic eczema and has contributed significantly to what was lacking in the literature globally, in Africa as well as South Africa. The work presented in this thesis has generated information essential in helping both patients and healthcare practitioners work together in order to help improve the outcome of atopic eczema.

Figure 1 which follows, synthesizes diagrammatically, the study's main objectives and how they were accomplished. It shows the key results stemming from this research and also highlights areas in which this research has filled previous gaps in the literature.

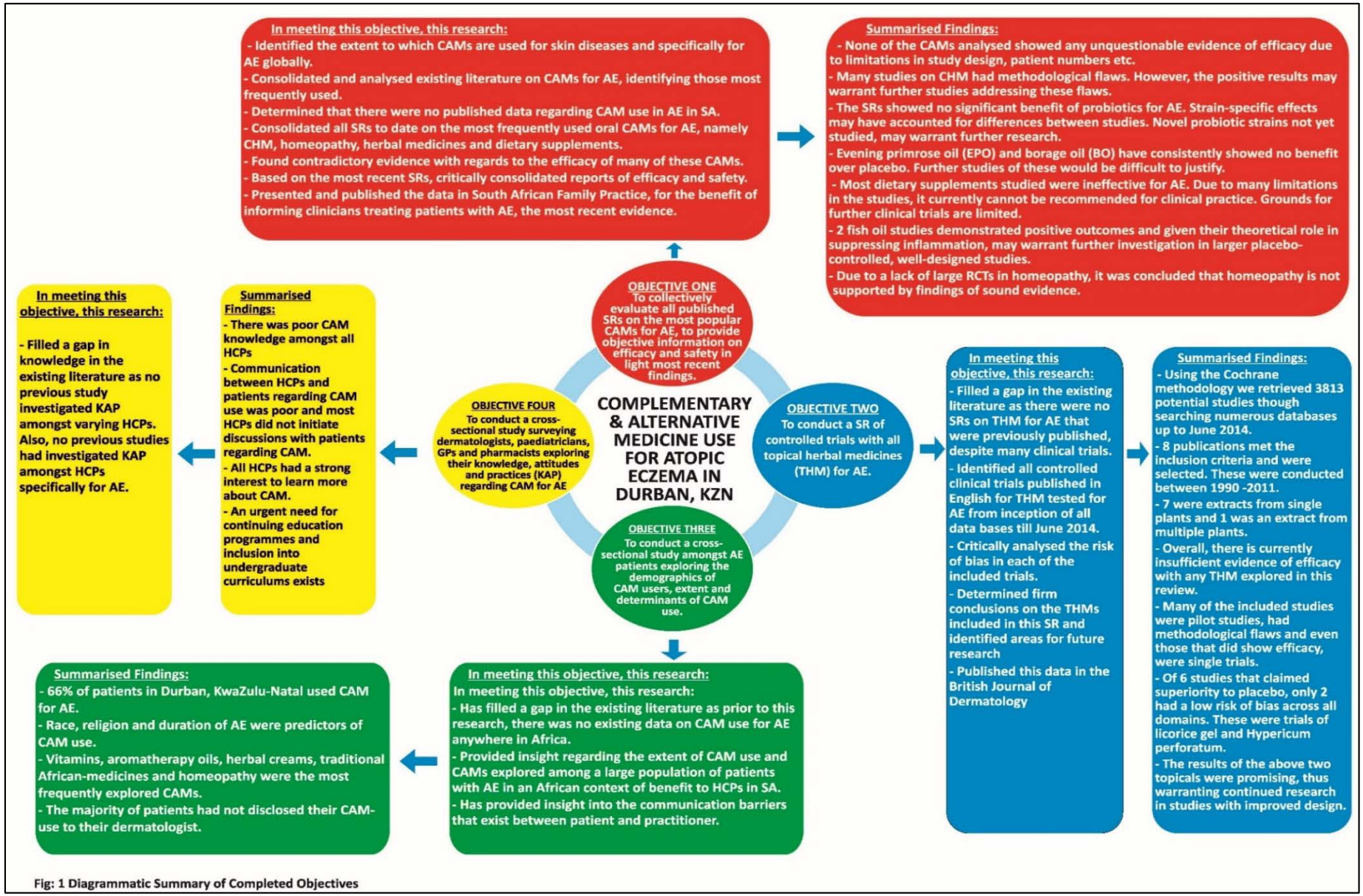

Fig: 1 Diagrammatic Summary of Completed Objectives

6.2. LIMITATIONS

As each objective had its own limitations, these have been discussed in detail within the context of each manuscript in the preceding chapters.

6.3. RECOMMENDATIONS

The prevalence of CAM is high, has been on the rise and will continue to increase as the population becomes more health conscious and more well-read. CAM can therefore not be considered a 'fad' and its impact on healthcare has to be continuously researched. The following recommendations arise from this thesis:

- This study identified frequently used CAMs; some of which many patients have reported positive results. An analysis of the efficacy of these specific CAMs in clinical trials, randomised, controlled and blinded, may be able to provide answers for possible integration of effective therapies into mainstream care.
- The results from this study are a reflection of practices of patients in Durban, Kwa-Zulu Natal. It would be necessary for similar studies to be conducted in other regions of Kwa-Zulu Natal and in other provinces in order to determine regional differences and ascertain if there is a similar trend amongst all patients in South Africa.
- As above, studies amongst healthcare professionals in other regions would also be beneficial in ascertaining regional differences in their knowledge, attitude and practices.
- The population of healthcare professionals in this research have indicated a dire need for more knowledge on CAM. Continuing education programmes on CAM for all healthcare professionals treating patients for atopic eczema should be offered regularly in seminars, talks, conferences or online.
- Furthermore, establishing the extent of exposure to CAM taught within the current curriculum in all universities that train undergraduate doctors and pharmacists in South Africa would need to be conducted. Inclusion of appropriate CAM education in undergraduate programmes for all students is essential in preparing the next generation of professionals treating patients. These courses need to be structured and established within university curricula to meet the needs and trends of the local population.
- Due to the large number of patients self-prescribing CAM and visiting alternative practitioners while on treatment with conventionally prescribed therapy; further studies investigating the costs of these CAMs and the costs of visits to CAM practitioners would

be uselful in helping ascertain the impact of this on the economy and the overall management of an atopic eczema patient.

- A comparitive cost analysis study of CAM vs. conventional treatment would also help ascertain the financial impact of these medicines on the economy and in patients with atopic eczema.
- From interviewing patients in both the public and private sector, it is apparent that there is a need for an establishment of an atopic eczema support center in local hospitals and clinics. This would allow more time for patients to get detailed advise on their medical treatment and interact in a more formal setting with others suffering from the same disease. A support center would help to better educate parents and caregivers on managing their children's eczema and improving their daily experiences with the disease.

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8. APPENDICES

8.1. APPENDIX 1: PATIENT QUESTIONNAIRE (ENGLISH)

The Use of Complementary and Alternative Medicine (CAM) for Atopic Eczema

Patient Survey

A. General and Demographic Information

A1. Patient Particulars

Patient Number ----------

A1. Practice attending for treatment

- ☐ Attending King Edward VIII Dermatology Outpatients
- ☐ Attending Specialized Dermatology Private Practice

Specify: .....

A2. Gender

- ☐ Male
- ☐ Female

A3. Religion

- ☐ Christian
- ☐ Muslim
- ☐ Hindu
- ☐ Jew
- ☐ Buddhist
- ☐ Other: .....

A4. Race

- ☐ Black
- ☐ White
- ☐ Indian
- ☐ Coloured
- ☐ Other: .....

A5. Your Age

- ☐ <30
- ☐ 31-40
- ☐ 41-50
- ☐ >50

A6. Age of Child (if child is the patient)

- ☐ 0-3 months
- ☐ 3-6 months
- ☐ 6-12 months
- ☐ 1-2 years
- ☐ 2-5 years
- ☐ 5-8 years
- ☐ 8-12 years
- ☐ >12 years

A7. Your Level of Education

- ☐ No school
- ☐ Primary School
- ☐ Secondary School
- ☐ College
- ☐ Postgraduate

A8. Average Gross Monthly Household Income

- ☐ Under R2000
- ☐ R2000-R5000
- ☐ R5000-R10 000
- ☐ R10 000-R20 000
- ☐ >R20 000

B. Treatment Management of Atopic Eczema

B1. How long have you/your child had atopic eczema.

- ☐ <1 month
- ☐ 1-3 months
- ☐ 3-6 months
- ☐ 6-12 months
- ☐ > 1 year

Specify .....

B2. What treatment prescribed by your dermatologist are you/your child using.

- ☐ Steroid creams e.g. steroid V®, Advantan®, Betnovate®, Dermovate®
- ☐ Steroid tablets or syrup e.g. Prednisone, Prelone®
- ☐ Antihistamines e.g. Zyrtec®, CTM®
- ☐ Immunosuppressant creams e.g. Protopic®/Elidel®
- ☐ Immunosuppressant tablets e.g. Azathioprine, Cyclosporin
- ☐ Emollients and Moisturizers
- ☐ Other

Specify:

.....

.....

.....

C. CAM Use And The Patient

C1. Are you using any other medicines or alternative treatment methods for yourself/your child's eczema.

- ☐ Yes
- ☐ No

If your answer to the above question is YES, then proceed with the following questions:

C2. How long has it been since you have begun using other medicines or alternative treatment methods for your/your child's eczema?

- ☐ <1month
- ☐ 1-3 months
- ☐ 3-6 months
- ☐ 6-12 months
- ☐ >1 year

C3. Is your dermatologist aware of any of the other medicines or alternative treatment methods that you/your child is using for eczema?

- ☐ Yes
- ☐ No

C3.1. If your answer to the previous question was NO, please choose the reason:

- ☐ I don't feel it is necessary for my dermatologist to know about other medicines that I am using.
- ☐ My dermatologist did not ask me about my other medicines.
- ☐ I am afraid to tell the dermatologist about my other medicines.
- ☐ Other: .....

C4. Indicate what types of other medicines or alternative treatments you/your child is using for eczema. Where possible, please indicate the name of the medicine used.

- ☐ Herbal creams .....
- ☐ Herbal tablets/capsules/powders/pellets .....
- ☐ Chinese herbal medicines .....
- ☐ Traditional Indian medicines(Ayuverdic).....
- ☐ Traditional African medicines .....
- ☐ Homeopathy.....
- ☐ Vitamin supplements.....
- ☐ Acupuncture.....
- ☐ Natural Health supplements .....
- ☐ Aromatherapy.....
- ☐ Refloxology.....

- ☐ Reiki……
- ☐ Chiropractic……
- ☐ Other …….

C5. How are you/your child using the other treatments for eczema.

- ☐ Together with medicines prescribed by the dermatologist.
- ☐ Mostly using other treatment methods only.
- ☐ Rarely able to use either.
- ☐ Other ……

C6. What are your reasons for using other medicines and alternative treatment methods for your eczema. You may select more than one reason if necessary.

- ☐ They are safer than conventional medicines.
- ☐ They are more natural.
- ☐ They have less side effects.
- ☐ They work better than conventional medicines.
- ☐ The effect is better when I combine it with the dermatologists medicines.
- ☐ It is a more holistic healthcare.
- ☐ It was recommended to me by family/friends.
- ☐ I read about in the media (magazines/internet).
- ☐ Other ……

C7. Have you noticed any improvement in your/your child's eczema with the other medicines or alternative treatment methods.

- ☐ Yes
- ☐ No
- ☐ Some
- ☐ Don't know

Thank you for taking your time to participate in this survey.

8.2. APPENDIX 2: HEALTHCARE PRACTITONER SURVEY

The Use of Complementary and Alternative Medicine (CAM) for Atopic Eczema

A Survey for Healthcare Practitioners

A. Practitioner Particulars

A1. Type of Practice

- ☐ General Medical Practice (Private)
- ☐ Specialized Dermatology Practice (Private)
- ☐ Specialized Dermatology Practice (Public Sector)
- ☐ Retail Pharmacy Practice Retail Pharmacy Practice
- ☐ Other: ……

A2. Gender

- ☐ Male
- ☐ Female

A3. Religion

- ☐ Christian
- ☐ Muslim
- ☐ Hindu
- ☐ Jew
- ☐ Buddhist
- ☐ Other: ……

A4. Your Age

- ☐ <30
- ☐ 31-40
- ☐ 41-50
- ☐ >50

A5. Your Qualifications

- ☐ MBChB

☐ FCDerm

☐ BPharm

☐ Other: .....

A6. Race

☐ Black

☐ White

☐ Indian

☐ Coloured

☐ Other: .....

B. Views/Attitudes on CAM for Atopic Eczema

Please provide your opinion on the following by choosing the appropriate response for each item:

	Agree	Disagree	Neutral
1. CAM provides a more holistic approach to health than conventional medicines.	O	O	O
2. Most CAMs are safe and have very few side effects.	O	O	O
3. CAM can offer patients benefits that conventional medicines cannot.	O	O	O
4. The results of complementary therapies are due to the placebo effect.	O	O	O
5. Patients whose physicians are knowledgeable about CAM practices, in addition to conventional medicine, have better clinical outcomes.	O	O	O
6. Physicians should have knowledge about the most prominent CAM treatments.	O	O	O
7. While we need to be cautions in our claims, a number of CAM therapies hold promise for the treatment of symptoms, conditions and/or diseases.	O	O	O
8. CAM therapies should be subjected to more scientific testing before being accepted by conventional doctors.	O	O	O

9. CAM can produce longer lasting and more complete clinical results than conventional medicines.	O	O	O
10. I am annoyed when I find out my patients are using CAM without telling me.	O	O	O
11. CAM means quackery and makes fraudulent claims.	O	O	O
12. Interferes with standard medical care.	O	O	O

C. Knowledge of CAM for Atopic Eczema

C1. Please rate how familiar you are with the following CAMs used for atopic eczema:

	Unfamiliar	Slightly Familiar	Very Familiar
1. Homeopathy	O	O	O
2. Chinese Herbal Medicines	O	O	O
3. Probiotics	O	O	O
4. Dietary Supplements	O	O	O
5. Oral Herbal Products e.g. evening primrose oil, borage oil	O	O	O
6. Topical Herbal Creams e.g. calendula, chamomile, St John's Wort	O	O	O

C2. Are there any other CAM products not mentioned in the above question that you are familiar with for the treatment of atopic eczema.

☐ Yes

☐ No

C2.1. If your answer to the previous question was YES, please state which other products you are familiar with.

D. Practices regarding CAM for Atopic Eczema

D1. Do you recommend any CAMs to your patients for their eczema.

- ☐ Yes
- ☐ No

D1.1. If your answer to the previous question was YES, please state which CAMs you recommend for eczema.

Please write your answer here:

D2. Do any of your patients ask about CAM for their eczema.

- ☐ Yes
- ☐ No

If NO proceed to question D3

D2.1. If your answer to the previous question was YES, roughly how many patients ask about CAM for their eczema.

- ☐ Very few
- ☐ A fair number
- ☐ Most
- ☐ Other: …….

D2.2. If your answer to D2 was YES, state which CAMs patients frequently ask about.

Please write your answer here:

D3. How often do you ask your patients about what CAMs they have used or are using for their eczema.

- ☐ Never
- ☐ Seldom
- ☐ Occasionally
- ☐ Frequently
- ☐ Always
- ☐ Other: .....

D4. Please select the best option to the statements below:

	Never	Rarely	Sometimes	Often	Always
4.1. I initiate discussions with patients regarding CAM for their eczema.	○	○	○	○	○
4.2. I have a discussion when a patient requests a CAM for their eczema.	○	○	○	○	○
4.3. I ask about CAM use (always or often) when taking a medication history for a new patient.	○	○	○	○	○
4.4. I am confident discussing CAM therapies with patients.	○	○	○	○	○
4.5. I believe that health practitioners treating patients for their eczema should regularly ask patients if they are using CAM therapies.	○	○	○	○	○

4.6. I am happy to refer patients to CAM practitioners e.g. Homeopaths or Chinese herbalists for complementary treatment for their eczema.	○	○	○	○	○

E. Education regarding CAM for Atopic Eczema

This section is to ascertain how healthcare professionals access information or view further education regarding CAM. Please choose the best suited option.

	Yes, frequently	Yes but rarely	No
1. Did you have any training on CAM.	○	○	○
2. Do you access any medical journals to source information on CAMs for eczema.	○	○	○
3. Do you access any information on the internet with regards to CAMs for eczema.	○	○	○
4. Do you have discussions with other colleagues about CAM use for eczema.	○	○	○
5. Is CAM for eczema discussed in congresses you have attended.	○	○	○

Please answer Yes or No to following questions:

	Yes	No
6. Do you feel that universities should include CAM as part of their curriculum.	○	○
7. Do you feel that learning about CAM would better prepare you for treating patients with eczema.	○	○
8. Are you interested in learning more about CAMs for eczema.	○	○

Thank you once again for taking your time to participate in this survey.

8.3. APPENDIX 3: LETTER TO HEALTHCARE PRACTITIONER INVITING PARTICIPATION IN STUDY

UNIVERSITY OF
KWAZULU-NATAL

Dear Colleague

We, the Departments of Pharmaceutical Sciences (Division of Pharmacology) and Dermatology at the University of KwaZulu-Natal (UKZN) are currently embarking on a study on the use of complementary and alternative medicines (CAM) for atopic eczema. CAM is defined as a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine. The extensive use of CAM for atopic eczema has been recognised in a number of published international studies. However, currently there is no data available pertaining to CAM practices for atopic eczema in South Africa. Part of the study is to conduct a survey of the knowledge, attitudes and practices of qualified healthcare professionals like yourself on the use of CAM for patients that you may be treating for atopic eczema.

Your responses to the questions in this survey will be amalgamated with those of others and analysed as a collective. There will be no analysis of individual practices. The information obtained will be published in a peer reviewed journal. This survey has received ethics approval from the University of KwaZulu-Natal's Biomedical Research and Ethics Committee. I sincerely appreciate your assistance in completing this survey. We value & respect your privacy and will ensure that all responses will be strictly confidential and anonymous.

Please click on the following LINK TO SURVEY to begin the survey.

Participation in this survey is entirely up to you.

If you have any questions, you may address your queries to Ms Yasmeen Thandar at yasmeent@dut.ac.za

We also encourage you to pass this invitation on to any colleagues you think would be interested in completing the survey.

Many thanks for your cooperation.

Ms YasmeenThandar
Prof Julia Botha
Prof Anisa Mosam

8.4. APPENDIX 4: LETTER TO HEALTHCARE PRACTITONER REQUESTING PERMISSION TO INTERVIEW PATIENTS AT PRIVATE PRACTICE

University of KwaZulu-Natal
Faculty of Health Sciences
Department of Pharmacology

28 March 2014

Request for permission to conduct a survey amongst eczema patients attending your practice

Dear Doctor

My name is Yasmeen Thandar, and I am a Pharmacology lecturer at the Durban University of Technology and a PhD student in the Discipline of Pharmaceutical Sciences, Division of Pharmacology at the University of KwaZulu-Natal. I am currently studying the use of complementary and alternative medicines (CAM) in patients with eczema. Part of this study is to conduct a survey amongst patients attending private dermatology practices to assess to what extent they are using CAM. Details of the study can be read in the attached protocol.
This study is conducted under the supervision of Prof. Julia Botha of the Discipline of Pharmaceutical Sciences, Division of Pharmacology, UKZN and Prof. Anisa Mosam of the Department of Dermatology, UKZN. The University Research Committee and BREC of UKZN has provisionally approved the study.

I hereby request permission to conduct a survey of patients attending your practice. The survey should only take about 10 minutes of your patients' time and will not intervene with your consultation time.

The following documents have been included for your perusal:

- PhD protocol
- Provisional ethics approval

Your consideration in this matter is greatly appreciated.

If you require any further information, please do not hesitate to contact me at:
Email: yasmeent@dut.ac.za Cell: 083 459 4381 Office no: (031) 373 2402/6

8.5. APPENDIX 5: INFORMED CONSENT DOCUMENT FOR HEALTHCARE PRACTITIONER

CONSENT DOCUMENT (for healthcare practitioner)

Consent to Participate in Research

STUDY TITLE: **AN INVESTIGATION INTO THE USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) FOR ATOPIC ECZEMA**

You have been invited to participate in the above mentioned study. The researcher is

Ms Yasmeen Thandar, a pharmacologist and a PhD student at UKZN. The study will be conducted under the supervision of Prof. Julia Botha of the Discipline of Pharmaceutical Sciences, Division of Pharmacology, UKZN and Prof. Anisa Mosam of the Department of Dermatology, UKZN.

Part of the study is to conduct a survey of the knowledge, attitudes and practices of qualified healthcare professionals like yourself on the use of CAM for patients that you may be treating for atopic eczema. For this you are required to complete a questionnaire.

Your participation in this research is voluntary and there is no known risk to you for participating in this study. All information provided will be strictly confidential.

You may contact the **Biomedical Research Ethics Office** on **031-260 4769 or 260 1074** or Email BREC@ukzn.ac.za if you have questions about your rights as a research participant.

Your invaluable time is highly appreciated.

Agreement to participate in the study:

The research study, including the above information, has been described to me. I understand what my involvement in the study means, and I voluntarily agree to participate. I have been given an opportunity to ask any questions that I might have about participation in the study.

_____ _____

Signature of decision maker **Date**

_____ _____

Signature of witness **Date**

8.6. APPENDIX 6: INFORMATION DOCUMENT FOR HEALTHCARE PRACTITIONER

INFORMATION DOCUMENT (FOR HEALTHCARE PRACTITIONER)

(Please refer to the UKZN Biomedical Ethics Terms of Reference at http://research.ukzn.ac.za/ResearchEthics11415.aspx)

Study Title: AN INVESTIGATION INTO THE USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) FOR ATOPIC ECZEMA

Good-day to you and thank you for affording us your time.

Understanding This Document:	In order to take part in this research study, you need to understand the risks and benefits so that you can make an informed decision. This is known as informed consent. Once you understand the study, if you agree to participate, you will be asked to sign the informed consent sheet. Your decision to take part in the study is voluntary. The study is being conducted by Ms Yasmeen Thandar, a pharmacologist and lecturer at Durban University of Technology under the supervision of Prof Julia Botha of the Discipline of Pharmaceutical Sciences, Division of Pharmacology, UKZN and Prof Anisa Mosam from the Department of Dermatology, UKZN.
Why Are We Conducting This Study?	Many patients are using various forms of complementary and alternative medicines (CAM) for their eczema. This study is to understand the knowledge, attitudes and practices of healthcare professionals like yourself on the use of CAM for eczema. It is hoped that this information will enable us to determine if a gap exists between what patients are using and the practitioner's awareness and understanding of these treatments.
How Many People Will Take Part In The Study?	We intend to include 275 healthcare practitioners in this study which is made up of the following: • 20 dermatologists • 70 retail pharmacists • 185 general practitioners
What Is Required Of You In This Study?	All that is required of you in this study is to complete a once-off survey questionnaire. This questionnaire should only take about 10 minutes of your time.
What Are The Study Risks?	There are no risks to you for participating in this study.
What Are The Benefits Of The Study?	There is no direct benefit to you. The results of this study are intended to help healthcare professionals understand if the role, if any, of CAMs for eczema.
What Are The Costs?	There will be no cost to you as a result of taking part in this study.
What About Confidentiality?	Every effort will be made to keep personal information confidential. The Organization that may inspect and/or copy your research records for quality assurance and data analysis will be the Biomedical Research Ethics Committee. The confidentiality of computer records is safely guarded. No information by which you can be identified will be released or published.

Whom Do I Call If I Have Questions?	For more information regarding the research or research related risks or injuries, please feel free to ask the researcher:
Information regarding the research or research related risks or injuries	Ms Yasmeen Thandar on 031 3732402 or 083 459 4381 or email directly to yasmeent@dut.ac.za
Questions about your rights as a research participant	For questions about your rights as a research participant, contact the Institutional Review Board: BIOMEDICAL RESEARCH AND ETHICS ADMINISTRATION 031 2604769, Private Bag X 54001 Durban 4000 or email: BREC@ukzn.ac.za

8.7. APPENDIX 7: INFORMATION DOCUMENT FOR PATIENTS

INFORMATION DOCUMENT (FOR PATIENTS)

(Please refer to the UKZN Biomedical Ethics Terms of Reference at http://research.ukzn.ac.za/ResearchEthics11415.aspx)

Study Title: An Investigation Into The Use Of Complementary And Alternative Medicine (CAM) for Atopic Eczema

Good-day to you and thank you for affording us your time.

Understanding This Document:	In order to take part in this research study, you need to understand the risks and benefits so that you can make an informed decision. This is known as informed consent. Once you understand the study, if you agree to participate, you will be asked to sign the informed consent sheet. Your decision to take part in the study is voluntary. This means that you are free to choose if you will take part in the study and this will not affect any other treatment you receive. The study is being conducted by Prof Anisa Mosam from the Department of Dermatology, UKZN and Ms Yasmeen Thandar from the Department of Basic Medical Science, DUT.
Why Are We Conducting This Study?	This study will collect information on all treatments including any alternative and complementary medicines that you may be using to treat your/your child's eczema. It is hoped that this information will enable us to determine the best treatment options for atopic eczema for patients.
How Many People Will Take Part In The Study?	We intend to include 150 patients to participate in the study.
What Will Happen In The Study? Interview	Once you agree to take part in this study, the following will happen: You will be interviewed and some personal information such as age, gender, religion and ethnicity, will be collected on a data sheet. Details regarding the medicines and other treatments that you may be using for your/your child's eczema will also be collected on the data sheet. You may also be asked to provide reasons for your treatment choices. You are free to stop the interview at any time if you feel uncomfortable and this will not affect any care that you receive.
What Are The Study Risks?	There are no risks to you or your child participating in this study. The treatment plan will not be affected in any way and will be determined solely by the dermatologist.
What Are The Benefits Of The Study?	There is no direct medical benefit to you/your child if you agree to take part in this study. The results of this study are intended to help doctors determine the best possible treatment options for atopic eczema in the future. The principal investigator will benefit as this study is towards her PhD.

What Are The Costs?	There will be no costs to you as a result of taking part in this study.
What About Confidentiality?	Every effort will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law. The Organization that may inspect and/or copy your research records for quality assurance and data analysis will be the Biomedical Research Ethics Committee. The confidentiality of computer records is safely guarded. No information by which you can be identified will be released or published.
Whom Do I Call If I Have Questions? Information regarding the research or research related risks or injuries Questions about your rights as a research participant	For more information regarding the research or research related risks or injuries, please feel free to ask the study doctor: Prof A Mosam 031 360 3550, 031 260 4565 or, Ms Yasmeen Thandar on 031 3732402 or 083 459 4381. For questions about your rights as a research participant, contact the Institutional Review Board: BIOMEDICAL RESEARCH AND ETHICS ADMINISTRATION (which is a group of people who review the research to protect your rights) at 031 2604769, Private Bag X 54001 Durban 4000 or email: BREC@ukzn.ac.za

8.8. APPENDIX 8: CONSENT DOCUMENT FOR PATIENTS

CONSENT DOCUMENT (for patients)

Consent to Participate in Research

STUDY TITLE: **AN INVESTIGATION INTO THE USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) FOR ATOPIC ECZEMA**

I, _____agree to participate in this research study.

I agree that the study has been explained to me in a language that I can understand. I understand the study information sheet. I have discussed the advantages and disadvantages of participating in the study. I agree to divulging any personal and medical information for the purposes of this study only.

You may contact Prof A Mosam 031 360 3550, 031 260 4565 or Ms Yasmeen Thandar on 031 3732402 or 083 459 4381 at any time if you have questions about the research or if you are injured as a result of the research.

You may contact the **Biomedical Research Ethics Office** on **031-260 4769 or 260 1074** or Email BREC@ukzn.ac.za if you have questions about your rights as a research participant.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to stop at any time.

If you agree to participate, you will be given a signed copy of this document and the participant information sheet which is a written summary of the research. You will be asked to fill out a questionnaire. In this questionnaire, you are free not to answer any questions that you do not want to.

The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree to participate. I have been given an opportunity to ask any questions that I might have about participation in the study.

_____ _____

Signature of Participant **Date**

_____ _____

Signature of Witness (Where applicable) **Date**

_____ _____

Signature of Translator (Where applicable) **Date**

8.9. APPENDIX 9: PATIENT QUESTIONNAIRE (ISIZULU VERSION)

Ukusetshenziswa kwezinye izinhlobo zemithi ukwelapha i-eczema (utwayi)

Ucwaningo ngesiguli

A. Ulwazi ngawe

A1. Imininingwane yesiguli

Inamba yesiguli ----------

A1. Imininingwane yalapho othatha khona imithi

☐ Ngibonwa e-King Edward VIII njengesiguli esigulela ekhaya
☐ Ngibonwa udokotela ofundele ukulapha isikhumba (udokotela o-private)
Chaza: ……

A2. Ubulili

☐ Owesilisa
☐ Owesifazane

A3. Inkolo/ukholo

☐ UMkhristu
☐ I-Muslim
☐ UmHindu
☐ UmJuda
☐ Umlandeni wenkolo ka-Bhuda
☐ Okunye: ……

A4. Ubuhlanga

- ☐ Onsundu
- ☐ Omhlophe
- ☐ Indiya
- ☐ Ikhaladi
- ☐ Okunye: .....

A5. Iminyaka yakho/ubudala

- ☐ <30
- ☐ 31-40
- ☐ 41-50
- ☐ >50

A6. Iminyaka yengane (uma kuyingane egulayo)

- ☐ 0-3 wezinyanga
- ☐ 3-6 wezinyanga
- ☐ 6-12 wezinyanga
- ☐ 1-2 weminyaka
- ☐ 2-5 weminyaka
- ☐ 5-8 weminyaka
- ☐ 8-12 weminyaka
- ☐ >12 weminyaka

A7. Izinga lokufunda

- ☐ Angifundanga/angiyanga esikoleni
- ☐ Imfundo yamabanga aphansi (Primary)
- ☐ Imfundo yamabanga aphezulu (Secondary)
- ☐ Ngisekolishi
- ☐ Ngiyafunda kodwa senginazo iziqu zokuqala

A8. Izinga lokuhola ngenyanga

- ☐ Lingaphansi kwa- R2000
- ☐ R2000-R5000
- ☐ R5000-R10 000
- ☐ R10 000-R20 000
- ☐ >R20 000

B. UKULWASHWA KWESIKHUMBA ESINE-ECZEMA (UTWAYI)

B1. Sekunesikhathi esingakanani wena noma ingane ine-eczema (utwayi).

- ☐ <1 ngaphansi kwenyanga
- ☐ 1-3 yezinyanga
- ☐ 3-6 yezinyanga
- ☐ 6-12 yezinyanga
- ☐ > 1 ngaphezulu konyaka

Chaza ……

B2. Imuphi umuthi udokotela wakho wesikhumba othe wakubhalela wona ukuthi uwusebenzise wena okanye ingane yakho.

- ☐ Ukhilimu wama-steroid e.g. steroid V®, Advantan®, Betnovate®, Dermovate®
- ☐ Amaphilisi ama-steroid okanye i-syrup e.g. Prednisone, Prelone®
- ☐ Ama-Antihistamines e.g. Zyrtec®, CTM®
- ☐ Ukhilimu oyi-Immunosuppressant e.g. Protopic®/Elidel®
- ☐ Amaphilisi angama-Immunosuppressant e.g. Azathioprine, Cyclosporin
- ☐ Into yokuthambisa noma i-moisturizers
- ☐ Okunye

Chaza :

……

……

……

C. IZINHLOBO ZOKWELAPHA KANYE NESIGULI

C1. Ikhona eminye imithi oyisebenzisayo okanye izindlela ezinye ozisebenzisayo ukulapha i-eczema (utwayi) wena okanye ingane yakho.

- ☐ Yebo
- ☐ Cha

Uma impendulo yakho kulo mbuzo ongaphezulu okanye ongenhla bekuwu yebo,ungaqhubeka ngemibuzo engezansi:

C2. Sekunesikhathi esingakanani uqalile ukusebenzisa eminye imithi noma ezinye izindlela zokuzelapha i-eczema (utwayi) wena okanye ingane yakho?

- ☐ < ngaphansi kwenyanga
- ☐ 1-3 yezinyanga
- ☐ 3-6 yezinyanga
- ☐ 6-12 yezinyanga
- ☐ >1 ngaphezu konyaka

C3. Ngabe udokotela wakho wesikhumba uyazi mayelana nezinye izindlela ozisebenzisayo,nangeminye imithi oyisebenzisayo ukulapha i-eczema (utwayi) wena okanye ingane yakho?

- ☐ Yebo
- ☐ Chabo

C3.1. Uma impendulo yakho kumbuzo ongaphezulu/ongenhla bekuwu cha, khetha isizathu :

- ☐ Angiboni ukuthi isidingo sikhona ukuthi udokotela wami wesikhumba azi ngeminye imithi engiyisebenzisayo.
- ☐ Udokotela wami wesikhumba akaze angibuze ngeminye imithi engiyisebenzisayo.
- ☐ Ngiyesaba ukutshela udokotela wami wesikhumba mayelana neminye imithi engiyisebenzisayo.

☐ Okunye: .....

C4. Veza ukuthi hloboluni leminye imithi ye-eczema (utwayi) oyisebenzisayo okanye ezinye izindlela ozisebenzisayo wena okanye ingane yakho. Lapho kungakwazeka khona siyacela uveze igama lomuthi owusebenzisayo.

☐ Ukhilimu o-herbal (herbal medicine) .....

☐ Amaphilisi/amaphilisi ayimpuphu emthombo (herbal tablets/capsules/powder/pellets) .....

☐ Imithi yase-China .....

☐ Imithi yaseNdiya ephathelene nesiko lemvelo .....

☐ Imithi yase-Africa ephathelene nesiko lemvelo .....

☐ I-Homeopathy.....

☐ Ama-Vitamin supplements.....

☐ I-Acupuncture.....

☐ Ama-Natural Health supplements .....

☐ I-Aromatherapy.....

☐ I-Refloxology.....

☐ I-Reiki.....

☐ I-Chiropractic.....

☐ Okunye .....

C5. Uyisebenzisa kanjani leminye imithi ye e-eczema (utwayi) wena okanye ingane yakho.

☐ Ngiyisebenzisa kanye kanye naleyo engiyinikezwe udokotela.

☐ Izikhathi eziningi ngisebenzisa leminye imithi.

☐ Akujwayelekile ukuthi ngiyisebenzise

☐ Okunye .....

C6. Iziphi izizathu ezenza ukuthi wena nengane yakho nisebenzise eminye imithi nezinye izindlela zokuzelapha i-eczema (utwayi). Ungakhetha izizathu ezidlulele kwesisodwa uma kunesidingo.

- ☐ Ziphephile kunemithi yesayensi yokulapha (Conventional medicine).
- ☐ Le mithi yenziwe ngemvelo.
- ☐ Zinomthelela ohlukumeza kancane.
- ☐ Isebenza kangcono kunemithi yesayensi yokuzilapha (Conventional medicine).
- ☐ Umthelela ungcono kakhulu uma ngihlanganisa nalowo engiwunikwa udokotela wami wesikhumba.
- ☐ Uhlobo lomuthi elilapha umuntu ngokupheleleyo (ingqondo,umphefumulo kanye nenyama).
- ☐ Umuthi onconywe abomndeni nabangani.
- ☐ Ngifunde ngayo ezindabeni (emabhukwini nakwi-internet).
- ☐ Okunye ……

C7. Lukhona ushintsho othe walibona ngokusebenzisa eminye imithi nezinye izindlela zokwelapha i-eczema wena okanye ingane yakho.

- ☐ Yebo
- ☐ chabo
- ☐ Oluncane
- ☐ Angazi

Siyabonga ngokuthatha isikhathi sakho ukuzibandakanya kulolu cwaningo.

8.10. APPENDIX 10: CONSENT DOCUMENT FOR PATIENTS (ISIZULU VERSION)

INCWADI YEMVUME

Imvume yokuzibandakanya ocwaningweni

ISIHLOKO SOCWANINGO: UKUHLOLA KOKUSEBENZISWA KWEMINYE IMITHI NEZINYE IZINDLELA ZOKULAPHA I-ECZEMA (UTWAYI)

Mina, _____ngiyavuma ukuzibandakanya kulolu cwaningo.

Ngiyavuma ukuthi ngiluchazeliwe lolu cwaningo ngolimi engiluqondayo futhi ngiyaluqonda ulwazi engilunikiwe maqondana nocwaningo. Ngibonisiwe ngobuhle nangobubi bokuzibandakanya ocwaningweni. Ngiyavuma ukuveza ulwazi olumayelana nami uqobo noluphathelene nezempilo yami ngenjongo yalolu cwaningo kuphela.

Ungaxhumana noProf A Mosam 031 360 3550, 031 260 4565 noma Ms Yasmeen Thandar ku- 031 3732402 or 083 459 4381 nanoma ingasiphi isikhathi uma unemibuzo mayelana nalolu cwaningo noma usuzithola ulimele ngenxa yocwaningo.

Ungaxhumana nabakwa **Biomedical Research Ethics Office** ku **031-260 4769 or 260 1074** noma nge-Email BREC@ukzn.ac.za uma unemibuzo mayelana namalungelo akho njengozibandakanyayo ocwaningweni.

Ukuzibandakanya kwakho kulolu cwaningo kungukuzithandela kwakho, kanti angeke uhlawuliswe noma ulahlekelwe yimihlomulo yakho uma unqaba ukuzibandakanya noma unquma ukuyeka nanoma yingasiphi isikhathi.

Uma uvuma ukuzibandakanya, uyonikezwa ikhophi esayiniwe yalolu cwaningo futhi nephepha elinolwazi olufingqiwe mayelana nocwaningo. Uyocelwa ukuba ugcwalise uhlu lwemibuzo. Kulolu hlu lwemibuzo, ukhululekile ukuthi ungangayiphendula imibuzo ongathandi ukuyiphendula.

Ucwaningo, kuhlanganisa nolwazi olungaphezulu, luchaziwe kimina ngomlomo. Ngiyaqonda ukuthi ukuzibandakanya kwami kusho ukuthini futhi ngiyazivumela ngokuthanda ukuzibandakanya. Nginikeziwe ithuba lokubuza nanoma emiphi imibuzo engingase ngibe nayo ngokuzibandakanya ocwaningweni.

_____	_____
Kusayine ozibandakanyayo	**Usuku**
_____	_____
Kusayine ufakazi (uma kudingeka)	**Usuku**
_____	_____
Kusayine umhumushi (uma kudingeka)	**Usuku**

8.11. APPENDIX 11: INFORMATION DOCUMENT FOR PATIENT (ISIZULU VERSION)

INCWADI YOLWAZI NGOCWANINGO

(Siyacela udlulise e-UKZN Biomedical Ethics Terms of Reference at http://research.ukzn.ac.za/ResearchEthics11415.aspx)

Isihloko socwaningo: UHLOBO LOKUSEBENZISA EMINYE IMITHI NEZINYE IZINDLELA ZOKULAPHA I-ECZEMA (UTWAYI)

Sawubona,siyabonga ngokusinika isikhathi sakho

Ukuqonda leli phepha:	Ukuze uzibandakanye kulolu cwaningo, kufanele uqonde ubungozi nemihlomulo ukuze uthathe isinqumo esiphusile. Lokhu kungukwazisa ngokuvuma kwakho. Uma usuqonda ngocwaningo, uvuma futhi ukuzibandakanya, uyocelwa ukuba usayine incwadi yemvume. Isinqumo sokuzibandakanya kulolu cwaningo kungukuzithandela. Lokhu kuchaza ukuthi uvumelekile ukukhetha ukuzibandakanya ocwaningweni kanti lokhu angeke kube namthelela ekulashweni okutholayo. Lolu cwaningo lweznziwa ngu-Prof Anisa Mosam woMnyango weSikhumba e-UKZN kanye no-Ms Yasmeen Thandar woMnyango wakwa Basic Medical Science, DUT.
Silwenzelani lolu cwaningo?	Lolu cwaningo luzoqoqa ulwazi mayelana nakho konke ukwelashwa kuhlanganisa neminye imithi ekusizayo okungase kube uyayisebenzisa ukwelapha i-eczema (utwayi) enganeni yakho. Kunethemba lokuthi lolu lwazi luzoveza izindlela ezingcono zokwelapha labo abaphethwe i-eczema (utwayi).
Bangakakhi abantu abazozibandakanya kulolu cwaningo?	Sihlose ukubandakanya iziguli eziyi-150 kulolu cwaningo.
Kuzokwenzakani ocwaningweni? Isiqu 1 -ukubuzwa	Uma usuvumile ukuzibandakanya kulolu cwaningo kuzobe sekwenzeka lokhu okulandelayo: Uzobuzwa imininingwane eqondene nawe njengeminyaka yakho, ubulili, inkolo nobuhlanga bese kubhalwa phansi. Imininingwane mayelana nemithi kanye nokunye ukwelashwa okungase kube ukusebenzisela i-eczema enganeni yakho kuyoqoqelwa ephepheni lolwazi. Ungacelwa futhi ukuthi unikeze izizathu zokukhetha kwakho lokhu kulashwa. Ukhululekile ukuyeka ukuxoxisana nanoma yingasiphi isikhathi uma uzwa ukuthi awuphatheki kahle kanti lokhu angeke kube nomthelela kunakekelo olutholayo.
Bukuphi ubungzoi kulolu cwaningo?	Abukho ubungozi ozohlangabezana nabo wena noma ingane yakho kulolu cwaningo. Uhlelo lokwelashwa kwakho angeke luphazamiseke nanoma yingayiphi indlela kanti luyonqunywa kuphela wudokotela wesikhumba.

Yimiphi imihlomulo yalolu cwaningo?	Awukho umhlomulo-ngqo wemithi ozowuthola noma ingane yakho uma uvuma ukuzibandakanya kololu cwaningo. Imiphumela yocwaningo eyokuthi isize odokotela ukuthi bakwazi ukuthola izindlela ezingcono zokulapha i-eczema (utwayi) ukuze kusizakale abantu ngokuzayo. Umcwaningi obhekene nalokhu uzohlomula njengoba lolu cwaningo elwenzela iziqu ze-PhD.
Kubiza malini?	Akukuzukubiza lutho ukuzibandakanya kulolu cawningo.
Ubumfihlo?	Kuzokwenziwa ngawo wonke amandla ukuthi ulwazi ngawe ngqo lube yimfihlo. Kodwa asithembisi imfihlo ngokugcwele. Imininingwane mayelana nawe ingavezwa uma icelwa abomthetho. Inhlangano engahlola futhi/noma ikopishe amarekhodi akho okucwaninga ukuqinisekisa ikhwalithi nokuhlaziywa kolwazi kuyokwenziwa yi-Biomedical Research Ethics Committee. Ubumfihlo bamarekhodi agcinwe yikhompyutha buphephile. Alukho ulwazi ongahlonzwa ngalo oluyokhishwa noma lushicilelwe.
Ubani engingamfonela uma nginemibuzo? Ulwazi mayelana nocwaningo noma ulwazi mayelana nobungozi bocwaningo Imibuzo mayelana namalungelo akho njengozibandakanyayo	Ngeminye imininingwane mayelana nocwaningo noma nobungozi noma ukulimala, siyacela ungesabi ukubuza udokotela: Prof A Mosam 031 360 3550, 031 260 4565 okanye, Ms Yasmeen Thandar ku 031 3732402 noma 083 459 4381. Imibuzo mayelana namalungelo akho njengozibandakanyayo ocwaningweni, xhumana ne-Institutional Review Board: BIOMEDICAL RESEARCH AND ETHICS ADMINISTRATION (okungabantu abahlola ucwaningo ukuvikela amalungelo) ku 031 2604769, Private Bag X 54001 Durban 4000 or email: BREC@ukzn.ac.za

8.12. APPENDIX 12: LETTER REQUESTING PERMISSION FROM KEVIII HOSPITAL MANAGER FOR CONDUCTING RESEARCH ON SITE

University of KwaZulu-Natal
Faculty of Health Sciences
Department of Pharmacology

The Hospital Manager
King Edward VIII Hospital

28 March 2014

Request for permission to conduct research at the Dermatology Clinic at KEV III Hospital

Dear Dr. Gosnell

My name is Yasmeen Thandar, and I am a Pharmacology lecturer at the Durban University of Technology and a PhD student in the Discipline of Pharmaceutical Sciences, Division of Pharmacology, University of KwaZulu-Natal, South Africa.
I hereby request permission to conduct a study which involves an interview-assisted survey of patients attending the Dermatology Clinic at King Edward VIII Hospital. This survey is to fulfill objective three of my PhD which can be seen in my attached protocol. The study will be conducted under the supervision of Prof. Julia Botha of the Discipline of Pharmaceutical Sciences, Division of Pharmacology at UKZN and Prof. Anisa Mosam of the Department of Dermatology, UKZN.
The University Research Committee of UKZN has approved the study and I have received provisional ethics approval from BREC (Ref: BE219/14).
I have attached my protocol for your perusal.

A letter requesting permission to conduct the study will be sent to the Head of Department of Dermatology once your permission has been obtained.

Your time and consideration in this matter is greatly appreciated.

If you require any further information, please do not hesitate to contact me at:
Email: yasmeent@dut.ac.za Cell:083 459 4381 Office no: (031) 373 2402/6

8.13. APPENDIX 13: APPROVAL FROM THE DEPARTMENT OF HEALTH FOR CONDUCTING STUDY

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : HRKM151/14
Enquiries: Mrs G Khumalo
Telephone : 033 – 395 3189

Dear Ms Y Thandar

Subject: Approval of a Research Proposal

1. The research proposal titled **'An investigation into the use of complementary and alternative medicine (CAM) for atopic eczema'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

The proposal is hereby **approved** for research to be undertaken at King Edward VIII Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mrs G Khumalo on 033-395 3189.

Yours Sincerely

Dr. E Lutge
Chairperson, KwaZulu-Natal Health Research Committee
Date: 24/06/14

8.14. APPENDIX 14: FULL ETHICS APPROVAL

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

25 July 2014

Ms Yasmeen Thandar
Department of Basic Medical Sciences
P.O. Box 1334
Durban,4000
yasmeent@dut.ac.za

Dear Ms Thandar

PROTOCOL: An investigation into the use of complementary and alternative medicine (CAM) for atopic eczema. Ref: BE219/14

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 15 April 2014.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 14 July 2014 to queries raised on 02 June 2014 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 25 July 2014.

This approval is valid for one year from **25 July 2014.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **12 August 2014.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

Professor D Wassenaar (Chair)
Biomedical Research Ethics Committee
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban, 4000, South Africa
Telephone: +27 (0)31 260 2384 **Facsimile:** +27 (0)31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

8.15. APPENDIX 15: VIDEO RECORDING FOR BRITISH JOURNAL OF DERMATOLOGY

8.15.1. Appendix 15A: Correspondence From Editor Of British Journal Of Dermatology Regarding Video Recording

From: onbehalfof+bjd+bad.org.uk@manuscriptcentral.com on behalf of bjd@bad.org.uk
To: Yasmeen Thandar; mosama@ukzn.ac.za
Subject: Accept - BJD-2015-2447.R1
Date: Thursday, 09 June 2016 6:35:07 PM

Re: Topical Herbal Medicines for Atopic Eczema: A Systematic Review of Randomised Controlled Trials BJD-2015-2447.R1

Dear Yasmeen,

Thank you for submitting this paper to the British Journal of Dermatology. We are delighted to accept it for publication as Review Article. There may still be some minor changes to make to your manuscript, should this be the case our technical team will liaise directly with you. After the final amendments are made we will send your paper to the publishers and you will then receive page proofs.

The unedited version of the accepted manuscript will shortly be published online in the 'Accepted Articles' section of our online library. 'Accepted Articles' are publicly available, citable by their Digital Object Identifier and indexed by PubMed. The 'Accepted Article' will be replaced by the definitive version of the paper further to technical editing, typesetting and proof correction. If for any reason you would prefer your paper not to be made available in unedited form, please contact John Caulfield (john@bad.org.uk) at the Editorial Office.

Additionally, I would also like to offer you the opportunity to provide us with a short author's video interview of the lead and/or senior author answering the following questions about the paper: 1, Why did you do this study? 2, How did you do it? 3, What were your main findings? 4, Why is this study relevant to dermatologists and their patients with atopic eczema? The addition of a video recording alongside your original article will greatly increase the readership and interest in your article. Please contact John Caulfield (john@bad.org.uk) in the BJD Editorial Office for advice on technical aspects of creating this recording. The duration of the recording should be no more than 3 minutes. When you submit the recording, it will be subjected to fast-track peer review by our on-line team. Would the end of June be OK as a deadline for this recording?

Yours sincerely,

Alex

Professor Alex Anstey
Editor
British Journal of Dermatology

British Journal of Dermatology
BAD House
4 Fitzroy Square
London
W1T 5HQ

Media Guidelines
If you are considering notifying the media of your research, we would appreciate it if you could adhere to the journal's media guidelines:

https://protect-za.mimecast.com/s/meb0B3IA1myFY?domain=onlinelibrary.wiley.com

8.15.2. Appendix 15B: Correspondence From Editor Of British Journal Of Dermatology Regarding Video Recording

From: John Caulfield
To: Yasmeen Thandar
Subject: RE: Accept - BJD-2015-2447.R1
Date: Wednesday, 13 July 2016 3:08:59 PM
Attachments: image001.jpg
image002.jpg
image003.jpg
image004.jpg
image005.jpg
image006.jpg
image007.jpg
image008.jpg

Dear Dr Thandar,
Thank you for your e-mail. I have just finished downloading this file, this is a great example of what we are looking for.

Many thanks

John Caulfield
Editorial Manager

British Journal of Dermatology /
Clinical and Experimental Dermatology
Willan House
4 Fitzroy Square
London
W1T 5HQ

Tel: +44 (0)20 7391 6346
Fax: +44 (0)20 7388 0240
E-mail: john@bad.org.uk

From: Yasmeen Thandar [mailto:yasmeent@dut.ac.za]
Sent: 13 July 2016 13:46
To: John Caulfield
Subject: RE: Accept - BJD-2015-2447.R1

Dear John

Please let me know if the link that I sent to you in a separate email yesterday works.

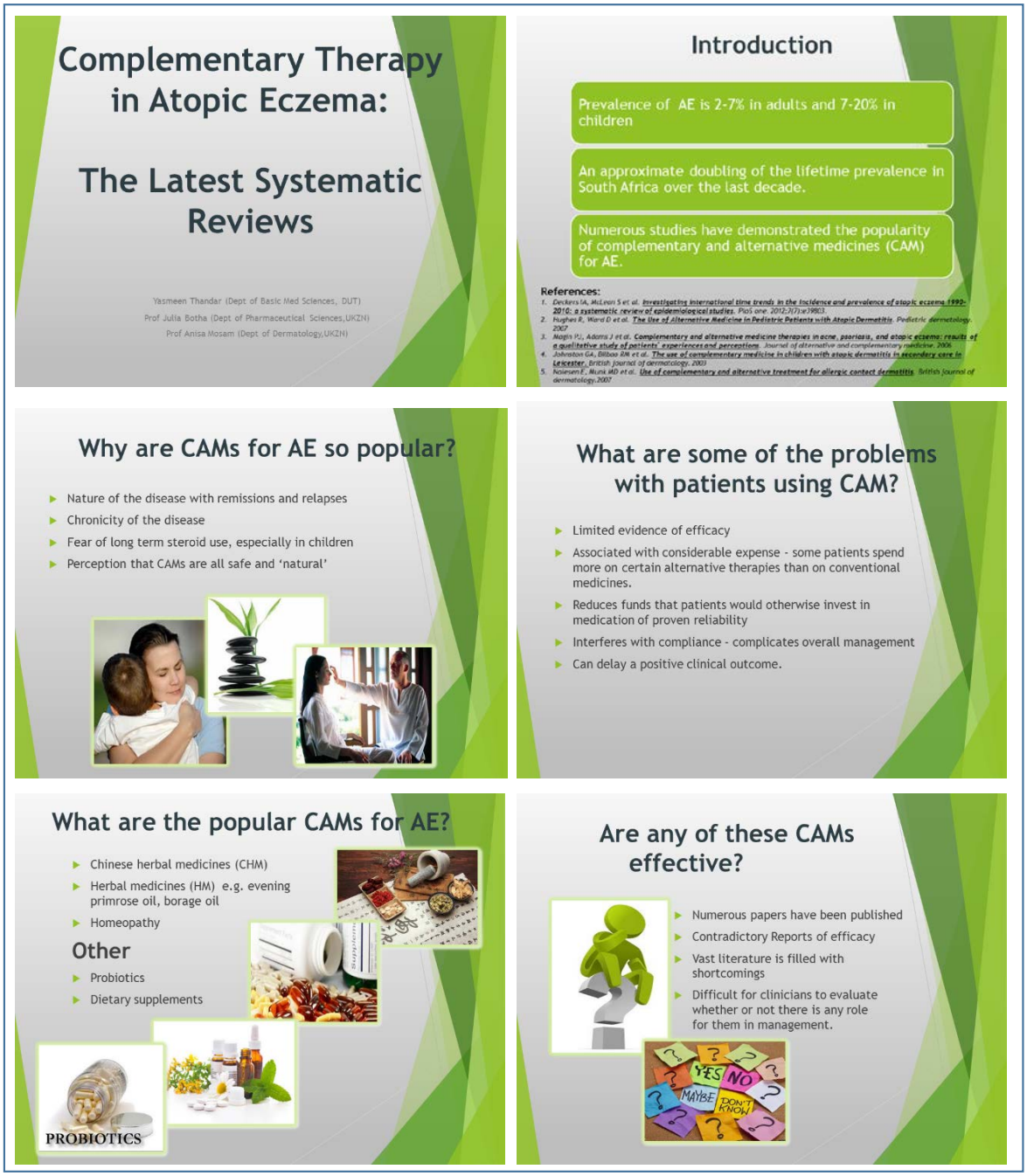
Warm regards

Yasmeen Thandar
BPharmMMedSc(Clinical Pharmacology)
Lecturer
Department of Basic Medical Sciences
Faculty of Health Sciences
Durban University of Technology, Ritson Campus

Email : yasmeent@dut.ac.za
Phone : 031-3732402
Cell : 0834594381
Fax: 0865789647

8.16. APPENDIX 16: CONFERENCE PRESENTATIONS

8.16.1. Oral Conference Presentation: SA Dermatology Society Annual Congress, Johannesburg, 2014



What do Systematic Reviews (SRs) tell us ?

- The SR provides a verdict on unsettled medical debates based on a painstaking reassessment of all the relevant research.
- This overview aims to summarise the findings from the most recently published SRs
- Provides objective information to busy, often sceptical allopathic practitioners

In press: South African Family Practice. ***Complementary Therapy in Atopic Eczema: The Latest Systematic Reviews.***
Thandar Y, Botha J, Mosam A.

Methodology

Literature searches were carried out using the following data bases:

- EBSCO, Medline (via PubMed)
  Cochrane Library, Google Scholar, Summon
- up to November 2013
- Varying search terms
- English SRs in peer reviewed journals
- Controlled clinical trials with eczema
- Patients of any age

Chinese Herbal Medicines

- 3 SRs identified
- 1999 - included only two RCTs that were dealt with in both subsequent SRs
- 2010 - Cochrane Collaboration reviewed 4 RCTs of Zermaphyte and concluded that it may be effective in AE although the studies were small and heterogenous
- 2013 - most recent SR (Tan et al.) - Zermaphyte RCTs and other CHMs.

Table I Summary of RCTs of CHM for AE

Reference Citation	Participants	Study Rationale & Design	Results
Sheehan MP & Atherton DJ. Br J Dermatol 1992;126:179-84	Children	DB* cross-over RCT CHM† (Zermaphyte) (n=47) vs. placebo (n=47)	CHM† more effective than placebo
Sheehan MP et al. Lancet 1992; 340:13-7	Adults 16-65 yrs	DB* cross-over RCT CHM† (Zermaphyte)(n=40) vs. placebo (n=40)	CHM† more effective than placebo
Huang YQ et al. Shan Xi Zhong Yi 2004; 5:396-8	Children 3-11 yrs	SB§ RCT CHM†(Jian Pi Shen Shi) (n=49) vs. WM‡ (n= 49)	CHM†+WM‡ more effective than WM‡
Hon KLE et al. Br J Dermatol 2007;157:357-63	Children & adults 5-21 yrs	DB* RCT CHM† (Pentaherbs) (n=42) vs. placebo (n=43)	CHM† significantly improved QoL NSD¶in clinical scores
Kobayashi H et al. Evid Based Complement Alternat Med 2010;7:367-73	Adults 20-40 yrs	DB*RCT CHM† (Hochu-ekki-to) (n=43) vs. placebo (n=48)	NSD¶in clinical scores
Cheng HM et al. Int Arch Allergy Immunol 201;155:141-8	Age not specified	DB* RCT CHM† (Xiao-Feng-San)(n=47) vs. placebo (n=24)	CHM† more effective than placebo

**Double Blind †Chinese Herbal Medicine ‡Western Medicine §Single Blind ¶No Significant Difference*

Homeopathy

- Homeopathy is based on 2 main beliefs:

'like cures like'

remedies retain biological activity after repeated dilution and sucussion

- Despite being of doubtful value, it is still popular for treating eczema
- Only 1 SR was found
- Only 3 controlled clinical trials which met his inclusion

Table II Summary of Controlled Trials of Homeopathy for AE

Reference citation	Participants	Study Rationale & Design	Results
Koll T, et al. Complement Ther Med 2008; 16:15-21	118 children 1-16 yrs	H* (n=54) vs. conventional medicines (n=64) CC† assessment @ 0, 6 & 12 months	Similar improvement in perception of symptoms & QoL (patient/parent) Ratings by physicians favoured H*
Witt CM, et al. Dermatology 2009; 219:329-40	135 children 1-14 yrs	H* (n=48) vs. conventional medicines (n=87) CC† assessment @ 0, 6 & 12 months	NSD¶at 6 and 12 months Costs higher in H* group
Siebenwirth J, Forsch Komplementarmed 2009;16:315-23	14 adults 18-35yrs	H* (n=5) vs. placebo (n=11) DB‡ RCT Treatment & monitoring for 32 weeks	NSD¶in any parameters (e.g. clinical score, QoL)

**Homeopathic Treatment †Comparative Cohort, Open, Non-randomised*
‡Double Blind ¶No Significant Difference

Probiotics

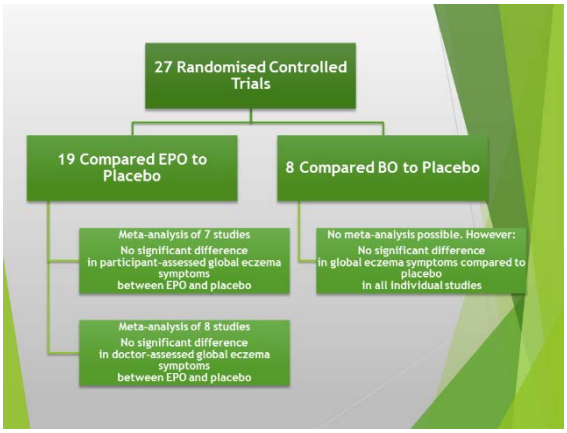
- Unknown whether the alteration of intestinal microbiota in eczema patients is causative or a result of the eczema
- Probiotics (live microorganisms) have been proposed to benefit eczematous patients.
- 3 recent SRs
- latest -2009 (Boyle et al). Cochrane Review of high quality and superseded the previous 2.

Findings from Probiotic SRs

- Pooled data analysis showed no benefit for:
  - investigator-rated eczema severity
  - itching and sleep disturbance
  - QoL
  - need for other eczema treatment
- Subgroup analysis comparing 3 studies (Lactobacillus rhamnosus GG) with 4 other Lactobacillus strains - opposite results in SCORAD, suggesting a strain-specific effect
- The reviewers concluded that research into as yet unstudied, probiotic strains may be warranted in eczema

Evening Primrose Oil (EPO) and Borage Oil (BO)

- Due to conflicting results regarding efficacy and safety of GLA, including findings of 2 SRs (1989,2006) a Cochrane Review was carried out in 2013 (Bamford et al.)
- 27 RCTs were considered worthy of inclusion.



Dietary supplements

- The most recent SR is a Cochrane Review (Bath-Hextall et al.) in 2012 which evaluated RCTs of an extensive range of dietary supplements for the treatment of AE.
- 11 RCTs met the inclusion criteria.

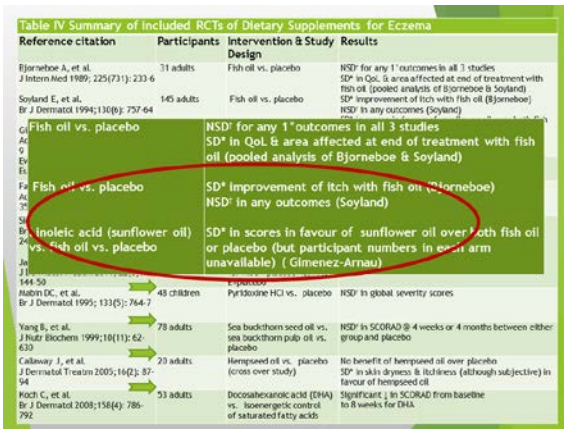


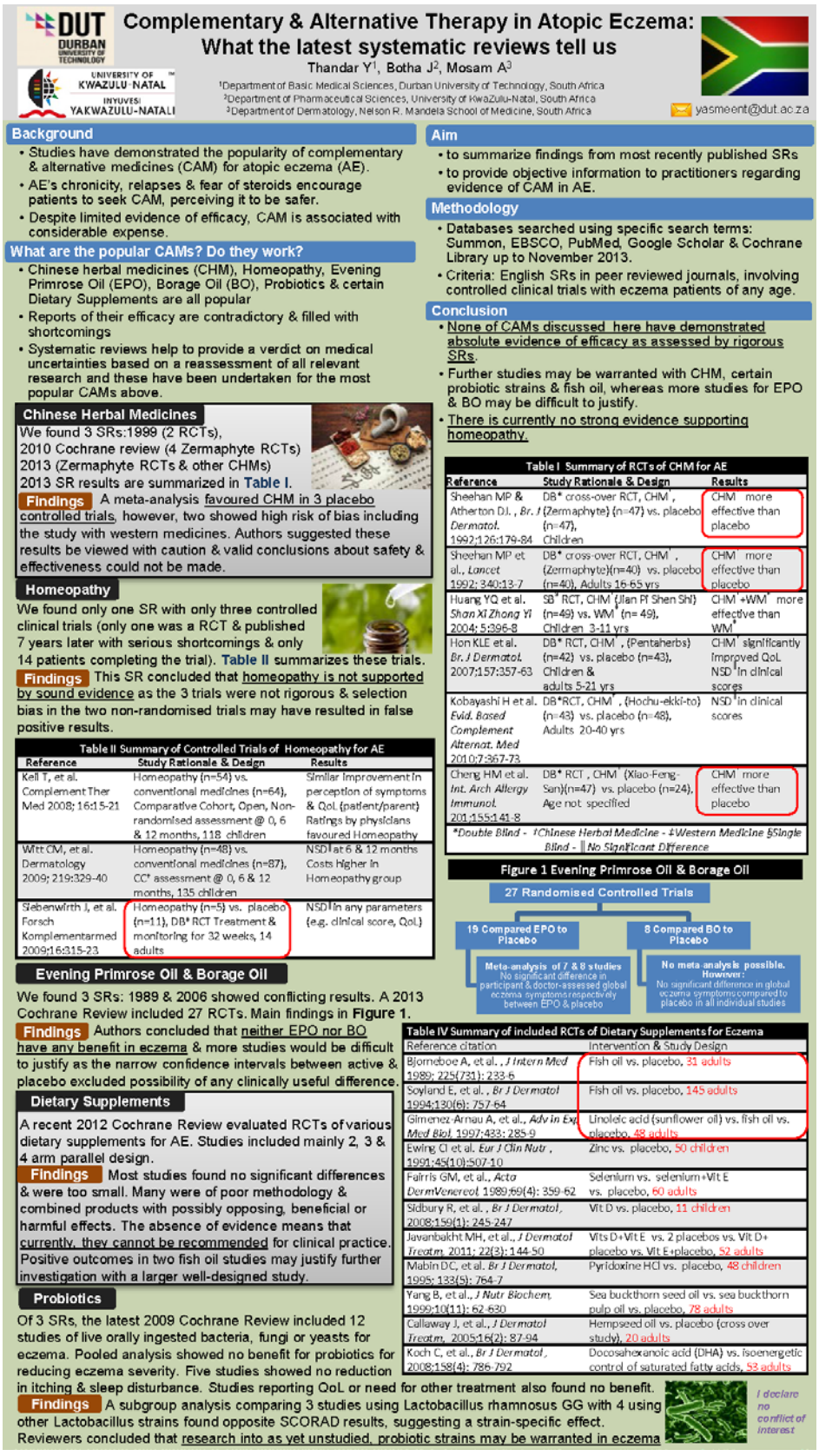
Table IV Summary of Included RCTs of Dietary Supplements for Eczema

Reference citation	Participants	Intervention & Study Design	Results
Bjorneboe A, et al. J Intern Med 1989; 225(731): 233-6	31 adults	Fish oil vs. placebo	NSD† for any 1° outcomes in all 3 studies SD* in QoL & area affected at end of treatment with fish oil (pooled analysis of Bjorneboe & Soyland)
Soyland E, et al. Br J Dermatol 1994; 130(6): 757-64	145 adults	Fish oil vs. placebo	SD* improvement of itch with fish oil (Bjorneboe) NSD† in any outcomes (Soyland)
Fish oil vs. placebo			NSD† for any 1° outcomes in all 3 studies SD* in QoL & area affected at end of treatment with fish oil (pooled analysis of Bjorneboe & Soyland)
Fish oil vs. placebo			SD* improvement of itch with fish oil (Bjorneboe) NSD† in any outcomes (Soyland)
inoleic acid (sunflower oil) vs. fish oil vs. placebo			SD* in scores in favour of sunflower oil over both fish oil or placebo (but participant numbers in each arm unavailable) (Gimenez-Arnau)
144-50			
Nabin DC, et al. Br J Dermatol 1995; 133(5): 764-7	48 children	Pyridoxine HCl vs. placebo	NSD† in global severity scores
Yang B, et al. J Nutr Biochem 1999; 10(11): 62-630	78 adults	Sea buckthorn seed oil vs. sea buckthorn pulp oil vs. placebo	NSD† in SCORAD @ 4 weeks or 4 months between either group and placebo
Callaway J, et al. J Dermatol Treatm 2005; 16(2): 87-94	20 adults	Hempseed oil vs. placebo (cross over study)	No benefit of hempseed oil over placebo SD* in skin dryness & itchiness (although subjective) in favour of hempseed oil
Koch C, et al. Br J Dermatol 2008; 158(4): 786-792	53 adults	Docosahexanoic acid (DHA) vs. isoenergetic control of saturated fatty acids	Significant ↓ in SCORAD from baseline to 8 weeks for DHA

Conclusion

- None of the alternative therapies discussed have demonstrated evidence of efficacy as assessed by rigorous SRs
- Further studies may be warranted with some (CHM, certain probiotic strains and fish oil)
- Further studies with EPO and BO may be difficult to justify
- Homeopathy is not supported by sound evidence.

8.16.2. Poster Conference Presentation: World Congress Of Dermatology (WCD), Vancouver, 2015



Complementary & Alternative Therapy in Atopic Eczema: What the latest systematic reviews tell us

Thandar Y[1], Botha J[2], Mosam A[3]

[1]Department of Basic Medical Sciences, Durban University of Technology, South Africa
[2]Department of Pharmaceutical Sciences, University of KwaZulu-Natal, South Africa
[3]Department of Dermatology, Nelson R. Mandela School of Medicine, South Africa

yasmeent@dut.ac.za

Background

- Studies have demonstrated the popularity of complementary & alternative medicines (CAM) for atopic eczema (AE).
- AE's chronicity, relapses & fear of steroids encourage patients to seek CAM, perceiving it to be safer.
- Despite limited evidence of efficacy, CAM is associated with considerable expense.

What are the popular CAMs? Do they work?

- Chinese herbal medicines (CHM), Homeopathy, Evening Primrose Oil (EPO), Borage Oil (BO), Probiotics & certain Dietary Supplements are all popular
- Reports of their efficacy are contradictory & filled with shortcomings
- Systematic reviews help to provide a verdict on medical uncertainties based on a reassessment of all relevant research and these have been undertaken for the most popular CAMs above.

Aim

- to summarize findings from most recently published SRs
- to provide objective information to practitioners regarding evidence of CAM in AE.

Methodology

- Databases searched using specific search terms: Summon, EBSCO, PubMed, Google Scholar & Cochrane Library up to November 2013.
- Criteria: English SRs in peer reviewed journals, involving controlled clinical trials with eczema patients of any age.

Conclusion

- None of CAMs discussed here have demonstrated absolute evidence of efficacy as assessed by rigorous SRs.
- Further studies may be warranted with CHM, certain probiotic strains & fish oil, whereas more studies for EPO & BO may be difficult to justify.
- There is currently no strong evidence supporting homeopathy.

Chinese Herbal Medicines

We found 3 SRs:1999 (2 RCTs), 2010 Cochrane review (4 Zermaphyte RCTs) 2013 (Zermaphyte RCTs & other CHMs) 2013 SR results are summarized in **Table I.**

Findings A meta-analysis favoured CHM in 3 placebo controlled trials, however, two showed high risk of bias including the study with western medicines. Authors suggested these results be viewed with caution & valid conclusions about safety & effectiveness could not be made.

Table I Summary of RCTs of CHM for AE

Reference	Study Rationale & Design	Results
Sheehan MP & Atherton DJ. , *Br. J Dermatol.* 1992;126:179-84	DB* cross-over RCT, CHM†, {Zermaphyte} {n=47} vs. placebo {n=47}, Children	CHM† more effective than placebo
Sheehan MP et al., *Lancet* 1992; 340:13-7	DB* cross-over RCT, CHM†, {Zermaphyte}{n=40} vs. placebo {n=40), Adults 16-65 yrs	CHM† more effective than placebo
Huang YQ et al. *Shan Xi Zhong Yi* 2004; 5:396-8	SB* RCT, CHM† {Jian Pi Shen Shi} {n=49} vs. WM‡ {n= 49), Children 3-11 yrs	CHM†+WM‡ more effective than WM‡
Hon KLE et al. *Br. J Dermatol.* 2007;157:357-63	DB* RCT, CHM†, {Pentaherbs} {n=42} vs. placebo {n=43), Children & adults 5-21 yrs	CHM† significantly improved QoL NSD¶ in clinical scores
Kobayashi H et al. *Evid. Based Complement Alternat. Med* 2010;7:367-73	DB*RCT, CHM†, {Hochu-ekki-to} {n=43} vs. placebo {n=48), Adults 20-40 yrs	NSD¶ in clinical scores
Cheng HM et al. *Int. Arch Allergy Immunol.* 201;155:141-8	DB* RCT , CHM† {Xiao-Feng-San}{n=47} vs. placebo {n=24), Age not specified	CHM† more effective than placebo

*Double Blind - †Chinese Herbal Medicine - ‡Western Medicine §Single Blind - ‖ No Significant Difference

Homeopathy

We found only one SR with only three controlled clinical trials (only one was a RCT & published 7 years later with serious shortcomings & only 14 patients completing the trial). **Table II** summarizes these trials.

Findings This SR concluded that homeopathy is not supported by sound evidence as the 3 trials were not rigorous & selection bias in the two non-randomised trials may have resulted in false positive results.

Table II Summary of Controlled Trials of Homeopathy for AE

Reference	Study Rationale & Design	Results
Kell T, et al. Complement Ther Med 2008; 16:15-21	Homeopathy {n=54} vs. conventional medicines {n=64}, Comparative Cohort, Open, Non-randomised assessment @ 0, 6 & 12 months, 118 children	Similar improvement in perception of symptoms & QoL {patient/parent} Ratings by physicians favoured Homeopathy
Witt CM, et al. Dermatology 2009; 219:329-40	Homeopathy {n=48} vs. conventional medicines {n=87}, CC* assessment @ 0, 6 & 12 months, 135 children	NSD¶ at 6 & 12 months Costs higher in Homeopathy group
Siebenwirth J, et al. Forsch Komplementarmed 2009;16:315-23	Homeopathy {n=5} vs. placebo {n=11}, DB* RCT Treatment & monitoring for 32 weeks, 14 adults	NSD¶ in any parameters {e.g. clinical score, QoL}

Evening Primrose Oil & Borage Oil

We found 3 SRs: 1989 & 2006 showed conflicting results. A 2013 Cochrane Review included 27 RCTs. Main findings in **Figure 1.**

Findings Authors concluded that neither EPO nor BO have any benefit in eczema & more studies would be difficult to justify as the narrow confidence intervals between active & placebo excluded possibility of any clinically useful difference.

Figure 1 Evening Primrose Oil & Borage Oil

Dietary Supplements

A recent 2012 Cochrane Review evaluated RCTs of various dietary supplements for AE. Studies included mainly 2, 3 & 4 arm parallel design.

Findings Most studies found no significant differences & were too small. Many were of poor methodology & combined products with possibly opposing, beneficial or harmful effects. The absence of evidence means that currently, they cannot be recommended for clinical practice. Positive outcomes in two fish oil studies may justify further investigation with a larger well-designed study.

Table IV Summary of included RCTs of Dietary Supplements for Eczema

Reference citation	Intervention & Study Design
Bjorneboe A, et al. , *J Intern Med* 1989; 225(731): 233-6	Fish oil vs. placebo, 31 adults
Soyland E, et al. , *Br J Dermatol* 1994;130(6): 757-64	Fish oil vs. placebo, 145 adults
Gimenez-Arnau A, et al., *Adv in Exp Med Biol*, 1997;433: 285-9	Linoleic acid (sunflower oil) vs. fish oil vs. placebo, 48 adults
Ewing CI et al. *Eur J Clin Nutr* , 1991;45(10):507-10	Zinc vs. placebo, 50 children
Fairris GM, et al., *Acta DermVenereol* 1989;69(4): 359-62	Selenium vs. selenium+Vit E vs. placebo, 60 adults
Sidbury R, et al. , *Br J Dermatol*, 2008;159(1): 245-247	Vit D vs. placebo, 11 children
Javanbakht MH, et al., *J Dermatol Treatm*, 2011; 22(3):144-50	Vits D+Vit E vs. 2 placebos vs. Vit D+ placebo vs. Vit E+placebo, 52 adults
Mabin DC, et al. *Br J Dermatol*, 1995; 133(5): 764-7	Pyridoxine HCl vs. placebo, 48 children
Yang B, et al., *J Nutr Biochem*, 1999;10(11): 62-630	Sea buckthorn seed oil vs. sea buckthorn pulp oil vs. placebo, 78 adults
Callaway J, et al., *J Dermatol Treatm*, 2005;16(2): 87-94	Hempseed oil vs. placebo (cross over study), 20 adults
Koch C, et al., *Br J Dermatol*, 2008;158(4): 786-792	Docosahexanoic acid (DHA) vs. isoenergetic control of saturated fatty acids, 52 adults

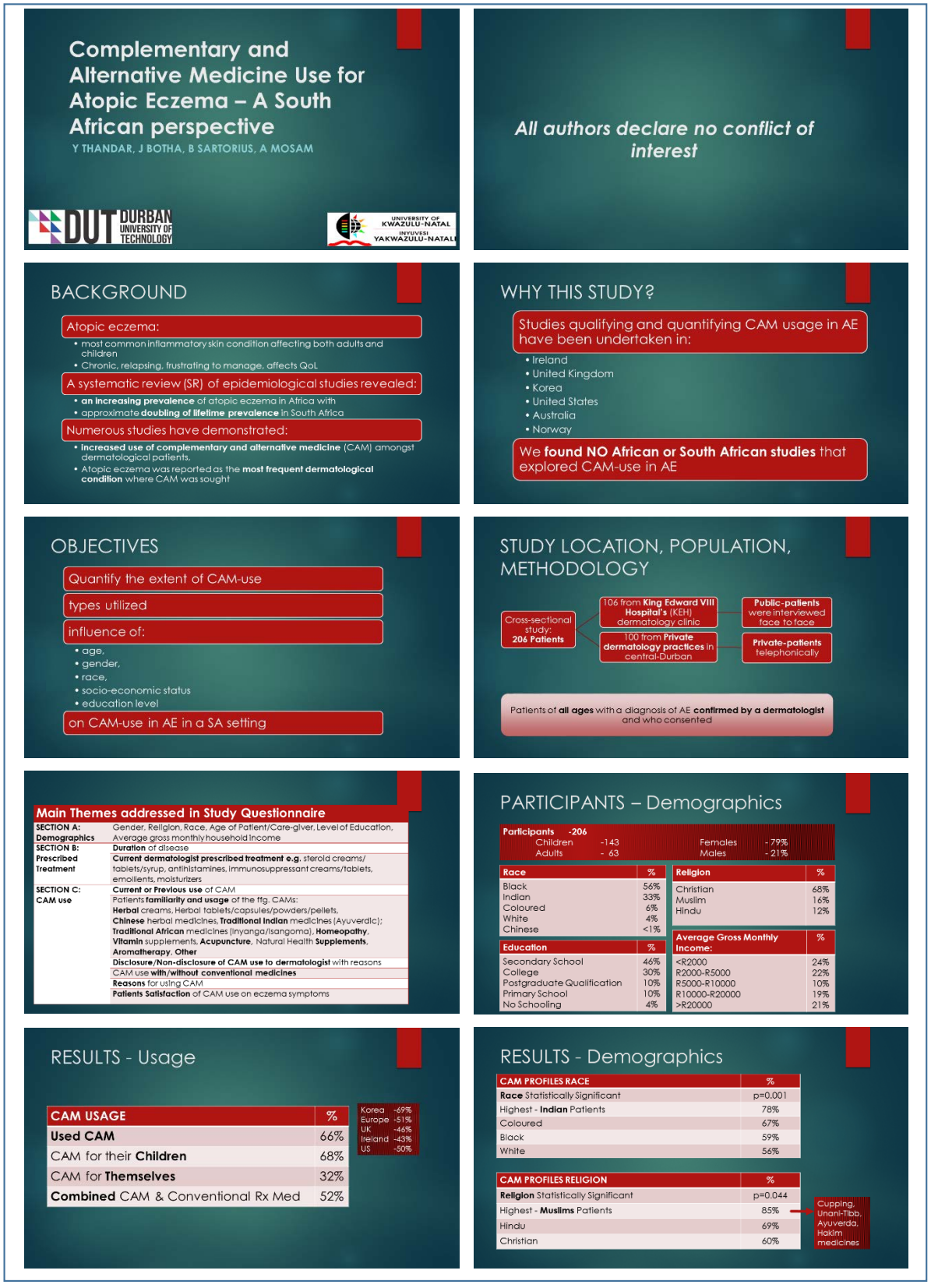
Probiotics

Of 3 SRs, the latest 2009 Cochrane Review included 12 studies of live orally ingested bacteria, fungi or yeasts for eczema. Pooled analysis showed no benefit for probiotics for reducing eczema severity. Five studies showed no reduction in itching & sleep disturbance. Studies reporting QoL or need for other treatment also found no benefit.

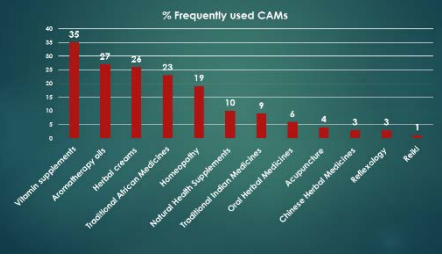
Findings A subgroup analysis comparing 3 studies using Lactobacillus rhamnosus GG with 4 using other Lactobacillus strains found opposite SCORAD results, suggesting a strain-specific effect. Reviewers concluded that research into as yet unstudied, probiotic strains may be warranted in eczema

I declare no conflict of interest

8.16.3. Oral Conference Presentation: SA Dermatology Society Annual Congress: Unity In Dermatology, Cape Town, 2016



RESULTS – Various CAMs explored



RESULTS - Reasons & General Attitude towards CAM

REASONS FOR USING CAM	
It was **recommended** to me by family/friends	42%
I read about it in the **media**	23%
My **GP** recommended it to me	12%
The **pharmacist** recommended it to me	5%
The **paediatrician** recommended it to me	2%
GENERAL ATTITUDES TOWARDS CAM	
They are more **natural**	35%
I find that they are **safer** than conventional medicines	28%
They have less **side effects**	28%
Effect is better when I **combine it** with dermatologist's medicines	12%
It is a more **holistic** healthcare	11%

RESULTS – Disclosure to Dermatologist

Dermatologist…	%
"was aware"	41%
"was unaware"	59%

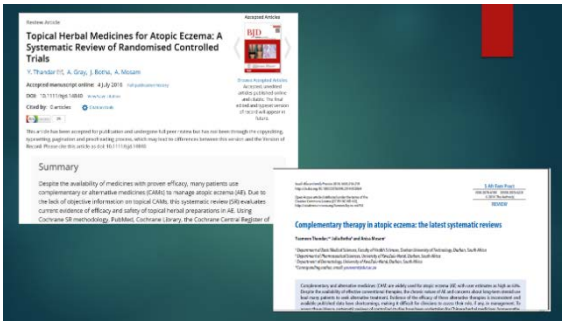
Reasons for non-disclosure…	%
"the dermatologist did not ask"	48%
"it was not necessary for their dermatologist to know"	33%

CONCLUSION

High percentage of CAM use - 66%

Healthcare professionals

- need to be conversant with the **multitude of CAMs** explored
- **Understanding these medicine** and their evidence base
- discuss the usage – breakdown communication barriers, develop a better confidence in treatment
- improve patient compliance and help influence a better **overall clinical outcome.**



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8.16.4. Poster Conference Presentation: European Academy Of Dermatology And Venereology Congress (EADV), Vienna, 2016

Topical Herbal Medicines for Atopic Eczema: A Systematic Review of Randomised Controlled Trials

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BACKGROUND

Atopic eczema (AE) is a chronic debilitating condition affecting quality of life of many patients.
Due to the concern about side effects of topical steroids, patients are continually seeking complementary and alternative medicines (CAM), which they assume to be safer.
We found no documented evidence regarding the role of topical CAMs in the management of AE.
To attain clarity on their efficacy and safety, we conducted a systematic review (SR) .

METHODOLOGY

We used the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. to conduct this SR.
Databases were searched from inception until June 2014.
Figure 1 provides details on the methodology.
Essential data was extracted from each study
A risk of bias assessment was conducted according to the Cochrane domain-based evaluation. See **Figure 2.**

INCLUDED STUDIES

All controlled clinical trials of topical herbal medicines for AE in humans of any age were included regardless of the control intervention or randomisation.
Only English publications were considered.
Topical herbal medicines were defined as those containing extracts of multiple or single plants. These could include non-herbal ingredients used in the extraction process or in preparation of the test or vehicle.
Eight publications were finally selected.

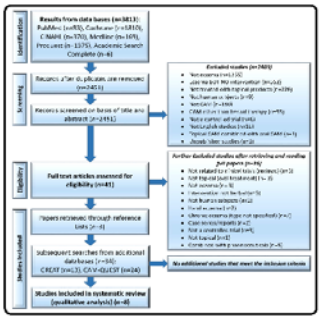

Figure 1 Flow diagram showing selection process of controlled clinical trials of topical herbal medicines for AE

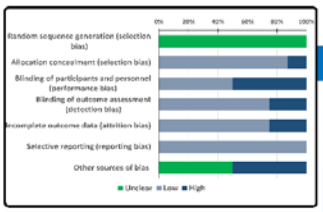

Figure 2 Risk of bias graph represented as percentages across all studies

MAIN FINDINGS

7 studies were conducted using extracts of single plants & 1 was an extract from multiple plants.
Of 6 studies that claimed superiority to placebo, only 2 had a low risk of bias across all domains. These were trials of **Licorice gel** & **Hypericum perforatum.**
The results of these are promising despite variations in diagnostic criteria & a lack of validated tools for outcome assessments, thus warranting continued research in studies with improved design.
No meta-analysis was performed due to heterogeneity in all studies.

CONCLUSION

There is currently insufficient evidence of efficacy for any topical herbal extract in AE.
Many had methodological flaws & even those showing efficacy were single trials with small patient cohorts.
This study provides clarity to prescribers & patients about the current lack of evidence for efficacy & safety of CAMS for AE, & has helped to identify opportunities for future research.

List of Included Studies

1. *2% sunflower oleodistillate (Stelatopia®)*
2. *Cream containing hyperforin - major constituent of Hypericum perforatum L (St. John's Wort) (Schempp, 2003)*
3. *Hamamelis virginiana distillate cream (Korting; 1995)*
4. *Chamomile extract (Kamillosan®) cream (Patzelt-Wenczler;2000)*
5. *Topical evening primrose oil (Anstey; 1990)*
6. *1% & 2% Licorice gel (extracted from Glycyrrhiza glabra L roots) (Saeedi;2003)*
7. *Ointment containing alcohol based plant extracts of Mahonia aquifolium, Viola tricolor & Centella asiatica & their ingredients as pharmacological active substances (Klovekorn, 2007)*
8. *Virgin coconut oil (Veralio-Rowell; 2008)*