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Natural Products and Dermatological Hypersensitivity Diseases

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1. Introduction

The management of dermatological hypersensitivity diseases is a lifelong struggle for most patients. Often, patients are advised to avoid triggers and aggregating factors that lead to flare ups which eventually becomes second nature to them. However, when the symptoms of these conditions become unbearable and conventional medicine no longer provides relief, an increasing proportion of allergy patients are looking to alternative treatments for comfort. Natural products are compounds isolated from natural sources (usually plants or animals) that have potentially beneficial bioactivity. However, many types of compounds can be defined as natural bioactives including synthesized molecules that are based upon naturally occurring compounds. As such, we will define the term “natural bioactive” as any compound whose parent compound structure occurs in nature. Medical research is exploring these compounds as potential treatment sources for a myriad of conditions, including the dermatological hypersensitivity diseases. With the growing interest in natural health products it could be possible that disease sufferers, by self exploring alternative treatments, are potentially leading the search towards the next new approved and medically accepted treatment.

2. Current treatments and management in dermatological hypersensitivity diseases

The management of atopic and hypersensitivity diseases are initially addressed by life style modifications. With all hypersensitivity diseases, be it food allergies, contact hypersensitivity, or allergic asthma, suffers quickly become aware of their disease triggers and begin a lifelong course of avoidance (Custovic *et al.*, 1998). Unknown triggers can be identified medically using a skin prick/patch test. This involves a controlled dermal exposure to the known and the most frequent allergens, and triggers are identified from the resultant skin reactions (Li, 2002). Pharmacological treatments are added into the treatment schedule as the severity of disease progresses, following well-developed treatment ladders (algorithms) (Schmitt *et al.*, 2008). As the patient moves into the stronger classes of treatments in these schedules, the associated side effects become more severe, influencing treatment decisions, ultimately compliance rate and exploration of alternative treatments.

2.1 Life style modifications and diet

The effect of diet on allergies and atopic diseases mitigation has been well studied, but has produced conflicting results (Allan & Devereux, 2011; Devereaux & Yusuf, 2003; Finch *et al.*,

2010; Wichers, 2009). In children with a family history of atopic diseases, research has been focused towards the effects of maternal diet during pregnancy, lactation, and then subsequently in the infant when and which foods are introduced. Of particular interest is the effect of probiotics on the development of allergies which will be discussed below (section 4.2.4). In patients with food allergies triggers are eliminated from the diet, however other foods have been suggested which might be beneficial to allergy sufferers. Some of these compounds include poly-unsaturated fatty acids (PUFA); Vitamins C (Chang *et al.*, 2009), D, E, Zinc, Selenium. However, these findings have been met with mixed results (Finch *et al.*, 2010).

2.2 Medical treatment

Medical treatments are initiated as the severity of symptoms become worse and the disease becomes intolerable (Schmitt *et al.*, 2008). For each condition, drug classes have been recommended to be added in a specific order/time in the treatment schedule. However, due to the nature of these conditions treatment is individually tailored depending on patient response and their tolerance of the side effects. These patients follow a defined treatment plan consisting of pharmacological classes, based on their indications and complications. When treatment is initiated for a patient, the success of treatment always needs to balance with the side effect the treatment has on patient quality of life. (R. Finkel *et al.*, 2009). The following is a brief overview of some conventional treatments for hypersensitivity disease such as steroids and anti-histamines. Some of these compounds originated from natural sources but have been modified extensively to improve both their efficacy and potency. As such, these medications are not strictly considered “naturally sourced.” In section 3 below, we will address “naturally sourced” treatments for comparison.

2.2.1 Corticosteroids

Corticosteroids are a class of steroid hormones that are frequently used as a first line treatment in many immunological and dermatological diseases (Richard Finkel, 2009). They can be classified as short to long acting (1-55+ hours) and are applied topically or systemically. They are very effective at mitigating inflammation; however, their side effects limit their long term use. Many of the new treatments are being sought as corticosteroids sparing alternatives (Del Rosso & Friedlander, 2005).

Mechanism of Action: Corticosteroids bind intracellular receptors forming dimers that bind to the glucocorticoid response element of the promoter region of steroid responsive genes, which up regulates 10-100 genes (Bologna *et al.*, 2008). They also act by inhibiting nuclear factor κ B (NF- κ B) which dramatically decreases the inflammatory response through the down regulation of certain cytokines, cell adhesion molecules and other inflammatory mediators. (Ex: TNF α , GM-CSF, several interleukins (ex. IL-1, IL-2, IL-6, IL-8); Intercellular adhesion molecule-1 and E-selectin; cyclooxygenase, etc). (D'Acquisto *et al.*, 2002; Richard Finkel, 2009)

Topical Benefits: Reduced itching, improvements in sleep, appearance of skin, self-esteem and quality of life (Miller & Eichenfield, 2006). *Side effects* (Miller & Eichenfield, 2006) Short Term – stinging on application (for potent preparations); Medium to Long Term – local complications (i.e. skin thinning, striae, glaucoma from periocular use, contact sensitization and tolerance), etc. ; Systemic effects – suppression of the hypothalamic-pituitary-adrenal axis, Cushing's syndrome, decreased immunity.

Systemic Benefits (Miller & Eichenfield, 2006): Relief from itching, skin redness and infiltration and reduced oozing; *Side Effects* (Miller & Eichenfield, 2006): Short term – increased appetite, psychosis and dyspepsia; Long term – hypertension, osteoporosis, adrenal suppression, striate and muscle atrophy, Cushing's Syndrome, decreased immunity.

2.2.2 Emollients

Emollients are creams designed to alleviate the symptoms of pruritus in dermatitis (Bolognia *et al.*, 2008). They are normally applied daily and act by coating the skin and creating an artificial barrier. They are composed of either water free or water-in-oil ointments with urea (10-20%) or lactic acid (5-12%). The underlying principle of this treatment is to 'correct' the barrier defect of the skin in AD. *Benefits*: Reduce skin dryness, itching and penetration of skin by irritants and allergens; prevention of skin cracking; possible reduced need for topical corticosteroids, possible enhanced response when used with topical corticosteroids. *Side Effects*: Possible stinging on application (R. Finkel *et al.*, 2009).

2.2.3 Topical calcineurin inhibitors

These compounds are among the newest class of immunomodulatory compounds that have been approved for use in inflammatory skin diseases (2000) (Grassberger *et al.*, 2004). Members of this class include Pimecrolimus, Tacrolimus and Ascomycin. All originated as natural products isolated from the fermentation products of the bacteria *Streptomyces sp.* (Richard Finkel, 2009). This class has the advantage of treating AD refractory to corticosteroids and reducing the amount of corticosteroids required in severe cases (Spergel & Leung, 2006).

Mechanism of Action: Inhibits calcineurin phosphatase by binding to FK506 binding protein which then complexes to calcineurin preventing its activation (Assmann *et al.*, 2000). Activated calcineurin dephosphorylates the cytoplasmic subunit of the nuclear factor of activated T cells (NFAT), which then translocates to the nucleus where it forms a complex that assists in transcription of numerous cytokines (ex. Th1: IL2, INF γ ; Th2: IL4, IL5) (Grassberger *et al.*, 1999; Sakuma *et al.*, 2001).

Indications: (Bolognia *et al.*, 2008)

Pimecrolimus – Mild to moderate atopic dermatitis, other inflammatory dermatoses

Tacrolimus – Moderate to severe atopic dermatitis, other inflammatory dermatoses

Benefits: Reduced itching and improvements in sleep, appearance of skin, self-esteem and quality of life (Grassberger *et al.*, 2004; Miller & Eichenfield, 2006)

Adverse Effects

Short term – mild stinging or burning upon application; normally improves after a week

Long term – (>5 years) – Tacrolimus: safety unknown, use with caution with excess exposure to UV light; Pimecrolimus: safety profile based on 5 years of use appears good.

2.2.4 Immunomodulators

This class of drugs/compounds function by attenuating the immune response underlying the hypersensitivity reaction. Some of these compounds have been used as immunosuppressants in transplant medicine while others are either components of the immune system or a new class of treatments known as 'biological agents' which are

artificially created monoclonal antibody designed to target errant members of the immune system (R. Finkel *et al.*, 2009). Interestingly some of the immunosuppressants have their origin as natural products including: cyclosporine (isolated from fungus *Tolypocladium inflatum*), mycophenolate mofetil (isolated from fungus *Penicillium stoloniferum*) tacrolimus (isolated from *Streptomyces tsukubaensis*) as well as others (R. Finkel *et al.*, 2009).

Interferon γ

Was investigated for use in atopic dermatitis due to its pathological dysregulation, and was found to be effective in short term (Hanifin *et al.*, 1993) and long term studies (Stevens *et al.*, 1998). However, its low response rate and high costs deter its regular use and implementation.

Biological Agents – Monoclonal Antibodies

These agents are biologically engineered antibodies directed against specific targets in the immune system. Some of these agents have made it to market for specific conditions (see table1). Omalizumab is a humanized mouse monoclonal antibody targeting the IgE Fc Region. It binds free IgE but not IgE bound to Fc ϵ RI on mast cells, so in this way it sequesters free IgE without activating bound IgE and causing mast cell degranulation (Presta *et al.*, 1993). Omalizumab has been approved by the FDA for use in severe recalcitrant asthma (Strunk & Bloomberg, 2006) and has been investigated for severe cases of atopic dermatitis with positive results (Lane *et al.*, 2006).

AGENT	TARGET / MOA	CONDITION
Alefacept, Efalizumab	T-cell activation, T-cell trafficking	Psoriasis
Etanercept, Infliximab, Adalimumab	TNF α	Psoriasis
Anakinra	IL-1	Rheumatoid arthritis
Rituximab	CD20 (B-cells)	B-cell mediated skin diseases

Table 1. Examples of Biological Agents employed in Dermatological Conditions

Immunosuppressants: Cyclosporine, methotrexate, Mycophenolate mofetil

These drugs act by modulating different functions of the immune system and decreasing their activity. These drugs while very potent in activity require caution in use, because of associated side effects including nephro-, neuro-, and hepatotoxicity (R. Finkel *et al.*, 2009).

2.2.5 Other medical treatments

Anti-Microbial:

This class of pharmaceuticals are commonly used against infections caused by pathological secondary barrier defects in the epidermis. Infections can be caused by intense scratching leading to excoriations or due to immune suppression from other treatments. Common infections associated with atopic dermatitis include bacterial (*S. aureus*), viral (*Molluscum contagiosum*, HSV) and fungal (*Candida sp.*, *Malassezia sp.*) (Bolognia *et al.*, 2008).

Retinoids

Retinoids are related to Vitamin A and act by binding nuclear receptors (RAR, RXR) which directly and indirectly up regulate gene expression responsible for immune and inflammatory responses and proliferation and differentiation of epithelial cells (Bolognia *et al.*, 2008). Retinoids require careful consideration before use due to side effects including local effects, systemic, psychological but more importantly teratogenic effects (David *et al.*, 1988).

Anti-Histamines

This class of drugs has multiple therapeutic targets including allergic and inflammatory conditions, motion sickness and nausea, gastric acid secretion and others (Richard Finkel, 2009). They play a role in urticaria prevention (Jauregui *et al.*, 2007) and symptomatic treatment in other mast cell conditions (Herman & Vender, 2003; Montoro *et al.*, 2007) especially for edema control and pruritus.

Mast Cell Stabilizers

Members of this class of drugs include cromolyn and nedocromil, and are used in mast cell mediated allergic conditions. They function by inhibiting the IgE mediated release of histamine by stabilization of the membrane (Corin, 2000).

2.2.6 Other treatments

In addition to medicinal treatments prescribed by practitioners are a series of physical and alternative treatments. Very popular with dermatological treatment is the use of UV light and tanning beds, especially for psoriasis. Although the mechanism of action is unknown, it is thought that UV activates Psoralen which inhibits cellular proliferation. In certain conditions practitioners may prescribe Ichthyotherapy in which small fish (doctor fish) are employed to remove dead skin from lesions. Coal tar (mixture of hydrocarbons) is used as an emollient and remains a popular treatment in many dermatological centers (Bolognia *et al.*, 2008).

3. The use of Complementary and Alternative Medicine (CAM)

Complementary and Alternative Medicine (CAM): Group of diverse medical and health care interventions, practices, products or disciplines that are not generally considered as part of conventional medicine (NCCAM, 2011)

Complementary Medicine: Any of a range of medical therapies that fall beyond the scope of scientific medicine but may be used alongside it in the treatment of disease and ill health (NCCAM, 2011)

Alternative Medicine: Medical therapies that are used in lieu of conventional therapy (NCCAM, 2011),

(Note: There are many definitions that have been put forward for CAM, these are the ones designated by the National Center for Complementary and Alternative Medicine (USA)).

Recognition of the rising interest and potential importance of Traditional Medicine (TM) and CAM lead the WHO to survey its membership on their respective national attitudes and regulatory status of this branch of health care. They found in 2005 that 71% of respondents have laws, legislative mandates and National regulatory bodies in place for TM/CAM (WHO, 2005). In 1991, the United States created the Office of Alternative Medicine to

scientifically scrutinize alternative health practices for the benefit of public and health professionals knowledge. By 1998, due to increasing interest of the subject, this department was expanded into the National Center for Complementary and Alternative Medicine as a member institute of the United States Institutes of Health. It was from this department that a systematic classification of Complementary and Alternative Medicines was formed and grouped into 5 categories (Molassiotis *et al.*, 2005), see Table 1. It is from the biological based therapies and the Alternative Medical systems that sources of natural products are being explored for as potential disease treatments and being entered into clinical trials. It should be noted that treatments from the other groups have entered clinical trials for certain conditions with mixed results including massage (Schachner *et al.*, 1998), acupuncture (Salameh *et al.*, 2008), meditation (Chida *et al.*, 2007), prayer and others.

CLASSIFICATION		EXAMPLES
I	Alternative Medical Systems	Traditional Chinese Medicine, Ayurveda
II	Mind-Body Interventions	Meditation, Prayer, Healing or Support Groups
III	Biological Based Therapies	Herbs, Dietary Supplements, Vitamins
IV	Manipulation and Body Based	Massage, Chiropractive, Osteopathy
V	Energy Therapies	Qi Gong, Reiki

Table 2. Classification of CAM devised by Center for Complementary and Alternative Medicine

3.1 Demographics of CAM use in industrialized nations

There has been a well-recognized trend in the increasing use of CAM among the general public (Harris & Rees, 2000; Su & Li, 2011). In the 2002 US National Health Interview Survey (NHIS) of 31,044 adults, 36% of adults reported using CAM in the previous 12 months, and if a life time prevalence was included, this figure rose to 50% (Barnes *et al.*, 2004). The results from the 2007 survey saw the 12 month prevalence figure rise to 38.6% and among those positive respondents, the most common CAM was listed as ‘natural products’ (Barnes *et al.*, 2008). Earlier smaller scale national surveys conducted by Eisenberg *et al.* found prevalence rates of 33.8% in 1990 and 42.1% in 1997, although these values are higher (possibly due to the small samples size) it is generally agreed that CAM use is continually increasing (Eisenberg *et al.*, 1998). The NHIS surveys identified some demographic characteristics common among users which have been confirmed from other studies. CAM use is more prevalent among women, adults with higher education, those who engaged in leisure time and physical activity, those who had one or more existing health conditions and have made frequent medical visits in the past year (Barnes *et al.*, 2008; Eisenberg *et al.*, 1998; Metcalfe *et al.*, 2010; Sirois & Gick, 2002). Other identified factors are higher socioeconomic status, being married, those who wished to take a more active role in health care decision making and most interestingly those with a chronic health condition (Metcalfe *et al.*, 2010; Wiles & Rosenberg, 2001). The popularity of CAM use is also recognized in other industrialized countries ; the rates for Canada are estimated at 12-20% (Gavin & Boon, 2005) and 46% in Germany and 49% in France where alternative treatments are well engrained in the national consciousness (Fisher & Ward, 1994). The trend of increasing CAM can be identified from Germany (West) with its 12 months prevalence almost doubling since the 1970’s (See Figure

1) (Dixon *et al.*, 2003). It should be kept in perspective when looking at the trends of TM/CAM use that (as defined by the WHO) up to 80% of the world’s population uses TM/CAM as their sole source of health care in the places where Western health care is inaccessible ((World Health Organization., 2009).

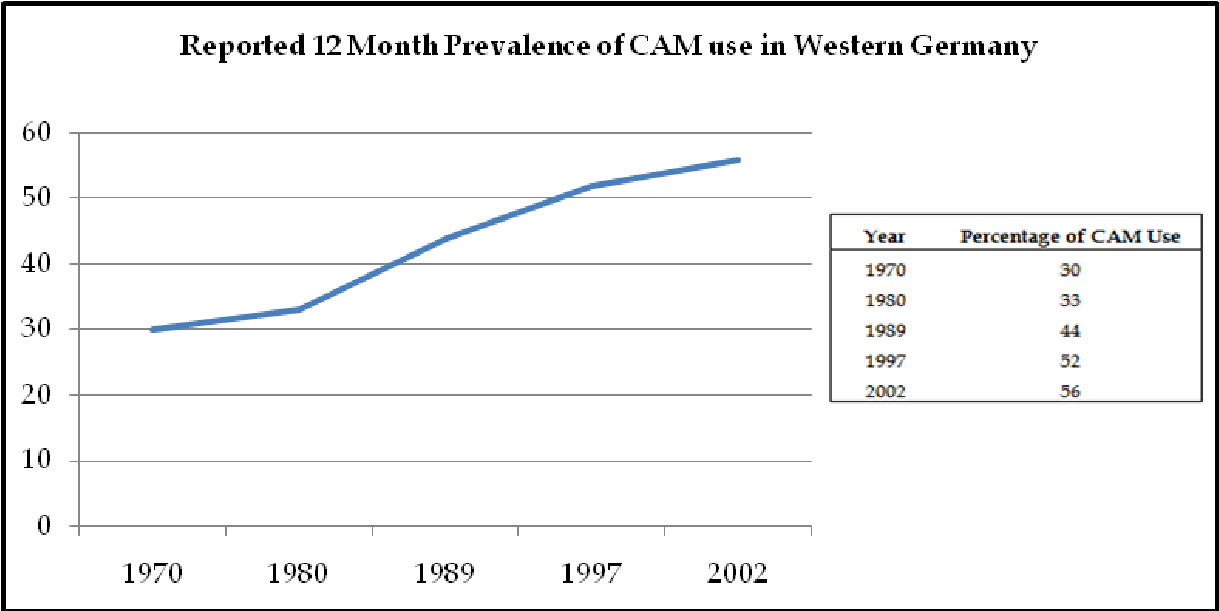


Fig. 1. Reported Use of CAM in Western Germany from 1970s to 2002

3.2 Patient and user attitude toward CAM

There have been many attempts to identify the reasons and motivations as to why members of the public are exploring alternative options for their well-being and health care. A large European study of 956 Cancer patients in 12 countries, found a prevalence rate of CAM use of 38.2% (Range of 14.8% to 73.1%). From those who reported using CAM therapy they were investigated first, for their motivation and second, how found out about them. The most common motivation for CAM use was to increase their body’s ability to fight disease (50.7%), followed by improved physical well-being (40.6%), and improvement of emotional well-being (35.2%). Sources of information about CAM were identified as friends (56.5%), family (29.1%), media (28.4%) and only 18.6% said their physician was the source (Molassiotis *et al.*, 2005). Use of CAM is associated with greater number of physical symptoms and with symptoms of greater intensity, longer disease duration (Sirois & Gick, 2002). The reasons for people to explore alternative treatment are varied, but what should be recognized is that are they exploring them. By having members of the public vetting these treatments in terms of personal satisfaction gives health care workers a unique opportunity by looking at the usage trends in members of the public as potential treatments sources.

3.3 Health care practitioners attitude towards CAM

The number of visits to practitioners of alternative therapies is now higher than the number of visits to all US primary care physicians (Pagan & Pauly, 2005). Physician and health care professionals response to CAM has been varied with differences depending on country,

region, age, experience and even sex. In a literature review by Sewitch *et al* found that characteristics of physicians whom are more likely to recommend CAM are younger, female, less experienced; while those less likely to recommend CAMs were older, male, more experienced physicians (Sewitch & Rajput, 2010). Older physicians are less likely to use CAMs themselves or recommend it to their family (Kurtz *et al.*, 2003). It should be noted that physicians are the most skeptical and least likely to recommend CAMs to patients, of all members of the health care profession. Rural health care providers offered CAM more frequently than their urban colleagues (Brems *et al.*, 2006). Between 60-80% of surveyed physicians express interest in CAM therapy (Corbin Winslow & Shapiro, 2002; Milden & Stokols, 2004) but few as 14% have recommended it their patients. Among physicians there is prejudice about the different types if CAMs, established practices such as acupuncture, chiropractor tend to be surveyed as the most likely to be beneficial to the patient; While reiki, bioelectromagnetics, aromatherapy have been ranked by doctors as having the least potential to be beneficial or event harmful to the patient (Levine *et al.*, 2003).

3.4 CAM and allergies

In a German study of 351 subjects with hypersensitivity (hay fever, asthma, atopic eczema, food allergies), 93 (26%) were found to be users of CAM. Of the 93 users, 94% previously were treated conventionally before starting CAM while 3 users used CAM before starting conventional treatment. Of those treated conventionally the majority (85%) were treated more than 10 years before trying CAM, they also score the efficacy of conventional medicine lower in their experience. Their reported motivations for using CAM were: conviction that CAM has less side effects (78%), wish to try everything (72%), unsatisfying results from conventional medicine (66%), and belief CAM is more natural (61%) (Schafer *et al.*, 2002) . In a review of 7 surveys of dermatological patients who used CAM they found life time prevalence of 35-65% (Ernst, 2000); among all the surveys they found severity of illness and length of disease had the greatest influence on CAM use. In Europe approximately 30% of patients with allergies report using CAM and this rises to approximately 50% of patients whom required in-patient treatment (Schafer, 2004). The use CAM is related to the severity of the symptoms of their conditions, patients who identify with having poor control are more likely to explore alternative treatments.

4. Search for natural products

Natural products are compounds that have been isolated from a living organism that have been found to be biologically active. A large proportion of the medicines in our current pharmacopeia have either originate as natural products or are inspired by a natural product using it chemical structure as framework on which to build on (Newman & Cragg, 2007). These compounds are being explore for, from all facets of nature including CAMs, our foodstocks, and on an increasing scale the marine sources. The remainder of the chapter will explore some of the natural products undergoing clinical trials for the treatment of Atopic dermatitis. Atopic dermatitis was selected due to its complex pathology, its association with the atopic march and the availability of an animal model which will be discussed below. The test compounds will be discussed below in the context of atopic dermatitis; however some of them are being tested in other related dermatological conditions.

4.1 Clinical trials

Any medicinal compound before entering into an approved treatment system (i.e. National Pharmacopeia) requires rigorous study and clinical trials, which have a defined set of trial steps, before they can be approved for use by National Regulatory bodies. In the United States this task is mandated by the Food and Drug Administration (FDA), in Canada by Health Canada and in the European Union by the European Medicines Agency (Rawson, 2000). All drug approvals required an evidence based approach to qualify their efficacy, evaluate the potential toxicity, and to prevent any unforeseen harm to patients. It is interesting to note that estimates now have the cost of marketed drugs from the R&D stage to consumer use at 500 million to 1 billion dollars and at a time frame of up to 10-15 years (DiMasi *et al.*, 2003). Only about 1 out of 1000 drugs from the animal testing stage (or preclinical phase) make it into clinical trials and from there only 1 in 5-10 eventually become approved. In this manner only 21 new drugs were approved by the FDA in 2010, 25 in 2009 and 21 in 2008 (Kaitin & DiMasi, 2011). However if natural compounds are identified from CAM treatment sources already employed by members of the public they may provide new treatment options which can enter rigorous evidence based trials which have already been vetted by members of the public.

Pre-Clinical Studies / Phase 0: Pre-clinical studies are conducted as *In vitro* (cell culture) and *In Vivo* (animal studies) as initial investigations into suspected potential biological activity. Phase 0 studies are human trials using microdoses to determine if its biological effects are what is expected (Υσηά Παυι, 2009)

Phase I: Small scale study of 20-100 healthy subjects, testing the safety, pharmacodynamics and pharmacokinetics of the study compound (Streiner & Normam, 2009), consists usually of either single or multiple ascending doses trials.

Phase II: Following the safety approval of drugs in Phase I, these are a small studies of 50-300 diseased subjects, designed to assess dosing requirements, efficacy, (Streiner & Normam, 2009) and safety profiles in people with the condition.

Phase III: Randomized controlled multicenter trials on large group of diseased patients with the target condition, this study are used to determine if the study compound has targeted therapeutic effects (R. Finkel *et al.*, 2009).

Phase IV: These studies occur after the drug has enter the market and is known as Post-Marketing Surveillance. They determine if any adverse events happen in large group of patients which were not previously identified. This phase is important is identifying any rare adverse events which occur in large treatment populations. This monitoring is responsible from removing from market approved drug which later have been found to be potentially harmful, examples are Troglitazone (Cohen, 2006; Gale, 2006) and Vioxx (Karha & Topol, 2004).

4.2 Atopic Dermatitis

Atopic dermatitis (AD) has been recognized since at least the 1500s (Wallach *et al.*, 2005) with its first formal medical description in 1933(Wise & Sulzberger, 1933). This condition is currently a popular target of medical research due to its increasing incidence (Peroni *et al.*, 2008; H. Williams, 1992), distressing rash and intense pruritic symptoms(Hanifin & Rajka, 1980), leading to general negative effects on the patients quality of life (Kiebert *et al.*, 2002) and its being refractory to treatment, along with a host of other reasons. With its long recognition in recent medical history, has led to many treatment options being made available. If any new product is found to possess immunomodulatory effects they tend to be

investigated as possible treatments for AD. The remainder of this chapter will look at Natural Products and Natural Preparations undergoing clinical trials for the treatment of AD.

PHASE	PARAMETERS
Pre-Clinical	In-Vitro (Cell Culture) and In Vivo (Animal Studies), determines biological activity, toxicity, etc
I	Small group health subjects; Pharmacokinetic and Pharmacodynamic properties, Single Ascending Dose, Multiple Ascending Doses
II	Small group diseased subjects, determine dosing requirements, drug efficacy
III	Larger group diseased subjects; Randomized Controlled Multicenter trials
IV	Post Marketing Surveillance Trial

Table 3. Phases of Clinical Trials

4.2.1 Animal Models: NC/Nga mice

One of the advantages of research into treatment for atopic dermatitis has been the development of an animal model that has been accepted to be representative of the disease (Suto *et al.*, 1999). Using this model, researchers are able to easily test products prior to proceeding to human clinical trials. NC/Nga mice are a strain that originated from the Japanese fancy mice (Nishiki-Nezumi), established as an inbred strain in 1955 (Matsuda *et al.*, 1997). Researchers noticed the development of spontaneous dermatitis like lesions that appeared just before or after weaning but the cause and pathogenesis had been unclear. A study was conducted to compare these lesions to those of human Atopic Dermatitis (Suto *et al.*, 1999). Mice raised in specific pathogen free (SPF) air controlled bio-clean rooms did not develop lesion, but when moved to air uncontrolled rooms, spontaneously several different type of lesions developed after 8 weeks. These mice developed clinical signs similar to AD: itching, erythema and hemorrhage, edema, superficial erosion, deep excoriation, scaling and dryness of the skin, and retarded growth. Infectious causes were ruled out by co-rearing with BALB/c mice which did not develop lesions. The histopathological changes which were consistent with Atopic Dermatitis as well as clinical lab values such as IgE hyperproduction (Matsuda *et al.*, 1997), overproduction of Th2 specific cytokines (Suto *et al.*, 1999; Vestergaard *et al.*, 1999). A literature search conducted in May 2011 resulted in 245 and 185 articles when the following keywords were used together: NC/Nga Mice, Atopic Dermatitis.

4.2.2 Animal trials

The following is a list of compounds (albeit not exhaustive) investigated using the NC/Nga mice model as potential treatments for Atopic Dermatitis. All were oral feeding studies in which the test compound was compared to a control. The efficacies of test compounds were determined by the improvement in symptoms of skin erythema, edema, excoriations, dryness, and scratching behavior. Other parameters measured depended on the trial and included plasma Ig levels, cytokines and chemokine profiles, and evaluation of skin biopsies. All of these studies had positive outcomes based on the design parameters and were recommended by their research teams for use in human clinical trials.

Rumex Japonicus Houtt

Rumex is an herb used in the traditional medical systems originating from Eastern Asian countries (Japan, Korea, China) for the treatment of various skin diseases including AD (H. S. Lee *et al.*, 2006). Previous studies have shown that it contains components with anti-oxidant and antibacterial properties (Elzaawely *et al.*, 2005). Identified Bioactive compounds include anthraquinone derivatives: emodin, chrysophanol, physcion. These compounds studied from other natural sources are reported to have antibacterial, antifungal, anti-inflammatory, immunosuppressive and antiviral properties (H. S. Lee *et al.*, 2006). After 42 days, mice treated with the test compound were found to have significant decreases in the severity of all symptoms when compared to the control, particularly the scratching behavior, which is the most distressing symptom of AD. There was a decrease in plasma IgE and IL4 (which mediate type I hypersensitivity) and noticeable decrease of inflammatory changes in the skin biopsies. The results were more pronounced in the higher concentration groups indicating this compound causes a dose response (H. S. Lee *et al.*, 2006).

PG 102 – Actinidia Arguta

Actinidia Argurta, commonly known as Hardy Kiwi, is a fruit native to Korea, Northern China and Siberia. Compound PG102 and isolated from this fruit by Park *et al.* in 2005 and found to have oral immune modulating effects in mice (Park *et al.*, 2005). A follow up study conducted to determine the effect on the NC/Nga mice model (Park *et al.*, 2007), found that after 9 weeks, PG102 showed statistically significant beneficial effect on AD symptoms and scratching behavior, while noted immunomolecular effects showed a decrease in IgE, IgG, IL4 while IL12 was increased. Other reported effects including the prevention of eosinophilia, decreased levels of eotaxin and TARC, inhibiting the infiltration of inflammatory cells into the dermis, preventing the thickening of the epidermis and dermis and reduced expression of Th2 mediated cytokines and chemokines (Park *et al.*, 2007). All of these effects are beneficial in attenuating the pathophysiological changes seen in Atopic dermatitis. Kim *et al.* tested the extract for efficacy compared to dexamethasone (corticosteroid) and tacrolimus and found PG102 attenuated the physical symptoms of AD similar to dexamethasone and more efficiently than tacrolimus. It also had positive effects on the molecular inflammatory markers as well (ex. IgE, IL4, INF γ and others). However, all three compounds affected the physical changes in the dermis in a similar manner (Kim *et al.*, 2009). The initial results indicated this compound shows a promising potential for future use as an oral dietary supplement for the long term treatment of AD.

Saururus Chinensis Baill

Saururus is a perennial herbaceous plant used in Korean folk medicine for the treatment of various conditions such as edema, jaundice, gonorrhea and used has been employed as an antipyretic, diuretic, and anti-inflammatory agent (Choi *et al.*, 2008). It has been shown to have anti-oxidant activity (Y. S. Lee *et al.*, 2004) and has been used in the management of various skin diseases including AD in Eastern countries. It contains flavonoids (quercetin, quercitrin, isoquercitrin, rutin) as active components which are reported as possessing number of biological effects: antiallergic, anti-inflammatory, antiviral, antiproliferative, anticarcinogenic (Scalbert & Williamson, 2000). After 63 days this compound was found to significantly improve skin severity scores and improved itching behavior, with the higher concentration performing better. Molecular evaluation found a decrease in IgE but no changes in IL4.

Lyophyllum Decastes

Lyophyllum is an edible mushroom cultivated in Japan that is commonly known as 'Fried Chicken Mushroom'. In a previous study, 11 polysaccharide extracts were found to have anti-tumour activity (Ukawa *et al.*, 2000) particularly (1-3)B-D-Glucan and (1-6)B-D-Glucan. In 2006, it was examined for its potential effect on the AD mice model (Ukawa *et al.*, 2007) using a 6 week feeding study. At the end of the study the treatment group had significant decreases in skin severity scores, as well as decreases in serum IgE, Histamine, and IL-4.

Persimmon Leaf Extract

Persimmon is the edible fruit of the *Diospyros kaki* Thunberg (Ebenaceae) tree which grows in China, Korea and Japan (Matsumoto *et al.*, 2002). Kaempferol, a flavonoid contained in the leaf, was found to inhibit antigen and calcium ionophore A23187 induced histamine release. Kaempferol-3-glucoside (astraglandin) has been shown to have anti-pruritic effects (Ishiguro & Oku, 1997). Kotani *et al.* found the leaf extract inhibited the release of histamine from human basophilic cell line KU812 (M Kotani, 1999) promoting them to study the effect on NC/Nga model (Kotani *et al.*, 2000). A 14 week oral feeding study using both Persimmon Leaf extract and Astraglandin alone found both were effective in decreasing the severity of skin scores, inhibiting IgE, IL4, IL13 and Histamine release (Kotani *et al.*, 2000). A similar follow up study was conducted confirming these earlier results and included measurement of Transepidermal water loss (TEWL) (Major pathology in AD due to dermal barrier dysfunction) and was found to be improved by the extract (Matsumoto *et al.*, 2002).

Konjac Glucomannan

Konjac is a plant found in eastern Asia and is very popular in Japan as cooking supplement. Two compounds of interest have been isolated from this product and tested as possible treatments: Konjac glucomannan which has been tested in mice and Konjac ceramide which entered human trials (see section 4.2.4). Glucomannan, a dietary fiber isolated from the tubers of *Amorphophallus konjac*, is a highly viscous polysaccharide composed of glucose and mannose residues (Onishi *et al.*, 2005). During the 1970's dietary fibers were investigated as part of the epidemiology of colon cancer (Burkitt, 1971a, 1971b). During mice feeding studies it was observed that serum IgE levels decreased and IgA and IgG increased (Lim *et al.*, 1997) indicating dietary fibers indirectly influenced immunoglobulin production. This theory was investigated in NC/Nga mouse model during an 8 week controlled feeding trial. Skin severity symptoms were significantly improved and scratching events were decreased to 1/3 to 1/6 of controls. Serologically it almost totally suppressed IgE levels and decreased the total Immunoglobulin, with a noted decreased in IL-4 and INF γ . Since the compound suppressed both Th1 and Th2 related cytokines its mechanism of action cannot be attributed to Th1/Th2 polarization (Onishi *et al.*, 2004, 2005). Follow up studies found that it decreased scratching behaviour in a dose dependent manner (OnishiKawamotoSuzuki *et al.*, 2007), and prevented IgE class switching in Balb/c mice following injection of keratinocyte extract (Oomizu *et al.*, 2006). It was also found to suppress allergic rhinitis like inflammation following nasal challenge with ovalabumin (OnishiKawamotoUeda *et al.*, 2007).

Gyokuheifusan

This is a traditional Chinese Medicine formulation that has been used for the treatment of allergic and respiratory disease (ex. infections, allergic rhinitis, asthma, and others) (Fang *et*

al., 2005).This preparation contains three herbal medications: *Astragalus membranaceus*, *Atractylodes ovata*, *Saposhinkovia divaricate*. In a study on the immunomodulatory effects of the formulation on allergic asthma, it was found to reduce the severity of asthma through normalization of INF γ /IL4 ratio (Th1/Th2 balance) (Fang *et al.*, 2005). These results were hypothesized to extent to AD, after a 4 week oral feeding treatment placebo control study it was found that dermatitis severity scores were improved significantly, as well as IgE and the IFN γ /IL4 balance (Nakatsukasa *et al.*, 2009).

COMPOUND	PARAMETER IMPROVEMENT	MOLECULAR IMPROVEMENTS
<i>Rumex Japonicus</i> <i>Houtt</i>	Skin Severity Scores, Scratching Behaviour, Skin inflammatory Changes	Decrease IgE, IL4
PG102 – <i>Actinidia Arguta</i>	Skin Severity Scores, Scratching Behaviour; Prevented eosinophilia, inflammatory cells entering dermis	Decrease IgE, IgG, IL4, TARC, Eotaxin; Increase IL12; Reduce expression of Th2 mediated cytokines
<i>Saururis Chinensis</i> <i>Baill</i>	Skin Severity Scores, Scratching Behaviour	Decrease IgE
<i>Lyophyllum</i> <i>Decastes</i>	Skin Severity Scores, Scratching Behaviour	Decrease IgE, IL4, Histamine
<i>Persimmon Leaf</i> <i>Extract</i>	Skin Severity Scores, Transepidermal Water Loss	Decrease IgE, IL4, IL13, Histamine,
<i>Konjac</i> <i>Glucomannan</i>	Skin Severity Scores, Scratching Behaviour	Decrease IgE, Ig, IL4, INF γ
<i>Gyokuheifusan</i>	Skin Severity Scores	Decrease IgE, IFN γ /IL4 balance

Table 4. Summary of Treatments Tested in Animal Models

4.2.3 Human clinical trials

When clinical trials are conducted for Atopic Dermatitis subjective symptoms such as erythema and pruritus, must be converted to objective and uniform results so that they may be compared with other studies. The following are some of the most commonly used systems and those employed in the following studies:

Transepidermal Water Loss (TEWL) (Pinnagoda et al., 1990): This is a measure of integrity of stratum corneum’s water barrier function; it provides information about the integrity of the skin, which becomes compromised in AD and may be influenced and improved with treatment. It is measured using tewameter, with units expressed as g/m²/h; with improvement indicated by a lower value.

Blood flow volume (BFV) :Measured as a parameter of inflammation using Laser Blood Flow Monitor; Arbitrary unit with improvement indicated by lower values.

Skin Color (a* Value): Erythema quantified by skin color reflectance it is measured using colorimeter

Visual Scoring – Visual judgment made by clinical investigator, scored 0-5

SCORAD (SCORing Atopic Dermatitis) (SCORAD, 1993): Standardized method for reporting dermatitis severity first published in 1993 by the European Task Force on Atopic Dermatitis, allows dermatitis severity to be reported numerically ranging from 0-103.

SCORAD Calculation = A/5 + 7 (B/2) + C

PARAMETER		TOTAL SCORE
A	SPREAD/BODY SURFACE AREA	100
	Judge based on rule of 9 for body surface area	
B	INTENSITY	18
	Erythema (1-3)	
	Edema (1-3)	
	Oozing/ Crusting (1-3)	
	Excoriation (1-3)	
	Lichenification (1-3)	
C	SUBJECTIVE SYMPTOMS	20
	Pruritus (1-10)	
	Insomnia (1-10)	

Table 5. Parameters for SCORAD Calculation

4.2.4 Human clinical of trials of natural products

WBI-1001 (IPBD: 2-isopropyl-5-[(E)-2-phenylethenyl] benzene-1,3-diol)

This compound is derived from a metabolite of a unique group of bacterial symbiots of entomopathogenic nematodes. It was found to inhibit inflammatory cytokine secretion by activated T cells including: TNFα, INF γ as well as inhibit allergic contact dermatitis in a mouse edema model (Bissonnette *et al.*, 2010). A phase 2A, double blind, vehicle controlled study resulted in statistically significant improvement in SCORAD, pruritus, and the amount of affected body surface area. These improvements were reached after 3-5 weeks of treatment. A 12 week Phase IIb trial was conducted (NCT01098734) as of June 9th 2011, the results are still pending publication.

Konjac Ceramide

Konjac ceramide is the second compound of interest isolated from konjac. Ceramides are a normal component of the lipid membrane, and their deficiency has been suggested as one of the pathological factors resulting in skin barrier disruption (Imokawa *et al.*, 1991), having being previously studied in the treatment of dermatitis (Berardesca *et al.*, 2001). Glucosylceramides are isolated, purified and produced as a nutritional supplement (Kimata, 2006) and oral intake has been found to decrease transepidermal water loss in normal adults (Miyanishi *et al.*, 2005). Konjac due to its high concentration of ceramide was studied for its effect on AD as an oral supplement. Following a 4 week oral feeding trial in 50 children, the SCORAD index was significantly improved when compared to the control group. INFγ and IL-12 were significantly increased while IL-4 and IL-13 were decreased indicating a skewing of the cytokine pattern towards a Th1 type. Interestingly in this study, ceramide was found to attenuate allergen specific response to HDM (house dust mite) and JCP (Japanese cedar pollen) by improving skin symptoms and wheal response but had no effect following dermal challenge of Egg white, histamine or buckwheat (Kimata, 2006).

Borage Oil: Gamma-Linolenic Acid

In patients with AD, an abnormality in metabolism of polysaturated fatty acids (PUFA) is commonly observed (Wright, 1991). PUFA are structural components of cell membrane

phospholipids which are important in maintaining membrane fluidity (Wright, 1991), as well as being important as precursors for pharmacologically active immunological agents (ie Eicosanoids) (R. Finkel *et al.*, 2009). Borage oil contains a high content (24%) of γ -linolenic acid (GLA) which is a metabolite of linoleic acid, one of the essential fatty acids. It is postulated an abnormality in essential fatty acid metabolism affects production of GLA and its incorporation into membranes, occurs in AD (Horrobin, 2000; Wright, 1991). Previous studies have shown GLA supplementation lead to improvements in multiple diseases including seborrheic dermatitis in children (Tolleson & Frithz, 1993). In a small Japanese study in a pediatric population, undershirts coated with Borage oil were given to 32 children in a double-blind, placebo controlled study (Kanehara *et al.*, 2007). After 2 weeks it was found that there was a statistically significant improvement in symptoms of itch and erythema, but no improvement papules, erosions, and trans-epidermal water loss (Kanehara *et al.*, 2007). In a literature review of 12 trials (oral and topical) on the efficacy of Borage Oil in the treatment of AD by Foster *et al.* in 2010 found that 5 studies show statistically significant improvement, while 5 showed borage oil to be ineffective and 2 studies were shown only to have partial response (Foster *et al.*, 2010). The efficacy of borage oil in the treatment of AD remains questionable, a previous product EpoGam used for treatment of AD was removed from market in 2002 in the UK when it was found to be ineffective. This product contained primrose oil which contains lower concentration of GLA than borage oil but was based on the same pathophysiologic principle (H. Williams, 2003). Borage oil while providing some benefit in some studies requires future study to determine its efficacy and it remains to be determine if it will be steroid sparing.

Emollient Therapy

Emollient therapy is a mainstay in the management of the symptoms of AD (Szczepanowska *et al.*, 2008). While studies into the prevention of AD are less common, Simpson *et al.* proposed that 'skin barrier protection from birth using bland emollients is a safe and feasible strategy for AD prevention' (Simpson *et al.*, 2010). This was based on the results from previous studies that found use of petrolatum early in life may be protective against AD development, there was trend towards increased TEWL and skin hydration before development of AD, use of emollients in premature infants protects against skin inflammation and emollients are effective at preventing flares in established AD (Simpson *et al.*, 2010). In 20 high risk infants (based on the ISSAC criteria (Asher *et al.*, 2006)) emollient therapy was initiated in the first week of life in order to maintain intact skin barrier. After 2 years it was found that only 15% of subject developed AD when conservative estimates of high risk infants would be positive for AD in the range of 30-50% suggesting this treatment could have both a protective and preventative effect (Simpson *et al.*, 2010).

Probiotics

Living or inactivated organisms that are claimed to exert beneficial effects on health when ingested are referred to as Probiotics (Schrezenmeir & de Vrese, 2001). The use of probiotic and prebiotics in the field of allergology is a controversial subject, with the results of prenatal and postnatal supplementation for the prevention of atopic dermatitis having mixed results (J. Lee *et al.*, 2008). Probiotic intestinal colonization is theorized to affect the Th1/Th2 immunological maturation prior to the establishment of atopic dermatitis (Gruber *et al.*, 2010). Physiologically the normal gut milieu has an immune system that is balance between protective mucosal immunity and systemic tolerance. In food allergies the balance

is impaired and oral tolerance of dietary antigens is not achieved. Risk Factors for the development of food allergy include immature gut barrier and type II Th2 cell skewed cytokine profile are present in early infancy. This may lead to atopic sensitization as antigen uptake is aberrant and Th2 cells further produce IL4 a cytokine essential for B cell differentiation into IgE producing cells and IL5 which is important for eosinophils. Normal bacterial flora at birth is shown to counterbalance the Th2 activity and promote oral tolerance. The predilection of bacteria to promote the differentiation of Th1 cell lineage may be due to specific CpG motif characteristics of bacterial DNA which has been shown to induce polyclonal B-cell activation and secretion of Th1 Cytokines IL6, IL12 and interferon γ (Passeron *et al.*, 2006). The guts of infants born in poor areas of developing countries where allergy prevalence is lower, are colonized earlier by enterobacteria, enterococci, lactobacilli, and eubacteria and displays a higher turnover of different *E. coli* strains in the intestinal microflora (Matricardi *et al.*, 2003). In a meta-analysis of 21 studies (1997-2007) by Lee *et al.* (2007) containing 1898 subjects looking at Probiotics in the prevention of atopic dermatitis found a risk reduction of 61% in the development of atopic dermatitis in high risk infants (J. Lee *et al.*, 2008). Newer studies have found conflicting results (Boyle *et al.*, 2011) so its use remains controversial. Strains of bacteria that have been investigated include *Lactobacillus rhamnosus* GG (Gruber *et al.*, 2007), *Bifidobacterium lactis* (Kukkonen *et al.*, 2007), *Mycobacterium vaccae* and others (Matricardi *et al.*, 2003). In studies of the use of the Probiotics following the establishment of AD has been met with mixed results. In one study it was found that while probiotics did improve SCORAD results they were not statistically significant when compared to placebo (Viljanen *et al.*, 2005). Other studies have shown the probiotics following established AD in children did improve SCORAD (Passeron *et al.*, 2006).

St. John's Wort Cream

St. John Wort is a family of plants with worldwide distribution accounting for about 370 species. It has been used as a herbal treatment for depression (Rapaport *et al.*, 2011), ADHD (Chan, 2008) and other psychological condition, however without proven clinical effects. It has been traditionally used for the topical treatment of wounds, burns, nerve lesions and has been used as a remedy for eczematous skin conditions (Schempp *et al.*, 2000). Hypericin is a major component of St. John wort and has been found to have bioactive properties exhibiting dose dependent photosensitizing activity (Schempp *et al.*, 2000). Hyperforin, a second compound, was found to have anti-bacterial activity (Gurevich *et al.*, 1971). After a 7 day topical trial, the treatment compound was found to significantly improve SCORAD scores. Colony forming units of *S. aureus* were measured, and found to be decreased by the treatment compound when compared to control, however not significantly. No molecular markers of inflammation were measured in this study.

Herbal Preparations – Traditional Chinese Medicine

Multiple trials have been conducted using formulas of traditional Chinese medicine. These formulas have a long history of use and documentation within their medical systems. The difficulty in investigating these compounds are due to the manner of preparation and individuality of the treatment. In a 2007 study by Hon *et al.* of a five herb formulation (*Flos lonicerae*, *Herba menthae*, *Cortex moutan*, *Rhizoma atracylodes*, *Cortex phellodendri*) in a placebo controlled 12 week oral feeding trial found that while the treatment group and placebo group both improved symptoms there was no statistical significance between the two. However in the treatment group, the number of days of corticosteroids use during the

month was significantly decreased, improving the quality of life of the subject (Hon *et al.*, 2007). In a follow up study it was found the formulation suppressed brain-derived neurotrophic factor (BDNF), Thymus and activation regulated chemokine (TARC), INF- γ , and TNF α (Leung *et al.*, 2008).

COMPOUND	PARAMETER IMPROVEMENT	MOLECULAR IMPROVEMENTS
WBI-1001	SCORAD, Pruritus, Body Surface Area	Inhibited TNF α , Increased INF γ
Konjac Ceramide	SCORAD, Transepidermal Water loss, Allergen specific response	Increased INF γ , IL12; Decreased IL4, IL13
Borage Oil	SCORAD?, Itch, Erythema	Metabolism of PUFA
Emollient Therapy	Prevention of AD	
Probiotics		
St. John's Wort Cream	SCORAD, Decreased <i>Staph. Aureus</i> CFUs	
TCM		

Table 6. Summary of Treatments Tested in Human Clinical Trials

4.2.5 Approved compounds

The calcineurin inhibitors are among the most recent example of natural products that had been identified having potential biological activity, then successfully proceeded through the clinical trial phase and have been approved for use in the treatment of AD and other dermatological hypersensitivity conditions. The following natural product concoction is the most recent treatment approved for use in AD by the FDA. Using an understanding of the pathophysiology of AD, compounds were selected that targeted different facets of the pathology to work in concert in the treatment of AD.

Atopiclair MAS063D (Atopiclair)

Hydrolipidic cream developed for the management of Atopic dermatitis, containing moisturizing elements and natural products (Belloni *et al.*, 2005): The agent contains a combination of the bioactive compounds from *Vitis vinifera*, glycyrrhetic acid and Hyaluronic acid. Hyaluronic acid is barrier forming and hydrating agent, traditionally used as lubricant in surgery (Manuskiatti & Maibach, 1996). It is a naturally occurring glycosaminoglycan in the body found in healthy connective tissue and induces tissue hydration (traditionally used as lubricant in other areas of medicine – ocular surgery, orthopedic surgery). Telmesterine and extracts from *vitis vinifera* have been found to have anti protease activities, (inhibiting harmful enzymes that exuded by damaged skin; and antioxidant effects protecting against free radicals (Belloni *et al.*, 2005). Procyanidins found in *vitis vinifera* have been examined at the vascular endothelium, where they help to prevent oxidative damage, they also form a barrier to protect against elastase, collagenase, hyaluronidase, and B-glucuronidase. Glycyrrhetic acid is a compound found to have anti-inflammatory activity (Teelucksingh *et al.*, 1990) In 2003, the first vehicle controlled, double blind study of Atopiclair was conducted in a study group of 20 subjects with contact dermatitis. Subjects applied vehicle to one arm and treatment compound to the other and were measured at 24, 48 and 72 hours. Results from this compound were promising, with

significant improvements in Transepidermal water loss (by 50%), Blood flow volume, Skin color, Visual Scoring. Only itch magnitude results fell below significance but showed improvement (Hongbo Zhai, 2003). In a follow up study in 2004, Atopiclair was tested in patients with Atopic Dermatitis and found significant improvement in all patients after 22 days. Statistically significant improvements were measure in total body surface area affected, Itch score, SCORAD value, and Quality of sleep. In an informal survey following the study 93% of subjects responded positively to the product (Belloni *et al.*, 2005). Following this study Atopiclair was approved by the FDA for the use in the treatment of atopic dermatitis (Abramovitis & Perlmutter, 2007).

5. Conclusions

Natural Products have been identified as potential sources of bioactive compounds used in the treatment of immune disorders. Historically some of the major and most important pharmaceutical compounds have their origin as natural products (Newman & Cragg, 2007). Penicillin, discovered as a metabolite of mold in a petri dish, revolutionized the manner in which medicine has been practiced since wide spread implementation following World War II (R. Finkel *et al.*, 2009). Many of the classes of treatment compounds currently being used in immunology and dermatology have originated from natural products. It might hold true that the next revolutionary treatment might likewise have its origin from the natural world, potentially being already explored by patients looking into CAMs.

It is inevitable that nature will continue to provide pharmaceutical active compounds that will be used in all practices and disciplines of medicine. It is those conducting the exploration for these compounds to keep an open mind to the possibility that an already employed alternative medicine might provide the next clue or even a source unknown.

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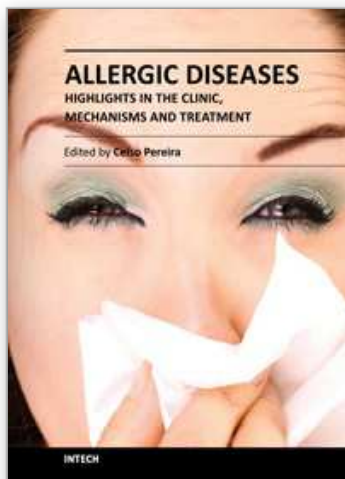
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The present Edition "Allergic diseases - highlights in the clinic, mechanisms and treatment" aims to present some recent aspects related to one of the most prevalent daily clinical expression disease. The effort of a group of outstanding experts from many countries reflects a set of scientific studies very promising for a better clinical care and also to the treatment and control of the allergy. This book provides a valuable reference text in several topics of the clinical allergy and basic issues related to the immune system response. The inflammatory reaction understanding in allergic disease is clearly evidenced, as well as new strategies for further researches.

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