International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 09 September 2024
DOI: 10.47191/ijcsrr/V7-i9-24, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

Plant-Based Therapies for Atopic Dermatitis Management: A Review

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ABSTRACT: Dermatological issues pose a frequent challenge for small clinical practitioners, presenting a spectrum of conditions encompassing otitis, pyoderma, anal sac problems, flea allergy, and atopic dermatitis (AD). Atopic Dermatitis (AD) is a chronic and recurring skin condition characterized by distributed skin lesions. In recent decades, researchers have shown a keen interest in AD due to its increased prevalence in developed countries. While various treatment strategies, including biological and immune modulators, are available for AD, each has certain limitations. Researchers have exhibited a significant interest in managing AD with herbal medicines. The use of herbal drugs for AD could potentially eliminate local and systemic adverse effects associated with long-term corticosteroid use, as well as reduce the high cost of therapy with biological drugs. This review discusses traditional East Asian herbal medicines as well as scientific data related to newer herbal extracts or compositions for the treatment of AD. The paper also delves into in vivo animal models and in vitro cell cultures that have been investigated with herbal medicines to establish a potential role in the treatment of AD. In conclusion, herbal medicines could serve as a better and safer complementary and alternative treatment option for AD.

KEYWORDS: AD, Atopic dermatitis, curcuma longa, DNCB, dog, dermatology, Terminalia chebula.

INTRODUCTION

Dermatological issues pose a frequent challenge for small clinical practitioners, presenting a spectrum of conditions encompassing otitis, pyoderma, anal sac problems, flea allergy, and atopic dermatitis (AD). Among these, AD stands out, affecting approximately 10% of dogs and emerging as the second most prevalent cause of pruritus and allergic skin diseases in these animals (Lund *et al.*, 1999, Hillier and Griffin 2001, Scott *et al*., 2001). This chronic inflammatory skin condition is characterized by persistent pruritus and distinctive skin lesions, presenting as red, unhealthy, and flaky skin. The relentless itch prompts patients to scratch, further aggravating the disease. The distinct pattern of skin lesion distribution in atopic dermatitis is a critical aspect of understanding the clinical presentation of this canine skin condition. Notably, the most commonly affected areas include the groin (88.40%), abdomen (78.80%), neck (76.90%), periocular region (75.00%), axilla (71.10%), muzzle, and paws (69.20%). Further involvement extends to the ear pinna (67.30%), limbs (48.07%), and tail (7.60%) (Brar *et al*. 2017). However, it is essential to acknowledge that lesion distribution may exhibit variability across different dog breeds (Nuttall *et al*., 2014). For instance, Dalmatians may manifest lesions on the lips, while German Shepherds could exhibit involvement in the elbows, hindlimbs, and thorax, accompanied by seborrhea or generalized disease. Boxers may present with urticaria and otitis, while Labrador Retrievers may exhibit dry skin (Wilhelm *et al.*, 2011).

The concept of "atopy," derived from the Greek term "atopia" denoting "different" or "out of place," was initially proposed by Coca and Cooke (1923) to encompass asthma and allergic rhinitis. However, Atopic Dermatitis (AD) was later incorporated into the realm of atopic disorders by Wise and Sulzberger (1933), primarily due to its observed association with asthma and allergic rhinitis. Notably, AD often precedes the manifestation of this atopic triad, underscoring its pivotal role within this clinical spectrum (Spergel and Paller, 2003). AD, characterized by persistent and intermittently recurring inflammatory cutaneous manifestations, is witnessing a global surge in prevalence, profoundly impacting the well-being of afflicted individuals (Christie *et. al.*, 2005). The hallmark features of AD include eczematous lesions exhibiting specific age-related patterns and intense pruritus, indicative of its intricate pathophysiological underpinnings (Lagan *et. al.*,2020).

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Prevalence of Atopic Dermatitis in India

Jyothi *et. al.,* (2013) studied the clinical efficacy of Tacrolimus topical in Atopic dermatitis and identified a range of sources contributing to dermatoses in dogs, encompassing mange, atopy, malasseziosis, pyoderma, hypothyroidism, dermatophytosis, and mixed infections. Among these, canine atopic dermatitis (CAD) stands out as the second most common dermatological ailment. It typically presents with notable symptoms such as intense redness and itching. Animals after treatment with Tacrolimus topical spray showed clinical improvement from the 7th day with complete clinical recovery within 20 days of treatment confirming the clinical efficacy of Tacrolimus topical in Atopic dermatitis. Sarma *et. al.,* (2013) examined 914 dogs for dermatological disorders among which 5.6% were found to have skin diseases. Demodicosis was the most common (51.92%), followed by scabies (28.85%), atopic dermatitis (7.70%), hot spots (5.76%), fungal dermatitis (1.9%), and mixed dermatitis (1.9%). Dogs under 1 year old were more susceptible. Males (67.31%) were more affected than females (32.69%). Spitz, Labrador, Pomeranian, and Non-descriptive breeds showed predisposition. Clinical symptoms included itching (55.77%), scratching (17.31%), alopecia (9.62%), and asymptomatic cases (17.31%). Raman *et. al.,* (2015) conducted a study to document the prevalence of allergic dermatitis among cases of dermatitis presented at various veterinary clinics and teaching hospitals They found that allergic dermatitis accounted for 1.93% (18 out of 930) of the cases, with the highest prevalence occurring in July (27.77%). Among the allergic dermatological conditions observed in the canine population, atopic dermatitis was the most common (61.11%), followed by flea allergy (16.66%), contact allergy (16.66%), and drug allergy (5.55%). Dogs aged two to four years were found to be the most susceptible to allergic dermatitis, with males showing a higher susceptibility compared to females.

Narang *et. al.,* (2015) investigated the prevalence of dermatological issues from May 2012 to April 2013 in canines. Among the 999 dogs screened, 181 exhibited dermatoses. These included fungal dermatitis (30.94%), infestations by ticks, fleas, and lice (20.44%), mange (11.60%), bacterial dermatitis (11.60%), non-specific/allergic dermatitis (13.81%), and mixed infections (11.60%). The peak occurrence was noted in July (34.83%), followed by June (23.72%), with the lowest frequency observed in March (7.26%). Males were found to be more susceptible to allergic dermatitis than females. Brar *et. al.,* (2017) studied cases of canine atopic and found a 27.90% diagnosis rate, with increased prevalence during the monsoon season. Labrador retrievers, Toy breeds, and German Shepherds aged 1–3 years were predominantly affected. Clinical signs observed in dogs with atopic dermatitis included pruritus (100%), erythema (82.69%), alopecia (75.00%), hyperpigmentation (36.00%), scales/crusts (25.00%), lichenification (21.15%), and excoriation (19.60%). The lesions were commonly found in areas such as the groin (88.40%), abdomen (78.80%), neck (76.90%), periocular region (75.00%), axilla (71.10%), muzzle, and paws (69.20%), ear pinna (67.30%), limbs (48.07%), and tail (7.60%). Bhagya *et. al.,* (2021) investigated the occurrence of dermatological diseases in 911 pugs, presented to Veterinary College Hospital, Bengaluru for one year and nine months (January 2018- September 2019). Out of 911 cases presented, 419 cases were of dermatological origin with an incidence of 46 percent. Commonly encountered skin diseases were pyoderma, canine atopic dermatitis, tick infestation, flea allergy dermatitis, demodicosis, otitis, canine scabies, Malassezia dermatitis, food allergy, acral lick dermatitis, dermatophytosis, and immune-mediated disease. Incidence of atopic dermatitis was higher in female dogs compared to males and incidence was more in pugs less than three years old. Skin lesions observed in atopic dogs were erythema, hyperpigmentation, papule, epidermal collarettes, lichenification, alopecia, excoriation, scales, salivary staining, and pustules. Ambiky *et. al.,* (2022) examined 245 cases of allergic dermatitis in dogs from 2019 to 2021 in Kerala, out of 245 cases, 63 were diagnosed with canine atopic dermatitis (CAD), constituting approximately 25.7% of the total allergic dermatitis cases. Atopic dermatitis showed a high incidence of 66.7% in dogs under 3 years old, with males being more affected, having a sex ratio of 1.74:1. Labrador retrievers were the most susceptible breed to atopic dermatitis, followed by Beagles, Pomeranians, and others. Singh *et. al.,* (2022) investigated the prevalence of canine atopic dermatitis (CAD) and their findings revealed that CAD had an incidence rate of 3.27% among the 612 dogs studied. The condition was more common in female dogs and predominantly affected those aged between 6 months and 3 years. Haritha *et. al.,* (2022) conducted a study from March 2022 to August 2022, to determine the prevalence of dermatological disorders in canines. They found an overall prevalence of 33.4%, with male dogs showing a higher prevalence (58.3%) and Labrador retrievers having the highest incidence at 30.8%. Dogs under one year old had a higher prevalence (42.3%). Common clinical manifestations included alopecia, pruritis, and erythema. Ectoparasites, particularly Demodex spp., were the most prevalent etiology (37.8%), followed by pyoderma (23.1%). Atopic dermatitis had the lowest incidence at 4.5%. Varughese and Chitra (2022) analyzed a variety of skin conditions and associated risk factors involved 273 dogs seen in Chennai, from September 2017 to February 2018. Pyoderma was identified as the most prevalent condition, affecting 60.8% of the cases. Following

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www.ijcsrr.org

closely, allergy and atopy emerged as the second most prevalent group of skin diseases, encompassing contact allergies, food allergies, flea bite allergies, moist eczema, and scrotal eczema, with an incidence of 10.3% among the dogs.

Worldwide Prevalence of Atopic dermatitis

Scott *et. al.,* (2001) reported that atopic dermatitis ranks as the second most prevalent cause of canine pruritus, following flea allergy dermatitis, with an estimated prevalence of around 10%.

Tarpataki *et. al.,* (2006) analyzed medical records of 600 dogs diagnosed with atopic dermatitis, focusing on history, geographical distribution, breed predilection, clinical signs, and allergen sensitivity determined by intradermal skin testing. The onset of atopic dermatitis was most prevalent between 4 months and 3 years of age in 66.6% of cases. Dogs in specific geographical regions exhibited varying sensitivities to different allergens, with Dermatophagoides farinae and human dander being the most common allergens. Certain breeds, including Hungarian Vizsla, Pumi, French bulldog, Doberman Pinscher, and Bobtail, showed a higher prevalence of atopic dermatitis compared to the general dog population, while breeds such as Cocker spaniels, French bulldogs, and Bullmastiffs were more prone to adverse reactions to food. Nødtvedt *et. al.,* (2006) examined the incidence of atopic dermatitis in dogs and revealed a rate of 1.7 cases per 1000 dog-years at risk among insured Swedish dogs from 1995 to 2002. Notably, bull terriers exhibited the highest risk at 21 cases per 1000 dog years, while other breeds like boxers and West Highland white terriers also showed elevated risks. Interestingly, there was no discrepancy in incidence between male and female dogs, and a slight rise in incidence over the study period was noted. Additionally, analysis of a subset of 15 high-risk breeds suggested a potential impact on overall survival for dogs with insurance claims related to the disease Couceiro *et. al.,* (2020) investigated the Prevalence of canine atopic dermatitis and found that out of 456 dogs examined from October 2018 to October 2019, 25.65% (117) were diagnosed with canine atopic dermatitis (CAD). Among these cases, 62.4% (73) were female, suggesting a potentially higher incidence of atopy in females. Additionally, 51.7% (29) of the diagnosed dogs belonged to the Shih-Tzu breed. While no confirmed sex-related predisposition was established, the study revealed an intriguing trend toward a greater prevalence of CAD among female dogs.

Pathogenesis of Atopic Dermatitis

The pathogenesis of atopic dermatitis remains elusive, yet it is widely acknowledged to stem from intricate interplays between genetic predispositions and environmental influences, culminating in epidermal barrier dysfunction, immune dysregulation, and perturbations in the cutaneous microbiome. A significant hurdle in deciphering this complex puzzle lies in discerning whether these factors serve as primary instigators of the disease or emerge as secondary consequences. This discussion delves into the evidence supporting the involvement of genetic and environmental factors, as well as epidermal barrier dysfunction, immune dysregulation, and dysbiosis of the cutaneous microbiome, shedding light on their potential roles in the onset and progression of atopic dermatitis. Grewe *et. al.,* (1994) investigated the expression of interferon-γ mRNA in eczematous skin lesions compared to normal skin, 13 out of 15 patients and interleukin-4 mRNA in 4 out of 15 patients. Following successful therapy of atopic dermatitis, the increased interferon-γ mRNA expression was significantly downregulated, suggesting its association with the clinical course of the condition. Thepen *et. al.,* (1996) examined T helper (TH) cell subpopulations in atopic dermatitis (AD) by assessing interleukin-4 (IL-4) and interferon-γ production. They observed a dynamic shift in TH cell response throughout AD, with an initial predominance of IL-4 production by TH2 and THO cells, followed by a subsequent shift towards interferon-γ production by TH1 and THO cells.

Olivry *et. al.,* (1999) aimed to characterize and compare the cytokine-gene expression in skin homogenates of dogs with atopic dermatitis (AD) and normal dogs. Using reverse-transcriptase polymerase chain reaction with canine-specific cytokine-gene primers, they found that IL-4 and IL-5 transcripts were more common in atopic skin, while IL-2 mRNA was more prevalent in normal skin. IFN-γ mRNA was detected in 5 out of 29 atopic specimens, mainly from dogs with chronic lesions. About one-fourth of atopic samples showed a clear type-2 cytokine profile, while the rest did not exhibit polarized repertoires. Conversely, one-fourth of normal control specimens displayed type-1 cytokine profiles. Roosje *et. al.,* (2002) demonstrated elevated levels of CD4+ T cells, particularly in the lesional and nonlesional skin of cats with allergic dermatitis. They observed an increased presence of IL4+ T cells in both affected skin areas compared to healthy control cats, indicating the involvement of IL4 in the inflammatory response associated with feline allergic dermatitis. Additionally, the detection of IL4 production by CD4+ T cells in clinically uninvolved skin suggests its potential role in initiating and perpetuating the disease process. Chen *et. al.,* (2004) elaborated on the interaction leading to a T cell response in the skin, initially Th2-mediated and later transitioning to Th1, along with a systemic Th2 response

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inducing IgE synthesis and eosinophil involvement. Olivry (2004) hypothesized the pathogenesis of canine atopic dermatitis (AD) by investigating epidermal lipids, epidermotropic and dermal immune cells, and cytokines detected in the skin of dogs with AD. In the acute phase, a putative epidermal barrier defect was proposed to facilitate the contact of environmental allergens and microbes with epidermal immune cells at sites of friction and trauma. Epidermal Langerhans cells were observed to capture allergens with antigen-specific IgE and migrate to the dermis and regional lymph nodes. Additionally, keratinocytes were found to release chemokines, including thymus and activation-regulated chemokine (TARC/CCL17). Histamine, proteases, chemokines, and cytokines, such as TNF-a and stem cell factor, were released by allergen-specific IgE-coated dermal mast cells. Granulocytes, allergen-specific Th2 lymphocytes, and dermal dendritic cells were also found to infiltrate early. Eosinophils were noted to degranulate upon allergen challenge, releasing proteins that induced dermal and epidermal damage and inflammation. In chronic canine AD, contributions from microbes, self-trauma, and neuromediators were suspected to perpetuate chronic inflammation. Chemokines were released in a continuous cycle, leading to the influx and activation of leukocytes and the further release of mediators. T lymphocytes expressing type-2 and type-1 cytokines, such as IL-12 and IFN-γ, were observed to infiltrate. The failure to down-regulate pro-inflammatory mechanisms was proposed to perpetuate cutaneous inflammation. Nødtvedt *et. al.,* (2006) studied the incidence of atopic dermatitis in dogs and revealed that dogs residing in urban areas born in the autumn season, and those belonging to specific high-risk breeds were more prone to recorded claims for the condition. Notably, environmental factors seemed to play a significant role, as evidenced by the higher prevalence among dogs in urban settings and certain geographical regions. This study underscores the importance of considering environmental influences in understanding and managing atopic dermatitis in dogs, highlighting the need for tailored preventive measures and interventions to mitigate these risks effectively. Nødtved *et. al.,* (2007) conducted a case-control study to assess environmental and dietary risk factors for the development of canine atopic dermatitis (CAD) in high-risk breeds. The study included 58 cases and 61 unaffected controls from Sweden. A logistic regression model was used, considering factors like gender, season of birth, environment, vaccination, and deworming practices. Surprisingly, these factors showed no significant effect on CAD development. However, the study found that feeding noncommercial diets to lactating bitches had a protective effect on offspring, halving the odds of CAD development. Favrot *et. al.*, (2010) revealed that environmental factors such as air pollution, noise pollution, and limited access to green spaces also contribute to the association with CAD. Additionally, lifestyle factors influenced by urban living, such as sedentary behavior and unhealthy dietary patterns, further exacerbate the risk of developing CAD in these environments. Meury *et. al.,* (2011) investigated Labrador and golden retrievers to explore factors like genetics, environment, and lifestyle affecting canine atopic dermatitis, comparing atopic and healthy dogs in Switzerland and Germany using a detailed survey covering birth conditions, care practices, and surroundings. Results showed increased disease risk linked to living in a shed as a puppy, early adoption, and regular dog washing, while lower risk was associated with rural living, other animal companionship, and forest walks. While causality wasn't confirmed, these findings suggest environmental factors may influence canine atopic dermatitis development. Ka *et. al.,* (2014) examined the influence of environmental factors, notably passive smoking, on the development of atopic dermatitis in dogs, an aspect seldom explored in veterinary research despite its established association with the condition in humans. The study encompassed 161 dogs attending dermatology and vaccination consultations over six months. Results indicated a substantial correlation between elevated levels of passive tobacco smoke exposure and the occurrence of atopic dermatitis in dogs, displaying a noteworthy odds ratio of 4.38 (95% CI, 1.10–17.44; p = 0.03). Peng and Novak (2015) analyzed the pathogenesis of atopic dermatitis (AD) and highlighted the multifaceted interplay between genetic predisposition, immune dysregulation, and environmental triggers. They underscored the dysregulated immune response typified by a Th2/Th1 cytokine imbalance, with Th2 cytokines like IL-4, IL-13, and IL-25 driving inflammation and impairing barrier repair mechanisms, while Th1 cytokines may have exacerbated inflammatory responses. Also, alterations in skin pH, influenced by genetic factors or environmental triggers, were identified as disruptors of the epidermal barrier function, modulating enzyme activity. These changes in pH levels could either enhance the activity of serine proteases and kallikreins, leading to the degradation of corneodesmosomes and intercellular adherence or attenuate the activity of enzymes involved in ceramide synthesis, resulting in reduced ceramide content in the skin. These disruptions in barrier function and lipid composition rendered the skin more susceptible to allergens, microbial colonization, and inflammation. Overall, the pathogenesis of AD involves a complex interplay of genetic, immunologic, and environmental factors culminating in chronic skin inflammation and barrier dysfunction. Majewska *et. al.,* (2016) studied gene expression differences related to T cell differentiation and cytokine synthesis in canine atopic dermatitis and found increased CD8+ T cells and Treg (CD4+CD25+ Foxp3+) cells, elevated IL-13 and

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TNF-α, and decreased IL-10 and TGF-β1 levels in cAD dogs compared to healthy dogs. Microarray analysis revealed gene expression differences related to T cell differentiation and cytokine synthesis, suggesting a role for CD8+ T cells and highlighted the importance of IL-13 and Treg cell function in CAD development. Anturaniemi *et. al.,* (2017) conducted a cross-sectional study to explore the relationship between environmental factors, phenotypic traits, and skin problems in dogs. Using data from the DOGRISK questionnaire, they analyzed 8643 dogs. The study found that living in a detached house, having other dogs in the household, and being born in the current household were inversely associated with owner-reported allergic/atopic skin symptoms, while factors like coat color and cleanliness of the household increased the risk. Certain breeds and breed groups showed higher proportions of owner-reported skin problems. In cases of veterinary-diagnosed canine atopic dermatitis (CAD), similar associations were observed. Hakanen (2018) investigated allergic manifestations in dogs, akin to those in humans, particularly focusing on the influence of living environments. Conducting a nationwide survey in Finland involving 5722 participants, the study found a higher prevalence of allergic symptoms in urban settings for both dogs and owners. Protective factors against allergic symptoms in dogs included rural living, larger family size, and regular contact with farm animals and other pets. Notably, there was a correlation between allergic dogs and allergic owners, indicating common underlying causal factors for allergic diseases in both species. Harvey *et. al.,* (2019) conducted a comprehensive study aiming to assess associations between environmental factors and case-control status in Labrador and golden retrievers, both at-risk breeds for canine atopic dermatitis (cAD). The study revealed several risk factors including rearing in an urban environment, male gender, neutering, flea control usage, and allowing dogs on upholstered furniture. Conversely, protective factors included living with other dogs (excluding cats) and engaging in walks in woodlands, fields, or beaches. Furthermore, among Labrador retrievers, chocolate-colored dogs exhibited a higher risk of CAD compared to black or yellow-coated counterparts. Rostaher *et. al.,* (2020) conducted a comprehensive examination of environmental factors and early-life determinants influencing CAD development. Their meticulous analysis unveiled the significant roles played by maternal allergic status, male sex, and mode of delivery, highlighting the intricate interplay between genetic predisposition and environmental factors in CAD pathogenesis. Takamori *et. al.,* (2018) investigated the role of IL-31 in the pathogenesis of atopic dermatitis (AD). They found that IL-31, a member of the IL-6 cytokine family, is primarily produced by activated CD4+ T cells, particularly Th2 cells, indicating its potential involvement in driving type-2 immune responses. Their research revealed elevated levels of IL-31 in specimens from AD patients, and IL-31-transgenic mice developed skin inflammation akin to AD, implicating IL-31 in the disease's pathogenesis. Despite these findings, the specific contribution of IL-31 to contact dermatitis/contact hypersensitivity (CHS), mediated by hapten-specific T cells including Th2 cells, remained unclear. To address this gap, the researchers investigated IL-31-deficient (Il31−/−) mice. Their study demonstrated that IL-31 deficiency did not impair the migration or maturation of skin dendritic cells, nor did it hinder the induction of hapten-specific T cells during the sensitization phase of FITC-induced CHS. Additionally, IL-31 deficiency did not affect the induction of local inflammation during the elicitation phase of both FITC- and DNFB-induced CHS. Interestingly, IL-31-deficient mice exhibited reduced scratching frequency and duration during FITC- and/or DNFB-induced CHS, suggesting a role for IL-31 in pruritus but not in the induction of local skin inflammation during CHS induced by FITC and DNFB. Wang *et. al.,* (2020) investigated DNCB-induced atopic dermatitis (AD) in BALB/c mice and found that the AD model group exhibited higher inflammation scores, redness, swelling, and hardening of the left ear skin, along with increased epidermal thickness, mast cell count, IL-4 expression in skin tissue, and serum IgE levels compared to the control group. Nakajima *et. al.,* (2021) elucidated that in atopic dermatitis (AD), Th2 cytokines downregulate filaggrin expression, compromising skin barrier integrity, and contributing to pruritus development, prompting scratching behavior exacerbating barrier disruption. Keratinocytes respond by producing pruritogens like TSLP, promoting itching and epidermal innervation by peripheral sensory nerves. Allergic skin disorders, exemplified by AD, are driven by type 2 immunity and inflammation, characterized by signature cytokines IL-4, IL-13, and IL-5 primarily produced by Th2 cells. Epithelial cell-derived cytokines such as IL-25, IL-33, and TSLP play pivotal roles in initiating inflammation by modulating various cells, including group 2 innate lymphoid cells. Furthermore, IL-31, a newly identified type 2 cytokine mainly produced by Th2 cells, induces itching by acting on sensory neurons in the skin. Biologics targeting these Th2 cytokines have exhibited significant efficacy in AD treatment, bolstered by both fundamental and clinical research.

Mice as atopic dermatitis research model

Matsuda *et. al.,* (1997) discovered that inbred NC/Nga mice developed spontaneous skin lesions reminiscent of atopic dermatitis (AD) when raised in non-sterile conditions. These mice exhibited elevated plasma levels of total IgE, correlating with the severity

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of dermatitis. Immunohistochemical analysis of the skin lesions revealed increased mast cells and IL-4-producing CD4+ T cells, indicative of IgE hyperproduction. This suggests that environmental factors may trigger AD-like symptoms in NC/Nga mice. Chan *et. al.,* (2001) established an experimental mouse model expressing epidermal interleukin-4 (IL4) to simulate human atopic dermatitis. These transgenic mice developed pruritic inflammatory skin disease spontaneously, mirroring key features of human atopic dermatitis, including xerosis, conjunctivitis, inflammatory lesions, and Staphylococcus aureus infection. Histopathological analysis revealed chronic dermatitis with infiltration of T cells, mast cells, macrophage-like mononuclear cells, and eosinophils. Furthermore, elevated levels of total serum IgE and IgG1 correlated with the onset and progression of skin disease. Notably, affected mice predominantly exhibited skin disorders in poorly-haired areas, notably the ear (100%), neck (65%), and eye (53%). Matsuoka *et. al.,* (2003) investigated the establishment of an animal model of atopic eczema/dermatitis syndrome (AEDS) by applying a crude extract of Dermatophagoides farinae (Df) mites to the skin of mice. They found that NC/Nga mice treated with the Df extract developed characteristic skin lesions resembling AEDS, along with elevated levels of specific IgE and IgG antibodies. In contrast, BALB/c mice treated with the extract did not exhibit typical skin lesions or increased mast cell accumulation. These findings suggest that repeated application of Df extract can induce AEDS-like lesions in NC/Nga mice, indicating the potential utility of this model for studying atopic dermatitis. Kim *et. al.,* (2013) investigated the role of Dermatophagoides farinae body extract (DfE) in inducing atopic dermatitis (AD)-like skin lesions in NC/Nga mice. They found that repeated application of DfE to barrier-disrupted skin led to AD-like skin symptoms histologically and immunologically, with altered expression of Th1, Th2, and Th17-related cytokines. These findings suggest that NC/Nga mice can be a valuable model for studying different stages of AD progression and evaluating potential therapeutic interventions.

1-Chloro-2,4-dinitrobenzene (DNCB)

1-Chloro-2,4-dinitrobenzene or DNCB is an aromatic hydrocarbon composed of a benzene ring linked to two nitro groups and one chloride with potential use as an indicator for glutathione S-transferase (GST) activity, in the evaluation of T-cell immunocompetence, and as a treatment for warts. The chloride group of dinitrochlorobenzene (DNCB) is susceptible to nucleophilic substitution and is a target for GST-dependent glutathione conjugation in vitro; upon conjugation of the thiol group of glutathione to the DNCB substrate, there is an increase in the absorbance at 340 nm, which permits an indirect quantitation of GST activity in a sample. DNCB induces a type IV hypersensitivity reaction in most patients; therefore, exposure to DNCB can yield an indirect measurement of T-cell activity in a patient and immunocompromised patients may demonstrate decreased hypersensitivity toward DNCB. Following direct application to a wart, DNCB induces an allergic inflammatory response that may cure the viral infection that caused the wart. Also, a skin irritant that may cause dermatitis of both primary and allergic types. Contact sensitization with DNCB has been used as a measure of cellular immunity. DNCB is also used as a reagent for the detection and determination of pyridine compounds. (PubChem Compound Summary for CID 6, 1-Chloro-2,4-dinitrobenzene). Jewell *et. al.,* (2000) investigated DNCB absorption across various skin types using in vitro methods and and they found that 26-day-old rat skin allowed better penetration of DNCB compared to other species tested. Absorption and conjugation formation were similar in pig and human skin. Occlusion increased DNCB penetration but did not affect conjugation. The glutathione-S-transferase activity was highest in human skin, followed by 26-day-old rat, pig, mouse, and neonatal rat skin. Glutathione levels were highest in mouse skin, followed by neonatal rat, 26-day-old rat, pig, and human skin. These findings suggest that glutathione levels in the skin influence the degree of DNCB conjugation during percutaneous absorption, with depletion occurring during DNCB penetration.

Chemical and physical properties of DNCB

Colour- Yellow crystals
Odour- Almond odor
Molecular weight- 202.55 g/mol
Boiling point- 315 °C
Melting point- 52-54 °C
Solubility in ether, benzene- 13.8 [ug/mL]
Solubility in water- 9.24 mg/L at 25 °C
Vapour pressure- 0.000085 [mmHg] at 25 °C
(PubChem Compound Summary for CID 6, 1-Chloro-2,4 dinitrobenzene)

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Metabolism and Metabolites of DNCB

In the Hazardous Substances Data Bank (2024), it is noted that the conjugation of drugs and other foreign compounds like DNCB with glutathione results in the creation of N-acetylcysteine (or mercapturic acid) derivatives. Bingham *et. al.*, (2001) demonstrated in metabolism studies that 1-chloro-2,4-dinitrobenzene leads to the depletion of hepatic GSH levels through biotransformation, displacing chlorine to produce 1-SG-2,4-dinitrobenzene.

Mechanism of action of DNCB

Cumberbatch *et. al.*, (2004) demonstrated that repeated topical exposure of BALB/c strain mice to chemical contact and respiratory allergens leads to selective activation of T helper (Th)1 and Th2 cells, respectively. In addition, it has been shown that respiratory allergens, such as trimellitic anhydride, stimulate epidermal Langerhans cell (LC) migration with delayed kinetics compared with contact allergens, such as 2, 4-dinitrochlorobenzene. Experiments using anti-interleukin (IL)-10 antibodies in vivo suggest that cutaneous IL-10 may contribute to the differential regulation of LC migration by these chemicals. To investigate further the mechanistic basis for the development of polarized immune responses, we have examined the production of epidermal cytokines provoked following a single topical application to BALB/c strain mice of 2, 4-dinitrochlorobenzene (1%), trimellitic anhydride (25%) or vehicle (acetone: olive oil, 4:1; AOO). Skin explants were excised from mice exposed on the dorsum of both ears for various periods (30min-6hr) to chemical and were cultured on medium before analysis of supernatants for the presence of tumor necrosis factor alpha (TNF-alpha), IL-1beta, IL-1alpha, IL-6, IL-10, IL-12p40, IL-12p70 and IL-17 using the Bio-PlexTM cytokine array system. Enhanced production of IL-1beta, a cytokine involved in the initiation of LC migration, was detected only following exposure to 2, 4-dinitrochlorobenzene, with 15- fold increases induced by 6hr of exposure. In addition, only exposure to 2, 4-dinitrochlorobenzene was associated with early (2 hr) secretion of IL-17. In contrast, up-regulation of IL-10, a cytokine that inhibits LC mobilization, was evident only for trimellitic anhydride during the first 3 hr of exposure, with 2 to 3-fold increases in IL-10 release being induced. Small increases in IL-1alpha levels were apparent for both chemicals. No alterations in either IL-6, IL-12p40, or IL-12p70 secretion were recorded and TNF-alpha remained undetectable throughout. These data suggest that discrete epidermal cytokine secretion profiles induced following exposure to chemical contact and respiratory allergens might contribute to the polarization of immune responses, possibly through effects on LC function. Seyfried and Wüllner (2007) explored the impact of the Thioredoxin (Trx)/Thioredoxin reductase (TrxR)-system on cellular functions, particularly in antioxidant defense. They investigated how the selective TrxR inhibitor 1-chloro-2,4-dinitrobenzene (CDNB) affected survival and redox status in neuronal cell lines. Their findings revealed that CDNB induced apoptosis without depleting glutathione or affecting mitochondrial complex I-activity. Interestingly, cells treated with CDNB exhibited an early increase in reactive oxygen species and rapid activation of stress-inducible protein kinases, such as c-Jun N-terminal kinase (JNK) and mitogen-activated protein kinase kinase 4 (MKK4). This suggests that TrxR inhibition by CDNB leads to the generation of reactive oxygen species and subsequent activation of stress-inducible kinases, all without compromising the cellular antioxidant status or mitochondrial function.

DNCB for induction of atopic dermatitis

Zhang *et. al.*, (2009) studied dinitrochlorobenzene (DNCB) as inducer in dermatitis in mice and the role of specific antibodies in pathogenesis. Female BALB/c mice were sensitized with 2% DNCB multiple times by painting it onto the shaved skin at different intervals, followed by the left ear at different intervals. The study highlights that treating animal with DNCB polarizes Th cells into Th2 differentiation by increasing the production of Th2 cytokines (IL-4, IL-5, and IL-10) while decreasing the production of Th1 cytokines (IFNγ and IL-2). This polarization contributes to the mechanistic basis for the predominant induction of DNCB-specific Abs and plays a crucial role in the pathogenesis of contact hypersensitivity. They measured DNCB-specific antibody levels in serum, including IgG, IgG1, IgG2a, IgG2b, and IgA. They found that exposure to DNCB led to elevated levels of various subtypes of specific antibodies by activated B cells. Meng *et. al.*, (2019) explored the therapeutic potential of paeonol for atopic dermatitis using BALB/c mice. They induced AD-like lesions by sensitizing the mice's shaved dorsal skin with 200 µl of 1% DNCB every other day for the first week, excluding the control group where acetone and olive oil (3:1 v/v) were applied topically. Subsequently, DNCB (0.5%) was applied twice a week for an additional 3 weeks to sustain inflammation. Olive oil was used to moisturize the skin lesions. Wang *et. al.*, (2020) studied the role of DNCB in atopic dermatitis, BALB/c mice were subjected to sensitization with 1.0% DNCB on the dorsal skin followed by challenging the skin on the left ears with 0.5% DNCB. The mice in the experimental group exhibited

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 09 September 2024
DOI: 10.47191/ijcsrr/V7-i9-24, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

notable changes in skin appearance, including redness, swelling, and hardening, along with increased inflammation scores, epidermal thickness, mast cell count, IL-4 expression in skin tissue, and serum IgE levels compared to the control group. Wang *et. al.,* (2022) examined the impact of bisdemethoxycurcumin (BDMC) on atopic dermatitis (AD) induced by 2,4-dinitrochlorobenzene (DNCB) in female BALB/c mice. The mice were sensitized with DNCB applied on their dorsal skin and right ears dissolved in acetone-olive oil, followed by regular DNCB challenges every other day over five weeks. Suryawati *et. al.,* (2022) explored the efficacy of a turmeric rhizome extract-based moisturizing nanoemulgel in mitigating atopic dermatitis-like symptoms induced by 2,4-dinitrochlorobenzene (DNCB) in BALB/c mice. The mice underwent sensitization with DNCB to induce atopic dermatitis-like symptoms, followed by rechallenges with DNCB on specific days.

Common Therapeutic approaches for managing Atopic Dermatitis

Treatment approaches for atopic dermatitis in dogs are tailored to the individual patient's clinical presentation. Generally, strategies for managing canine atopic dermatitis (CAD) encompass several key aspects. These include alleviating itching and inflammation through symptomatic treatments, employing allergen-specific immunotherapy, addressing and preventing secondary bacterial and yeast infections, enhancing skin barrier function, and identifying and mitigating factors that may exacerbate the condition, such as environmental allergens.

Corticosteroids

Paradis *et. al.,* (1991) conducted the first controlled trial to assess the effect of sequential administration of four antihistamines, prednisone, a prednisone-antihistamine combination, or placebo on reducing pruritus in 30 dogs with various allergic diseases, including 21 diagnosed with uncomplicated atopic dermatitis (AD). Despite differences in formulations and regimens among the drugs administered, the study was labeled as double-blinded. Dogs received an average dosage of approximately 0.4 mg/kg/day of oral prednisone for 7 days. Results showed that a "good-to-excellent" reduction in pruritus was observed in 57% and 77% of dogs after prednisone and prednisone plus antihistamine treatments, respectively. Guague Áre *et. al.,* (1996) assessed the efficacy of methylprednisolone in dogs with allergic skin disease, including 17 diagnosed with atopic dermatitis (AD). They administered methylprednisolone at a dosage of 0.4±0.8 mg/kg daily for 7 days followed by every-other-day administration. Remarkably, after two weeks of treatment, more than 75% of the dogs with AD showed improvement, indicating the high efficacy of this glucocorticoid compound. Ferrer *et. al.,* (1999) investigated the efficacy of arofylline for treating canine atopic dermatitis (AD) and also assessed the benefits of oral prednisone at two different dosages. The study, designed as a blinded randomized controlled experiment, included four groups of 10 dogs with AD. In one group treated with prednisone, dogs received 0.5 mg/kg twice daily for 1 week, followed by once daily for 1 week, then every other day for 2 weeks. In the second group, dogs were administered 0.25 mg/kg following the same decreasing regimen. Both prednisone-treated groups showed a significant reduction in both clinical and pruritus scores, even after just 1 week of treatment. The authors estimated an average reduction in pruritus scores of 48% and 56% in the "high" and "low" prednisone groups, respectively. Similarly, the reduction in lesional scores was 61% in the "high" group and 63% in the "low" group. Interestingly, there was no significant difference in pruritus or lesional score reduction between the two prednisone-receiving groups.

Pucheu-Haston (2006) investigated the effects of prednisolone administration in dogs and found that prednisolone suppressed the influx of neutrophils, eosinophils, CD1c+, and CD3+ cells, as well as the expression of IL-13, CCL2, CCL5, and CCL17. Cobb *et. al.,* (2005) compared the efficacy of a topical preparation containing 0.5% fusidic acid and 0.1% betamethasone-17-valerate with systemic therapy (parenteral dexamethasone and oral clavulanate-potentiated amoxicillin) in treating 104 dogs with acute moist dermatitis. Both treatment groups showed significant improvement after seven days, with no significant difference in overall response. Staphylococcus intermedius was the most commonly isolated organism, with no resistance observed to fusidic acid or clavulanate-potentiated amoxicillin.

Jensen *et. al.,* (2009) conducted a randomized study to investigate the efficacy of betamethasone, a corticosteroid, in comparison to pimecrolimus for treating atopic dermatitis (AD). In this study, fifteen AD patients were treated with betamethasone on one upper limb and pimecrolimus on the other, administered twice daily for 3 weeks. The results revealed improvements in various parameters associated with skin barrier function upon betamethasone treatment, including enhanced stratum corneum hydration, reduced transepidermal water loss, and decreased dye penetration. Electron microscopy analysis further indicated alterations in the skin barrier structure, characterized by inconsistent lipid bilayers and partially filled lamellar bodies. Sekine *et. al.,* (2012) investigated

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 09 September 2024
DOI: 10.47191/ijcsrr/V7-i9-24, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

the antipruritic effects of crotamiton, capsaicin, and a corticosteroid by examining their inhibitory effects on scratching behaviors induced by different pruritogens in mice. The application of topical corticosteroid (0.05% clobetasol propionate) significantly reduced scratching behaviors triggered by all tested pruritogenic agents. Puigdemont *et. al.*, (2013) evaluated the efficacy of a novel topical formulation of cyclosporine A (CsA) in dogs with atopic dermatitis (AD), 87.5% of dogs in the CsA group achieved an effective reduction in pruritus, compared to 28.6% in the placebo group by the trial's end. Bachmann *et. al.*, (2018) demonstrated the efficacy of a virus-like particle-based vaccine targeting canine IL-31 in alleviating pruritus symptoms in dogs sensitized to house dust mites. Dogs receiving the vaccine exhibited a robust IgG response after vaccination doses of 100 µg followed by two doses of 300 µg. This strong antibody response effectively eliminated itching symptoms, suggesting the vaccine as a promising alternative treatment for canine atopic dermatitis (CAD) due to its potential for inducing longer-lasting antibody protection compared to other treatments. Souza *et. al.*, (2018) in their retrospective analysis found that lokivetmab, a canine-specific monoclonal antibody (mAb) designed to target and neutralize IL-31. Noteworthy advantages of this medication over other antipruritic agents include its rapid onset of action, reduced dosing frequency, lack of age restrictions, and compatibility with concurrent drug therapies. Gross *et. al.*, (1997) documented a rare bullous dermatosis in adult dogs, likely resulting from the topical application of corticosteroids. Clinical symptoms included flaccid bullae, erythema, ulceration, hemorrhage, and hyperpigmentation. Histological examination revealed subepidermal bullae and vascular changes, indicative of corticosteroid-induced skin fragility. Lesions resolved upon cessation of corticosteroid use, suggesting a direct correlation between topical corticosteroid application and the development of this dermatosis. Kimura *et. al.*, (1999) conducted a histological investigation on dorsal skin reactions to continuous topical corticosteroid treatment in hairless descendants of Mexican hairless dogs. Four types of corticosteroids were tested: prednisolone (ST-1; weak), fluocinolone acetonide (ST-2; moderate), diflucortolone valerate (ST-3; strong), and mometasone furoate (ST-4; very strong). Grossly, sites treated with ST-3 and ST-4 exhibited moderate inflammatory reactions, with decreased pigmentation and thin texture after treatment. Histologically, corticosteroid efficacy correlated with the severity of skin changes, with prominent epidermal thinning observed from one week after treatment initiation. Lesions worsened progressively during treatment, and at two weeks post-treatment, epidermal thickness began to return to normal in sites treated with ST-1 and ST-2, but continued to thin in ST-3 and ST-4 treated skin. At three to four weeks post-treatment, dermal hyalinization of collagen bundles was evident in ST-3 and ST-4 treated sites, consistent with steroid-induced skin atrophy observed in humans. Furue *et. al.*, (2003) in their retrospective analysis on 1271 patients with atopic dermatitis (AD), revealed that while most patients were effectively managed with topical steroids, a significant proportion remained uncontrolled despite higher steroid application. Adverse effects, including telangiectasia and steroid-induced atrophy, were noted, necessitating individualized treatment strategies for non-responsive patients. Jensen *et. al.*, (2009) Despite its efficacy in alleviating clinical symptoms and reducing epidermal proliferation, betamethasone treatment led to epidermal thinning. This study underscores the potential of betamethasone for AD treatment, while also highlighting concerns regarding its adverse effects on skin integrity, particularly in the context of long-term use.

Plant-Based Therapies for Atopic Dermatitis Management

Uehara *et. al.*, (2001) studied the potential efficacy of oolong tea in aiding the clearance of atopic dermatitis lesions. Participants, while continuing their usual medications, were instructed to consume oolong tea daily (10g steeped in 1000 mL water per day, divided into three doses). Positive outcomes were observed within 1 to 2 weeks, with 63% of participants showing marked to moderate improvement in lesions after 1 month. Notably, 54% still exhibited a favorable response after 6 months. Marsella *et. al.*, (2002) investigated the effectiveness of applying capsaicin (0.025%) twice daily to manage pruritus in dogs with atopic dermatitis (AD) in a double-blinded, placebo-controlled trial. Significant improvement reported by owners ($P = 0.0006$) contrasted with observations by investigators. Owners noted a temporary increase in pruritus during the first week of capsaicin therapy. Capsaicin was generally well tolerated and lesional skin showed lower levels of Substance P (SP) compared to nonlesional skin ($P = 0.03$). Saeedi *et. al.*, (2003) evaluated efficacy of topical licorice extract in treating atopic dermatitis. They standardized the extract based on Glycyrrhizinic acid content and formulated different topical gels using various co-solvents, with propylene glycol yielding optimal results. In a double-blind clinical trial spanning two weeks, they compared 1% and 2% licorice topical gels with a base gel, finding that the 2% formulation was more effective in reducing erythema, edema, and itching scores. Kim *et. al.*, (2014) studied the effects of 7,8,49-trihydroxyisoflavone (7,8,49-THIF) on atopic dermatitis (AD)-like symptoms in mice. They found that 7,8,49-THIF alleviated AD symptoms, reduced eosinophil and mast cell infiltration, lowered transepidermal water loss, and decreased levels of cytokines and chemokines associated with AD. Kim (2018) investigated the pharmacological effects of gooseberry on

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 09 September 2024
DOI: 10.47191/ijcsrr/V7-i9-24, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

symptoms induced by 2,4-dinitrochlorobenzene (DNCB) in mice with atopic dermatitis (AD). The study found that gooseberry alleviated AD symptoms such as erythema, edema, and dryness, and reduced histamine and IgE serum levels in DNCB-induced AD model mice.Yang *et. al.,* (2021) evaluated the potential of neferine, a compound derived from lotus seeds, in treating atopic dermatitis (AD). In vitro studies demonstrated that neferine inhibited cytokine and chemokine expression in TNF-α/IFN-γ-stimulated human keratinocytes, along with reducing MAPK phosphorylation and NF-κB signaling. In vivo experiments using a mouse model of AD-like skin inflammation induced by DNCB showed that neferine significantly improved skin barrier function, reduced scratching responses and epidermal hyperplasia, and decreased TEWL, erythema, blood flow, and ear thickness while increasing skin hydration.

***Curcuma longa* L**

Curcuma longa, commonly known as turmeric, is a perennial herb from the ginger family, *Zingiberaceae*, cultivated primarily in Asia, particularly in India and China. Its rhizome, the medicinal part of the plant, yields a yellow powder, which is the source of turmeric. This ingredient is renowned for giving curry powder its distinctive yellow color and is widely used in Asian cuisines for both flavor and color. Turmeric has been treasured not only for its culinary allure but also for its esteemed place in traditional Chinese and Ayurvedic medicine. Renowned for its potent anti-inflammatory properties, it has long been revered as a remedy for a multitude of ailments. From easing jaundice to alleviating menstrual difficulties and colic, turmeric has been lauded for its therapeutic benefits (Labban *et. al.,* 2014). With a rich tapestry of biological activities, turmeric stands out for its multifaceted health-promoting properties. Its repertoire includes not only anti-inflammatory prowess but also antioxidant, anticarcinogenic, and antimicrobial capabilities (Verma *et. al.*, 2018). The major polyphenolic compounds found in turmeric rhizomes are curcuminoids, which include curcumin, demethoxycurcumin, and bisdemethoxycurcumin (Ravindranath and Satyanarayan, 1980; Satyawati *et. al.*, 1976). These compounds, collectively known as curcuminoids, constitute approximately 3-6% of turmeric. Curcumin, the most studied compound among them, acts as a potent scavenger of various reactive oxygen species (ROS), inhibits ROS-generating enzymes, and plays an active role in suppressing inflammation by inhibiting cyclooxygenase and lipoxygenase enzymes involved in the inflammatory process. Moreover, turmeric extract protects against oxidative damage, prevents lipid peroxidation, and inhibits the binding of toxic metabolites to DNA. With its multitude of health benefits, turmeric has garnered significant attention for its potential therapeutic applications in various diseases and conditions (Niranjan *et. al.,* 2008). Shin *et. al.,* (2015) investigated the effects of turmeric extract and curcumin on food allergy symptoms in mice and they found that turmeric significantly attenuated food allergy symptoms induced by ovalbumin (OVA), including decreased rectal temperature and anaphylactic response, while curcumin showed weaker improvement. Turmeric also inhibited OVA-induced increases in IgE, IgG1, and mMCP-1 levels, and reduced Th2-related cytokines while enhancing a Th1-related cytokine. These results suggest that turmeric maintains Th1/Th2 immune balance and possesses anti-allergic effects. Lee *et al.* (2016) demonstrated that oral administration of p-Hydroxycinnamic Acid (HCA), isolated from the roots of *Curcuma longa*, in a mouse model of ear Atopic Dermatitis (AD), mitigated various local and systemic AD manifestations. These included ear thickening, immune-cell infiltration, production of AD-promoting immunoregulatory cytokines in ear tissues, increased spleen and draining lymph node size and weight, elevated pro-inflammatory cytokine production by draining lymph nodes, and heightened serum immunoglobulin levels. HCA-treated AD mice exhibited significantly reduced gene expression of Th1-type cytokines TNFα and IFN γ, as well as decreased levels of Th2-type cytokines IL-4, IL-5, IL-6, IL-13, and IL-31. Furthermore, histopathological analysis revealed typical AD pathological features in untreated AD mice, such as hyperkeratosis, acanthosis, and parakeratosis, whereas HCA treatment mitigated tissue inflammation, dermal thickening, and immune-cell infiltration in these mice. Sharma *et. al.,* (2019) evaluated the ameliorative effect of curcumin on ovalbumin (OVA) induced atopic dermatitis (AD) in mice. Female BALB/c mice were subjected to skin OVA-patch application for 1 week, followed by a resting period of 2 weeks, and the same protocol was repeated thrice. Curcumin was administered daily at 20 mg/kg (i.p.) for 7 consecutive days during the last sensitization phase. Th2-promoting cytokines (TSLP/IL-33) and Th2 cytokines (IL-4/IL-5/IL-13/IL-31) were markedly suppressed, along with reduced STAT-6 phosphorylation and GATA-3 expression. Curcumin administration also restored the redox balance and phosphorylation status of P65-NF-κB. And histological examination epidermal thickness and infiltration of inflammatory cells in the dermal area were observed. Jantawong *et. al.*, (2021) investigated the acute and chronic toxicities of orally administered curcumin-loaded nano-complexes (CNCs) in mice and hamsters. In acute toxicity testing, CNCs were given at doses of 0.1-11.0 g/kg for mice and 0.2-21.4 g/kg for hamsters, while chronic toxicity testing

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 09 September 2024
DOI: 10.47191/ijcsrr/V7-i9-24, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

involved daily doses of 0.09-0.8 g/kg/day for mice and 0.18-1.61 g/kg/day for hamsters over 6 months. Low and medium CNC doses showed no adverse effects, but higher doses resulted in increased organ-weight-to-body-weight ratios, elevated biochemical parameters, and liver and lung inflammation. The LD50 values were determined as 8.9 g/kg in mice and 16.8 g/kg in hamsters. Abnormalities observed at high doses resolved within 28 days after treatment cessation, indicating very low toxicity, possibly due to the components of the nano-complex. Suryawati *et al.,* (2022) studied that Turmeric rhizome extract-based moisturizing nanoemulgel ameliorated atopic dermatitis-like skin lesions in mice by modulating Thymic Stromal Lymphopoietin, Interleukin-13, and Interleukin-17 in BALB/c mice. In this study, BALB/c mice were sensitized with DNCB to induce atopic dermatitis-like symptoms, followed by rechallenge with DNCB on specific days. From the 14th day, a moisturizing nanoemulgel containing 1% turmeric rhizome extract was applied to the sensitized skin for 2 weeks. The study concluded that moisturizing nanoemulgel effectively improved dermatitis by reducing TSLP, IL-13, and IL-17 levels and enhancing skin barrier function. Additionally, in histopathological examination, the treatment group showed milder epidermal hyperplasia, spongiosis, and a dermal infiltrate consisting of lymphocytes, neutrophils, and eosinophils in comparison to control. Wang *et. al.,* (2022) evaluated the inhibitory effect of bisdemethoxycurcumin (BDMC) on 2,4-dinitrochlorobenzene (DNCB)-induced atopic dermatitis (AD) in female BALB/c mice. The mice were sensitized with DNCB dissolved in acetone-olive oil on their dorsal skin and right ears, followed by a DNCB challenge every other day for five weeks. Oral administration of 200 and 400 mg/kg BDMC in 1% carboxy methyl cellulose significantly improved AD symptoms, reduced ear thickness and spleen index, inhibited inflammatory cells and mast cell infiltration, decreased skin thickness, and suppressed mRNA expression of chemokines and inflammatory cytokines. BDMC also inhibited the activation of MAPK and NF-kB signaling pathways. Furthermore, ELISA analysis revealed reduced serum IL-4 levels and IgE while increased serum IFN-y levels. Histopathological examination showed BDMC treatment reduced epidermal and dermal thickness, as well as DNCB-induced mast cell infiltration.

***Terminalia chebula* Retz.**

Terminalia chebula (T. *chebula*) is an evergreen flowering tree whose leaves, fruits, seeds, and barks are widely used in conventional folk medicine, belongs to the *Combretaceae* family, and is native to Asia, including India. Known by various common names (RAI and Joshi 2009)

Black myrobalan, ink tree, or chebulic myrobalan (English),
Haritaki (Sanskrit and Bengali),
Harad (Hindi),
Harada (Marathi and Gujrati)
Karkchettu (Telgu)
Kadukkaya (Tamil)

Turmeric is referred to as the "King of Medicine" in Tibet, in Indian mythology, this plant is supposed to be originated from the drops of Ambrosa (Amrita) which fell on the earth when God Indra drank it and since it carries away all diseases or it is sacred to God Siva (Hara), known as 'Haritaki' (Gupta, 2012). Rich in bioactive compounds like tannins, flavonoids, sterols, amino acids, fructose, and resins, T. *chebula* exhibits a diverse range of medicinal properties, including antibacterial, antifungal, anticarcinogenic, antioxidant, antidiabetic, anti-inflammatory, anti-HIV, and anti-aging activities. Notably, tannins such as chebulinic acid, chebulagic acid, gallic acid, chebulic acid, corilagin, and ellagic acid are among the chief constituents responsible for these therapeutic effects. Fruits of T. *chebula* are stomachic, tonic, carminative, expectorant, and antidysentery. Its common uses include rejuvenating, laxative (unripe), astringent (ripe), anthelmintic, nervine, expectorant, tonic, carminative, and appetite stimulant. It is used in people with leprosy (including skin disorders), anemia, narcosis, piles, chronic, intermittent fever, heart disease, teeth carious, bleeding, chronic ulcer, diarrhea, anorexia, cough and excessive mucus secretion, and a range of other complaints and symptoms. Additionally, its bark is utilized as a diuretic and cardiac tonic. (Bulbul *et. al.*, 2022) Chattopadhyay & Bhattacharyya (2007) investigated *Terminalia chebula* for tannin content, including chebulic acid, chebulagic acid, corilagin, and gallic acid. They identified 14 hydrolyzable tannin components from Terminalia chebula fruits. Additionally, the plant contains fructose, amino acids, succinic acid, beta-sitosterol, and other compounds. Various phenolic compounds, flavonol glycosides, triterpenoids, and coumarin conjugated with gallic acids, known as chebulin, were also isolated. Nam *et. al.,* (2011) studied the mitigation of 2,4-dinitrofluorobenzene-induced atopic dermatitis-related symptoms by *Terminalia chebula* Retzius (TcRSE) in male mice. C57BL/6 male mice underwent sensitization with DNFB on the abdominal skin and repeated DNFB challenges on the ear. TcRSE extracts

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 09 September 2024
DOI: 10.47191/ijcsrr/V7-i9-24, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

with a 100 µg/ml concentration were topically administered eight times, starting after the first DNFB re-sensitization for the DNFB challenge. With the control in expression of atopic molecular markers by adjusting the balance of expression between Th cell subsets, TcRSE demonstrated protective effects by reducing ear swelling, inhibiting eosinophil accumulation and IgE production, and suppressing inflammation through the downregulation of MMP-9 and IL-31, while promoting T-bet gene activity. Panunto *et. al.,* (2011) evaluated the safety of water extract from the dried fruits of *Terminalia chebula* Rezt., which was orally administrated in rats. For acute toxicity, a single oral administration was performed at 5,000 mg/kg body weight (five females, five males). The study of chronic toxicity was determined by oral feeding of both female and male rats (ten females, ten males) daily with the test substance at the dose of 300, 600, and 1,200 mg/kg body weight continuously for 270 days. The acute toxicity showed no signs of toxicity, such as general behavior changes, mortality, changes in gross appearance, or histopathological changes in the internal organs of rats. Chronic toxicity showed no abnormalities in the test groups compared to the controls. Hematological and blood chemical values in treated groups were normal compared to the control group. Sukakul *et al.,* (2013) demonstrated that topical application of 50 µl of *Terminalia chebula* extract at a concentration of 100 mg/ml on croton oil-induced mouse ear dermatitis helped reduce inflammation by decreasing redness, ear thickness, and ear plug weight. Cui *et. al.,* (2014) investigated the synergistic inhibitory effects of *Coptis chinensis* plus Myrobalan (*Terminalia chebula*) (CM) on the inflammatory response both in-vitro and in-vivo. In *an in-vitro* study, they induced inflammation in mouse peritoneal macrophages using lipopolysaccharide (LPS) and found that CM significantly promotes the growth and the phagocytosis of macrophages and inhibits the overproduction of NO, iNOS, TNF-α, and IL-6. For an *in-vivo* study, they established an animal model of inflammation by inducing ear swelling and paw edema using xylene and formaldehyde, respectively and CM showed an inhibitory effect on ear swelling and paw edema in mice. Rubab and Ali (2015) studied the impact of orally administered dry fruit extract of T. chebula (TCE) on Th1/Th2-mediated immune responses in mice. The study involved doses of 100, 200, 300, and 400 mg/kg of TCE administered daily for 10 consecutive days. Following this regimen, mice were immunized with goat RBC (gRBC) or ovalbumin. Results revealed that TCE supplementation led to enhanced expression of the Th1 cytokine, interferon γ, while reducing interleukin 4 levels. Additionally, an increase in the number of plaque-forming cells was observed in gRBC-immunized mice. Kim *et. al.,* (2022) evaluated the effect of *Terminalia chebula* Retz. (TC) extract ameliorates the symptoms of atopic dermatitis by regulating anti-inflammatory factors in vivo and suppressing STAT1/3 and NF-κB signaling in vitro. Male NC/Nga mice were subjected to 150 µl of 4% sodium dodecyl sulfate followed by Dermatophagoides farinae extract (Dfe) ointment on the dorsal skin and ear at 100 mg and 10 mg doses, respectively, twice per week for three weeks. TC was orally administered once daily for 14 days at 30mg/kg, 100mg/kg, and 300mg/kg in different groups, while 3mg/kg was a dose of dexamethasone. The TC group exhibited decreased serum levels of Histamine, IgE, MDC, TARC, RANTES, TSLP, IFNγ, MCP-1, IL-6, and IL-8. Additionally, TC significantly inhibited the translocation of STAT1, STAT, and NF-κB and the mRNA expression of pro-inflammatory cytokines and 7 chemokines. Also, in histopathological analysis significantly decreased epidermis and ear thickness compared to the control group, with less infiltrating cells was observed. In HPLC analysis, seven compounds were detected in TC, with chebulanin being the most abundant (10.81%). The other six compounds (chebulic acid, gallic acid, corilagin, chebulagic acid, ellagic acid, and chebulinic acid) were found in the 2.02-7.19% range. None of these compounds showed toxicity at the concentration used for treatment. Jo *et. al.,* (2022) investigated the protective effects of *Terminalia chebula* (TC) water extract on skin injury using human keratinocytes (HaCaT cells). They pre-treated HaCaT cells with TC for 1 hour and then stimulated them with tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) to induce skin inflammation and injury. The study observed a concentration-dependent reduction in mRNA levels of Th2 chemokines following TC treatment. Furthermore, TC significantly decreased the phosphorylation of signal transducer and activator of transcription 1 (STAT1) induced by TNF-α and IFN-γ.

CONCLUSIONS

Our data show that there are a *Curcuma longa* and *Terminalia chebula* plants which can be used as a treatment for AD. *Curcuma longa* and *Terminalia chebula* can be used as a treatment for AD because they have long been known to suppress inflammatory reactions. *Curcuma longa* and *Terminalia chebula* have been studied and may be used as an alternative treatment in treating AD with fewer adverse effects. However, its role did not change the position of standard treatment in treating atopic dermatitis. In conclusion, herbal medicines could serve as a better and safer complementary and alternative treatment option for AD.

International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 09 September 2024
DOI: 10.47191/ijcsrr/V7-i9-24, Impact Factor: 7.943
IJCSRR @ 2024
www.ijcsrr.org

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International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 09 September 2024
DOI: 10.47191/ijcsrr/V7-i9-24, Impact Factor: 7.943
IJCSRR @ 2024
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International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 09 September 2024
DOI: 10.47191/ijcsrr/V7-i9-24, Impact Factor: 7.943
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International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 09 September 2024
DOI: 10.47191/ijcsrr/V7-i9-24, Impact Factor: 7.943
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International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 09 September 2024
DOI: 10.47191/ijcsrr/V7-i9-24, Impact Factor: 7.943
IJCSRR @ 2024
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International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 07 Issue 09 September 2024
DOI: 10.47191/ijcsrr/V7-i9-24, Impact Factor: 7.943
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Cite this Article: Sushma Ghadigaonkar (2024). Plant-Based Therapies for Atopic Dermatitis Management: A Review. International Journal of Current Science Research and Review, 7(9), 7050-7069, DOI: https://doi.org/10.47191/ijcsrr/V7-i9-24