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A MECHANISTIC INSIGHT OF NATURAL PRODUCTS FOR ECZEMA TREATMENT (PART I)

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ABSTRACT

Eczema is termed as a chronic relapsing atopic dermatitis which is a chronic, inflammatory dermatosis mediated by immune system and is characterized by T-helper 2 immune response phenotype. Eczema is associated with disturbance in sleep and it also affects the quality of life. Emollient, antimicrobial agents, corticosteroid or immune-modulating agents are used for treatment of eczema. Pathogenesis of eczema involves complex interactions between susceptible genes, immunological factor, and defects in skin barriers, neuro-endocrine factors and factors related to environment like change in weather, food and aeroallergens. Because there is no cure till date for eczema, Chinese medicines which are part of dietary therapies are being adopted by the Asian patients. In the treatment of skin disorders and wounds a tremendous role has been played by Herbal extracts and isolated plant compounds. Recently a lot of new herbal drugs have been developed that were tested in controlled clinical or preclinical studies. St. John's wort, licorice, tormentil, bitter substances, evening primrose and many more biomedicines, topical agents: coconut oil, colloidal oatmeal, sunflower oil, mustard oil, glycerin, and oral Chinese herbal therapy are used to treat AD. Probiotics, and vitamins are also used as oral agents in treatment of AD and all these bioagents have shown good results in treatment of atopic dermatitis. Wind, dampness and heat are the three main pathogenic factors of eczema. Various Chinese herb such as cortex moutan radix (danpi), radix paeoniae alba (bai shao), potentilla chinensis ser (weilingcai) and radix glycyrrhizae (gan cao) are common treatments for eczema allergy. It is being indicated in pharmacological studies that these herbs have anti-allergic, anti-inflammatory and sedative action for itchiness. These studied medicinal plants were found to be effective in eczema therapy, further mechanistic and clinical studies are required to establish this claim.

Keywords: Natural Products, Eczema

INTRODUCTION

Against the majority of infections caused through the skin, human skin is regarded as the first line defense and barrier against the diseases that are affecting human populations. With the use of modern allopathic and natural remedies healthy skin can be maintained. Skin cancers, eczema, herpes infection, fungal infection, itching, insect bites, trauma, psoriasis, athlete's foot infections, rashes, skin pigmentation, acne are some of the ailments which majorly affects the population and are slowly becoming a burden on health care (Ahuja *et al.*, 2020; Rożalski *et al.*, 2016). Among these one of the most common one is Eczema which is defined as a chronic inflammatory, relapsing, and remitting disease which is basically classified as atopic and non-atopic and the difference between both the types is the serum IgE levels. Atopic dermatitis is associated with damaged epithelial barrier along with stimulated response of T helper cells 2. Natural sources either plant or animal source are used since ages in treatment of eczema due to its minimal side effects and its cost effectiveness. Despite of great advancements in the field of science and technology herbal remedies are still preferred for managing the various skin disorders. For cancers, diabetes and brain disorders herbal products are looked and used upon as a single line of treatment which proofs the purity, efficacy and safety of herbal medicine for managing the health care. In the treatment of dermatological infections like eczema many therapeutically and pharmacologically active herbal resources like Aloe, Neem, Liquorice, Tulsi,

marigold, Papaya, Ginger, coconut and almond oil are being taken into consideration. At present the main focus is on prevention and treatment of barrier function of the epidermal layer which is best achieved through the use of herbal plants and oil extracts being implied in form of creams, decocted extracts, poultice, paste, lotions and oils in the treatment of skin infection shaving the emollients, anti-inflammatory and soothing properties. This summarizes the use of herbal plants as a boon for treatment, prevention and cure of the dermatological disorders, further clinical studies are needed to identify the exact mechanisms involved (Ahuja *et al.*, 2020; Rożalski *et al.*, 2016).

Atopic eczema (also called atopic dermatitis) is defined as a chronic inflammatory skin disease which has characteristics red patches of itchy skin and in severe cases infected lesions (Boguniewicz & Leung, 2011). Cause of inflammation is leaky skin barrier and stimulated immune response which leads to impairment in barrier function of the skin (Leung, 2013). Two sub types of eczema are: atopic which is associated with increased IgE serum levels, and non-atopic with lesser serum IgE levels. Atopic eczema is prevalent among 80% of the population (Leung, 2013). The disease is related to other allergic responses such as food allergies, allergic rhinitis and asthma because of rise in IgE levels. Around 20% of children are affected by atopic eczema so it is regarded as a predominant childhood disease (Asher *et al.*, 2006).

In 2010, WHO classified eczema at the top in global burden skin diseases as it caused unhealthy state in the patients for a long time (Hay *et al.*, 2014). Reduction in sleep and increased psychological problems are the additional problems being faced by the children with extreme atopic dermatitis (Absolon *et al.*, 1997). In the United States, \$3.8 billion per year is the cost for treatment of atopic eczema, making it evident that atopic eczema is not only effecting the sufferer but it is also having substantial economic effect as well (Arkwright *et al.*, 2013). This proves the need of research into a more cost effective treatment.

METHODOLOGY

Through bibliographic search of scientific articles and books related to the topic on the main databases this review was being performed using different scholarly databases like Science Direct, PubMed, Google scholar, and Medline. The keywords consisted of: acne/atopic dermatitis, condition+ life quality, condition + treatment, condition + pathophysiology. The criteria taken into consideration when selecting the bibliographic material were titles and abstracts related to the theme for basic research (physiopathology and conditions' treatments) and for specific research (skin microbiome and probiotics use). Manuscripts that were not related to the topic, with no peculiar or interesting information, were excluded.

RESULTS AND DISCUSSION

Skin disease: An overview

Acne and Atopic Dermatitis

Because of the visibility and severe effect on the quality of life of the patient's greater discomforts are being caused by the skin conditions. In our skin communities of complex microorganisms like bacteria, fungi, and virus resides and their composition depends on various characteristics such as concentration sebaceous glands', hydration or loss of water content, alternation in temperature, gene related disturbances, and environmental factors as well (Y. E. Chen & Tsao, 2013).

Long periods of treatment and maintenance are required by chronic skin conditions such as acne and atopic dermatitis. Currently emphasis is being made to understand the adverse effects on the lifestyle of patient as no definitive cure is available till date for these conditions. Positive step in the direction of cure can be made by studying skin microbiome and maintaining its balance which may lead to eradication of medications having adverse effects and also may halt the use of systemic drugs and aggressive therapies. Topic therapeutic innovations involving microorganisms are need of future having main focus on establishing a balance between ecosystems of the host v/s microorganisms and it is possible only when microbiome of body is studied at different locations considering its time dependent and seasonal variation and other factors like hygiene and geographic location and it will not only serve as a boon for therapeutic treatment of dermatological disorders but also may lead to research and development of topical formulations which will eliminate the undesired

side effects and accumulation of drug on sites other than target (Gallo & Hooper, 2012).

Skin microbiome

Acidic pH and constant peeling can make the skin non-generous. An abundant colonization of bacteria, fungi, and viruses are being shown. Ecological and individual variations may affect the composition of these microorganisms. No constancy in literature is found when it comes to density of bacteria of the skin reason being the method used for quantifying the skin microorganism may vary (Grice *et al.*, 2009; Huffnagle & Noverr, 2013; Kong, 2011; Schommer & Gallo, 2013). Skin microbiome consist of 19 bacterial phyla and out of them Actinobacteria (51.8%), Firmicutes (24.4%), Proteobacteria (16.5%), and Bacteroidetes (6.3%) are of great importance. Corynebacteria, Propionibacteria, and Staphylococci were the genre which was identified in majority (Kong, 2011). Fungi which were commonly found were the ones which were belonging to Malassezia and Candida genera (Haider & Shaw, 2008; Rodoplu *et al.*, 2014).

Fungal microbiome is having no relationship of mutual benefits with members of bacterial microbiome (Rodoplu *et al.*, 2014). Focusing on the Cutaneous fungal microbiome and its effect on host still lower number of researches is being done. Greater advantages are being associated with wide diversity, as it is believed that the more diverse the ecosystem, the more rigid is it (Huffnagl

& Noverr, 2013). In sebaceous areas species which were found in abundance were Propionibacteria and Staphylococci, with predominance of Corynebacteria species in moist areas, and with higher prevalence of b-Proteobacteria and Flavobacterials mixed population of bacteria was found to be residing in dry areas.

Etiopathogenesis

Personal and/or family history of atopy is known to be one of the major diagnostic criteria. In the literature of India, the prospective studies are very limited. Personal and/or family history of atopy was shown in the study which was conducted in 130 children out of which 83 were boys and 47 were girls belonging to age group of 3 months to 1.5 years, with mean age of 2.2 years at onset of the disease. Comparison of data was then done with those data obtained from 130 age- and sex- matched controls, 24 (18.5%) patients were found to have personal history of AD and allergic rhinitis (AR) was found in 16 (12.3%), bronchial asthma (BA) was reported to be there in six (4.7%) of patients and AR and BA was also reported in two (1.5%) of the patients. In the control group corresponding figure was seven (5.4%). In 10 (7.7%) patients both personal and family history of atopy was present and two (1.5%) controls. 52 (40%) patients were reported to have the family history of atopy, BA was found in 28 (53.9%) and, AR was also reported in 10 (19.2%) patients and AD, with both BA and AD in three (5.8%) of patients and AR and AD was seen only in one (1.9%). In the control group studies the corresponding figures were found to be - 16

Table 1. Details of clinical studies done on AD

Use of “natural” oils for eczema	Formulation used	Mechanism of action	Reference
Olive oil	Oil	As per the evidence specifically hydroxytyrosol component present in olive oil having an antioxidant property have significant antifungal activity. ^{20, 21} So olive oil can be used to treat atopic dermatitis as it has emollient and antifungal effect.	(Karagounis <i>et al.</i> , 2019)
Sunflower seed oil	Oil	Linoleic acid constitutes 60% of the total constituents of sun flower oil, disturbed skin barrier functions in case of dermatitis can be restored on application of sun flower oil along with linoleic acid and it is also responsible for reducing the inflammation. These therapeutic properties of sun flower oil have proven its efficient use in case of atopic dermatitis.	(Karagounis <i>et al.</i> , 2019)
Oral evening primrose oil	Oil (Oral)	Patients of atopic dermatitis have low peripheral blood levels of GLA (gamma-linolenic acid) and its metabolite dihomo-gamma-linolenic acid. EPO lead to an increase in plasma GLA and DGLA levels this might be used as predictive parameter for responsiveness of Atopic Dermatitis to EPO therapy. Because Metabolization of GLA and DGLA to 15- hetre and PGE1 in the skin is responsible for production of anti-inflammatory metabolites requires to treat the inflamed skin in patients.	(Simon <i>et al.</i> , 2014)
Borage oil	Oil	Patients of AD have imbalanced levels of omega-6 essential fatty acids (omega-6 efas) , as a result there is impairment in the activity of the delta-6 desaturase enzyme which directly affects the metabolism of linoleic acid to gamma-linolenic acid (GLA) - which is further responsible to produce anti-inflammatory metabolites	(Foster <i>et al.</i> , 2010)
Almond oil	Oil	Almonds and almond oil have many properties including anti-inflammatory property, emollient action and it also act as a immunity booster, so it is used in treating dry skin conditions like eczema as it leads to reduction in post hypertrophic scarring , smoothening and rejuvenation of skin	(Ahmad, 2010)
<p>Tea Tree Oil</p> <p>It is basically the volatile essential oil mainly derived from native plant of Australia named <i>Melaleuca alternifolia</i>.</p> <p>Mostly TTO shows bactericidal action , but at low concentration. It may act as bacteriostatic agent. Its activity against antibiotic-resistant bacteria has attracted considerable interest, with methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)</p>	Tea tree oil (TTO).	It is being used for its antimicrobial and anti-inflammatory properties which is due to terpinen-4-ol one of the major component of the oil. One of the other important property of TTO is at concentrations of 1.0% or less most of the bacteria's are susceptible , Minimum effective conc of 2% have been reported for various organisms such as commensal skin staphylococci and micrococci, <i>Enterococcus faecalis</i> , and <i>Pseudomonas aeruginosa</i> (13, 79)	(Riley <i>et al.</i> , 2006)

Sandalwood album oil	Sandalwood album oil (SAO)	East Indian sandalwood oil (EISO), is an essential oil obtained from the Santalum album tree after distillation and it has an anti-inflammatory, anti-microbial and anti-proliferative activity that's why it has shown promising results in treatment of acne, psoriasis and eczema.	(Moy & Levenson, 2017)
Dupilumab (a fully human monoclonal IgG4 antibody)	Injection	Act by blocking Interleukin-4 and interleukin-13 which leads to suppression of inflammation caused by helper T-2, leading to normalization of barrier functioning.(7)	(Beck <i>et al.</i> , 2014)
Tacrolimus	Ointment	It is a topical corticosteroid (TCS) and is used as the first-line therapy for Atopic dermatitis as it is a topical calcineurin inhibitor and it acts by making bonds to an immunophilin, FK506 binding protein (FKBP), forming the complex which inhibits calcineurin phosphatase as a result interleukin-2 gene transcription, nitric oxide synthase activation, cell degranulation, and apoptosis all events dependent on calcium are inhibited.	(Martins <i>et al.</i> , 2015)
Azathioprine	NA	It is a thiopurine pro-drug having no immunosuppressive activity, AZA is converted into 6-mercaptopurine (6-MP) which is then converted into active metabolites (7), 6-thioguanine nucleotide (6-TGN), which is responsible for immunosuppressive action and methylated 6-methylmercaptopurine (6-MMP) in liver after metabolism. It gets incorporated into DNA in place of guanine nucleotides leading to breakage of strands, and finally resulting in cell-cycle arrest and apoptosis and inhibition of synthesis of nucleotide and proteins and ultimately causing the inhibition of proliferation of lymphocytes(8–10). However, immunomodulation is done by inducing apoptosis of T-cell by modulation of cell (Rac1) signaling (11)	(Garritsen <i>et al.</i> , 2018)
Cyclosporin	NA	Cyclosporine is a calcineurin inhibitor. Calcineurin is an enzyme which is responsible for activation of T-cells type of WBCs that play an important role in cell-mediated immunity. Transcription of IL 2 and some other cytokines is inhibited by cyclosporin which leads to an inhibition of activation of T cells which plays a major role in the pathogenesis of AD.	(Schmitt <i>et al.</i> , 2007)
Hydrocortisone	Cream	Hydrocortisone is a corticosteroid and it acts by binding to the glucocorticoid receptor which leads to downstream effects causing inhibition of phospholipase A2, NF-kappa B, other transcription factors of inflammation, as a result anti-inflammatory genes are promoted. Decrease in inflammation is required to treat eczema as a result positive results are obtained in patients with AD.s	(Rahman <i>et al.</i> , 2015; Reitamo <i>et al.</i> , 2002)
Tripterygium	NA	One of the active constituents of Tripterygium is Triptolide which possesses anti-inflammatory, anti-tumorigenic, and immunosuppressive activity. (Ziaei and Halaby, 2016). In China studies of eczema have also demonstrated a markedly positive effect on treatment with Tripterygium	(L. Liu <i>et al.</i> , 2019)

<i>Glycyrrhiza glabra</i> L	Licorice gel	Triterpenoids, such as glycyrrhetic acid and glycyrrhizin are contained in <i>Glycyrrhiza glabra</i> which have anti-inflammatory activity and anti-allergic activity. ^{9–11} Cortisol's inhibition of antibody formation is being reinforced by glycyrrhizin. Extract of licorice is considered as a successful agent for atopic dermatitis treatment.	(Akhavan & Rudikoff, 2003)
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(12.3%). In 52 patients, number of family members being affected was around 72, seven (9.7%) in the first generation seven (9.7%), 32 (44.4%) and 33 (45.9%) in the second and third generation. No patient was there who have both the affected parents (Dhar & Banerjee, 2010).

Low figures for personal and/or family history of atopy are being highlighted through this study in comparison to other series reason being the pediatric population was examined in test group and it might be possible that AD manifestations may develop later in life. The AR incidence was more than BA, whereas urticaria showed no difference in the study and control groups. An interesting observation was that as comparative to first generation (9.7%) more family members were found to be affected in second and third generation with percentage of (44.4%) and (45.9%). Thus, it can be concluded that lesser the family history of AD lesser will be the severity of the disease (Dhar & Banerjee, 2010; We & Laboratories, n.d.).

Prebiotics and probiotics

“Live microorganisms (e.g., bacteria, yeast) that are similar to beneficial microorganisms found naturally in gut of humans or are introduced into the body to meet desired health benefits in form of different probiotics supplements available commercially are responsible for promotion of food digestion along with improvement in immunity (Kechagia *et al.*, 2013; Thomas *et al.*, 2010). Gram-negative bacteria and *Staphylococcus aureus* have been found to be present in large number in those children with allergy, due to this poorly developed micro biota reduction in colonic T-regulatory cells has been noticed leading to decrease in potential for protection, as a result individual is predisposed to AD as comparative to the gut flora of healthy children with dominant lactobacilli i.e. well-developed microbiota leading to marked potential in protection from AD (Björkstén *et al.*, 1999). Probiotic bacteria which are mostly studied include *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis*, and *Streptococcus thermophilus* (Thomas *et al.*, 2010).

Decrease in SCORAD index has been found in children over the age of 1 year being treated with probiotics (different bacterial species or *Lactobacillus* species) in a recent meta-analysis (S. O. Kim *et al.*, 2014) with the limited side effects associated with it including increased incidence of wheezing bronchitis (Kopp *et al.*, 2008) infections, and bowel ischemia, with no proper evidence about the source of infections (Boyle *et al.*, 2009)

Prebiotics supplementation is regarded as another novel treatment to promote the healthy intestinal flora

in those who are prone to allergy. Prebiotics in form of oligosaccharides are basically the compounds added in food as dietary supplement or are naturally present in high quantity as in human milk that induce the growth or activity of beneficial microorganisms such as bacteria and fungi, creating healthy intestinal environment which protects the individual from allergy by modulating the post-natal immune system (Finch *et al.*, 2010; Moro *et al.*, 2006; Roberfroid, 2018).

Prebiotics in the treatment of AD

Lowering of the SCORAD index in children with AD was being found with the use of Prebiotics in one small RCT but use of Prebiotics alone for treatment of AD has not been recommended due to lack of evidence. In recently published meta-analysis which examined all RCTs which are published, promising results are being shown by synbiotics (combination therapy including prebiotics and probiotics) in treatment of AD and evaluation parameter used for its efficacy was improvement in SCORAD index (Y. Sen Chang *et al.*, 2016). Promising results in treatment of AD are being shown by combinational use of Synbiotics but further research is needed to be carried out for clarification of some aspects like strains, dosing regimen, and populations to be targeted.

Vitamin D

To establish a link between AD and vitamin D serum levels a number of studies has been performed which concluded that there is higher prevalence of AD in those living at higher latitudes

due to less exposure to sunlight, thus having less vitamin D production (Weiland *et al.*, 2004). A marked increase in antimicrobial peptide expression in healing skin lesions was noted with subsequent increase in calcidiol levels in serum, in one study of narrow-band UVB treatment (Vähävihi *et al.*, 2010)

Serum levels of vitamin D and correlation with AD prevalence and severity

Establishing this correlation through research by utilizing vitamin D serum levels data is always full of complexities. Controversy in results are being found as some researchers claim that no accurate picture of vitamin D can be provided by serum level while some believe that chronic inflammation which is one of the characteristic features of AD is the cause for low serum vitamin D level (Mangin *et al.*, 2014). In children correlation between vitamin D levels and the occurrence and severity of AD, has been examined in few studies, vitamin D deficiency was found to be there

in children with AD in one study, but no correlation was being established (Amon *et al.*, 2018). Other studies have found lower levels of mean serum vitamin D in patients with moderate- severe AD as comparative to those with mild AD (El Taieb *et al.*, 2013; Peroni *et al.*, 2011; S. S. Wang *et al.*, 2014). For now in treatment of AD, vitamin D supplementation is not recommended. However, further research is needed to be done as vitamin D supplementation has been suggested in several interesting studies.

Fish oil supplements

ω -6 and ω -3 are classified under polyunsaturated fatty acids, out of them more intake is of ω -6 fatty acids (Finch *et al.*, 2010). In the modern Western diet the consumption ratio of ω -6 fatty acids and ω -3 fatty acids is 20-30:1, relative to the traditional consumption ratio that was 1-2:1 (Dunstan *et al.*, 2003). This imbalance can stimulate mediators of inflammation like prostaglandin E2 which

acts on arachidonic acid (ω -6 fatty acid) leading to increase in immunoglobulin E (IgE) antibodies and T helper 2 cytokines, resulting in sensitization to allergens. However, concentration of inflammatory mediators is being reduced by ω -3 long chain (LC) polyunsaturated fatty acids (PUFA), which are found in high levels in fish oils by displacing AA thus IgE-mediated allergic disease development can be modulated by consuming diets rich in ω -3 LCPUFA. Further RCTs are needed to be performed for claiming the use of fish oil in treatment for AD.

Evening primrose oil and borage seed oil

Use of two natural, over the counter supplements named as Evening primrose oil (EPO) and borage seed oil (BO) both with high GLA have been highlighted for treating eczema. Gamma linolenic acid (GLA) is an omega-6 fatty acid present in the skin and most commonly found in the plant seeds oil such as in evening primrose oil 8-10% and in borage oil 23% playing key role in eczema leading to reduction in inflammation by blocking the production of leukotrienes on contrary its deficiency may lead to increase in inflammation (David F Horrobin, 2000; Finch *et al.*, 2010).

It has been reported in one case report that EPO if taken more than 1 year it may cause increased inflammation, thrombosis, and of immune system (Kakourou *et al.*, 2010). However beneficial effect of EPO on itching, crusting, and redness was noticeable between 4 and 8 weeks of treatment during the clinical studies performed but the use of EPO and BO is not recommended for treatment of AD because the magnitude of effectiveness is found to be reduced when compared with topical corticosteroids and further trials are needed to be carried out to prove for their efficacy for AD (Morse & Clough, 2006).

Importance of natural products based medicines

From many decades, medicines from natural origin, polyherbal formulations and/or decoctions of materials derived from plants have been accepted worldwide as an alternative of therapies for the purpose of treating, curing and preventing various acute and chronic skin

ailments like chronic herpes, psoriasis and atopic eczema in patients of all ages. In the pregnant woman as well because of their therapeutic efficacy and also based on clinical studies it has been proven that herbal drug in form of oral formulations comprising of (capsules, syrup, or granules) and topical drug delivery of natural drugs has shown remarkable potential for treating mild to severe AD. Natural herbal oils including coconut oil, mineral oil, lavender oil, grape seed oil, olive oil and sunflower which are used traditionally in treating various topical diseases like stretch marks, psoriasis, xerosis and mild to moderate AD used, comes under the class of natural herbal oils. Mentioned below is the list of herbal medicines/therapies or products of natural origin used for treating AD with the clinically proven efficacy such as-

1. Chinese herbal therapies,
2. Korean medicines,
3. Iranian medicines,
4. Honey
5. Natural herbal oils (coconut oil, olive oil and mineral oil),
6. Beeswax,
7. Dodder seeds and 8- Whey

In adults, children (4-16 years) and infants promising anti-AD efficacy effects are being shown by Chinese herbal therapies and Korean medicines in form of aqueous decoctions either alone or in combination with flying needles (acupuncture) or wet-dressings have proven their efficacy in treating AD in pregnant women. In regard to non-pharmacological approach natural herbal oils like virgin coconut oil, olive oil and mineral oil are applied topically proving their efficacy in treatment of AD by causing reduction in exacerbation and progression, with stronger anti-AD efficacy of coconut oil in children as well as adults and pediatric patients. Use of honey in adults and infants suffering from AD has also been proved to be effective either in combination with beeswax or / and olive oil. Literature analysis evidenced that natural herbal formulation which are administered either orally or applied topically resulted in reduction in SCORAD index, intensity of Erythema intensity, CDLQI index, pruritis, itching, TEWL and expression of different mediators of inflammation and improvement in contents of skin sebum, level of hydration and QOL scores. Using natural herbal medicines for treatment of atopic dermatitis is safe, cost-effective, and systemically non-toxic, patient compliant and efficacious compared to the conventional therapeutic regimen. Pictures of some of the herbal preparation used in eczema are given below in Figure1. 15–20% of the childhood population is estimated to be affected by atopic eczema with evidence of increasing prevalence and it has great impact on social, emotional, and financial well-being of whole world (Sugiura *et al.*, 1998; Williams *et al.*, 1999). Retardation of growth (in severe cases) and loss of comfort is usually seen in children suffering from eczema because of the intense sensation which provokes the urge to scratch, dry skin with scaling and lichenification. AD

can also inhibit the normal touching and bonding between infants and parents due to weepy scaly appearance of skin of infants and constant itching and irritability affecting the confidence of parents to care of their child.

Great amount of scratching is being shown to be there in preschoolers causing difficulty among parents. School-aged children are very much concerned about the physical appearance, here those suffering from AD usually lack behind doing things which other children of their age can do like swimming or wearing stuff of their choice like woolen stuff as it will exacerbate itching and feeling of uneasiness making them not to focus on learning and this may be the reason of their lesser interest in studies. Atopic eczema/ dermatitis was found to have a bigger impact on the family than diabetes, this has been demonstrated in quality-of-life studies. (Su *et al.*, 1997)

Atopic eczema - a complex trait with sub-optimal options of treatment

Due to the complexity of this disease the specific treatment modalities cannot be developed. For example, number of strong genetic risk factors and their variations are often seen in atopic eczema; however in some cases, no disease is there but the mutations prevail (Rodríguez *et al.*, 2009). Environmental allergens are also involved such as dust or animal hair which can precipitate or elicit a flare up. Therefore, it is believed that cause of atopic dermatitis is both genetic and environmental factors (Van Zuuren, 2013). This complexity is the reason of partial effectiveness of the treatments and currently no cure (Nuttin, 2015). Both in the skin and the systemic circulation there occurs interaction of leaky skin barrier and immune response; therefore, more emphasis is being laid to reduce the inflammation and repair the skin barrier at sites where inflammation or skin dryness is there. A number of different treatments are available due to its range of severity and complexity (Nowicki *et al.*, 2015).

Application of emollients is one of the most common treatments as they act by increasing the lipid content in the stratum corneum which is regarded as the outermost layer of the skin improving hydration which helps in repairing the barrier (Nowicki *et al.*, 2015). Emollients are insufficiently effective in the mildest cases so a combination therapy with another agent targeting the inflammatory response is targeted. Down regulation of synthesis of the proteins involved in inflammation is caused by topical corticosteroids via corticosteroid-receptor complex (Lebwohl & Friedlander, 2005). Immune mechanisms are also being targeted by topical calcineurin inhibitors which basically act by intracellular protein macrophilin-12 binding, thereby production of inflammatory cytokines interleukin (IL)-4 and IL-13 production is being reduced having no effect on dermal thickness (Gutfreund *et al.*, 2013).

Role of skin barrier

One of the largest organs in the body is our skin (Matsui & Amagai, 2015) and it is vital for survival, acting as a

physical barrier by preventing the entry of allergens and irritants and preventing the loss of water from the body (Leung, 2013). Epidermis, dermis and hypodermis are the three layers of which skin is composed of (A. I. Chen *et al.*, 2016). Stratum corneum— the outermost layer of the skin; control of trans-epidermal loss of water (TEWL) (Engesland *et al.*, 2016) *i.e.* via evaporation. 18-20 layers made up from dead cells containing keratin called corneocytes are included in stratum corneum being surrounded by lipid matrix mainly consisting of ceramides and cholesterol (Menon *et al.*, 2012). Physical skin barrier function is being provided by the epidermis through the lipid matrix along with corneodesmosomes and tight junctions containing the stratum granulosum layer below (Menon *et al.*, 2012). Filaggrin (filament-aggregating protein) an intracellular protein is regarded as important component of skin barrier function is important for formation of the stratum corneum (Gruber *et al.*, 2011). Filaggrin is formed from the dephosphorylation and proteolysis of profilaggrin responsible for formation of filaggrin at time of differentiation of keratinocytes to the corneocytes of the stratum corneum (Metzler, 1991). To strengthen the filamental network and add to the changes in shape of keratinocytes monomer, filaggrin gets binded to molecules of keratin as they mature into corneocytes. Hygroscopic amino acids at the surface of the stratum corneum are being released by proteolysis of filaggrin, when the dehydration of outer skin begins which contributes to natural moisturizing factor (NMF) for the skin keeping stratum corneum in a hydrated state (Robinson *et al.*, 2010). Skin pH is also maintained by filaggrin and its degradation products as the acidic pH of skin limits the colonization of the bacteria by acting as an antimicrobial defense (Bandier *et al.*, 2014). If the pH of the skin is increased, filaggrin proteolysis occurs contributing to acidic amino acids to make the pH of skin to return it to the optimal slightly acidic pH (Bandier *et al.*, 2014). Keratinocytes are held together by the tight junctions, controlling the paracellular flow of fluids playing a vital role as they act as the second protective barrier of the skin (De Benedetto *et al.*, 2011). The role of this barrier comes into light during the diseased state of stratum corneum acting as a second line of defense against allergens.

Mutations or genetic variants are the main factors which are responsible for dysfunctioning of the skin barrier, creating the difficulty in describing the causes of atopic eczema. To highlight potential risk factors for atopic eczema a number of genetic studies have been performed; they have discovered links that the alarming increase in the risk for the disease is due to the certain mutations or genetic variants (Barnes, 2010; Paternoster *et al.*, 2012; Sun *et al.*, 2011). Association studies of majority of gene candidates pointed null mutations in the filaggrin gene, *FLG*, and in the functions of genes involved with the type 2 T helper lymphocytes (Th2 cell) (Bin & Leung, 2016; S. J. Brown *et al.*, 2008). In 2006 loss in mutational functions in *FLG* were identified for the first time which is

regarded as strongest genetic risk factor for atopic eczema till date (Smith *et al.*, 2006). As discussed earlier, the gene filaggrin is of utmost importance and have a major role in skin barrier production so any loss of function mutation in it is the major risk factor of atopic eczema. Atopic asthma, allergic rhinitis and food allergies are some of the listed diseases which are time and again linked with mutations in filaggrin (Irvine *et al.*, 2011). Filaggrin is the main component responsible for cross linking of keratins leading to flattening the cells shape in the stratum corneum this marks as entry point for allergens as leaky barrier is created and inflammatory response is also stimulated due to consequent null mutations leading to malformed corneocytes (Matsui & Amagai, 2015). In atopic eczema there is an increased rate of Trans-epidermal loss of water is increased in atopic eczema and null mutation in filaggrin blocks its conversion into NMF(natural moisturizing factor) acting as the root cause of reduced hydration of skin (Matsui & Amagai, 2015).

Formation of colonies by bacteria plays a vital role and this happens when filaggrin is present in minute amounts and acidic pH is not maintained allowing the bacteria such as *S. aureus* to bind and severe condition of atopic dermatitis is created (Irvine *et al.*, 2011). SspA/V8 protease is secreted by the bacteria which acts as a mechanistic approach for damaging the barrier of skin as the proteins in the corneodesmosomes in the stratum corneum as well as proteins present in tight junctions of stratum corneum are also degraded, entry of allergens and irritants is allowed due to comprising of both the vital elements (Tamber & Cheung, 2009; B. Wang *et al.*, 2017). Decline in claudin-1 and claudin-23 which are known as the key proteins involved with functioning of tight junctions is also noticed in some cases to atopic dermatitis (Catchpole & Dyke, 1990). Tight junction functionality was also believed to be effected by filaggrin gene mutations but clinical studies on mouse models demonstrated that there is no direct effect of filaggrin insufficiency (Yokouchi *et al.*, 2015).

Tight junctions' acts as a physical barrier and have a crucial role in controlling paracellular fluids and spongiosis is often noticed with atopic eczema, where edema is occurred in the epidermis

between the keratinocytes. Another characteristic of atopic eczema which can be seen as scaliness (white flaky skin) is another characteristic of atopic eczema when skin was either observed directly or by light microscopy of section of diseased skin which showed augmented thickness of the stratum corneum which is because the keratinocytes in atopic eczema use to retain their nucleus attached instead of shedding it (Ermacora *et al.*, 1992). Transformation is undergone by epidermal cells normally leading to shedding off the skin due to its conversion from keratinocytes of the stratum basale in the lower epidermis, to corneocytes of the stratum corneum in the upper epidermis; this cornification process is hindered in atopic eczema (Yang & Chang, 2015).

Histological features of atopic eczema

In the biopsies study skin is stained with haematoxylin and eosin, the changes being observed were highlighted, comparing atopic eczema affected skin and a control sample. Characteristic features of atopic eczema are being illustrated: Increase in thickness of the stratum corneum (hyperkeratosis and parakeratosis) due to disruption to the process of cornification; reduction or damage of the proteins involved in tight junctions leads to occurrence of spongiosis which is the cause of uncontrolled movement of fluids in the paracellular space; infiltration of the dermis by immune cells due to entry of allergens through a leaky skin barrier is the immune response which is a primary feature of atopic eczema. So, three effects of eczema: 1: Increased thickness of stratum corneum; 2: Spongiosis - edema (water retained between cells); 3: Increased in of immune cell count.

Immune dysfunction in eczema pathogenesis

The balance of immune mechanisms in the skin is a closely regulated process, which involves a number of different immune and non-immune cells are involved in regulation of immune mechanism and they are interacting to protect the body from the entry of pathogens (Pasparakis *et al.*, 2014). However, increased immune response due to dysfunctioning of skin barrier is already being described above thereby causing atopic eczema and vice versa. Two cytokines IL-4 and IL-13 are being demonstrated to be in elevated state in atopic eczema, decreasing filaggrin expression (Howell *et al.*, 2009). Incubation of both interleukins with keratinocytes for a day lead to decrease in filaggrin expression and these cytokines effects the keratinocytes differentiation thus damaging the protective barrier, same happens in case when environmental allergens or triggers are used specifically (Howell *et al.*, 2009). Leaky skin barrier and atopic eczema is being caused by immune dysfunctioning and histamine act as a contributor (Gschwandtner *et al.*, 2013).

Keratinocytes differentiation was again being observed in this study as a cause of barrier damage and keratin 1 and keratin 10, loricrin and filaggrin which are important proteins of barrier were also being investigated and in presence of histamine reduction in expression of these proteins by 80-95% was being observed affecting the process of keratinocytes differentiation and protective barrier of skin and its effect on tight junction formation was also being demonstrated by the down-regulation of the claudins contributing to leaky skin barrier in case of atopic dermatitis (Gschwandtner *et al.*, 2013). In atopic eczema adaptive and innate immune responses are also possibly found to play their role. Association studies mentioned earlier on candidate gene and genome-wide have illustrated that atopic eczema is associated with variation in genes involved with adaptive Th2 cells response. Increased levels of the Th2 cell and its cytokines IL-4 and IL-13 are being observed in number of cases of atopic eczema which are root cause for instigation inflammation (Pylayeva-Gupta, 2011). For eosinophils and importantly IgE production IL-4 is the driving force which causes degranulation of

mast cells leading to stimulation of inflammatory response through FcεRI receptors (Stone *et al.*, 2010). IL-13 has not been as extensively studied in skin, however interaction of IL-13 with the IL-4Rα receptors found to be the mechanism involved in causing inflammation (Khurana Hershey, 2003). Scratching causes mechanical damage which is another mechanism of occurrence of atopic dermatitis. Keratinocytes when undergoes trauma they releases thymic stromal lymphopoietin (TSLP), another cytokine that is why increased levels of TSLP were seen in patients of atopic eczema which in turn activates Th2 cells producing IL-4 and IL-13 by acting on dendrite cells causing increased inflammation and atopic eczema (Corrigan *et al.*, 2009; Soumelis *et al.*, 2002) Individual's atopic eczema may also be caused by innate immune response. One of the first lines of response to pathogens is by antimicrobial peptides serves as first lines of response to the pathogens by secreting and activating once toll-like receptors (TLR) which identifies the pathogens but any defect in it is the major cause of bacteria colonies to be formed and this instigates the atopic eczema (Schauber & Gallo, 2009). In eczema-affected skin peptides are found to be reduced failing to prevent colonization and damage by pathogens such as *S. aureus* or infection with herpes simplex leading to eczema herpeticum (Howell *et al.*, 2006). Threshold in atopic eczema for the damage to occur is lowered by reduction in cathelicidin and human beta defensin 2 (Ong *et al.*, 2002; Reitamo *et al.*, 2002). Th2 cell activity is being increased due to release of alpha and delta toxins by *S. aureus*, activating the adaptive immune response and elevating the inflammation (Breuer *et al.*, 2005; Pasparakis *et al.*, 2014).

Environmental factors

Probably because of industrialization and changed life style AD is more frequently occurring in urban population as comparative to that of rural. Significant role is being played by the pollution it not only precipitates AR or BA but also AD (atopic dermatitis). New immigrants from rural areas to the industrialized countries are found to have greater incidence of having AD. The main reason of rising AD incidence in West is abnormal immunity system due to reduce exposure to bacteria and parasitic infections in childhood as a result over reaction to relatively innocuous antigens are caused basically termed as hygiene hypothesis. A study was performed comparing the severity of AD in children born and brought up in India with that of UK or US born children and less-severe form of the disease was being reported in Indian children due to strong immunity. Acquired factors – temperature, humidity, food habits, clothing and psychological impact shave influence on the clinical expression and disease severity which is being highlighted in this study (Patki, 2007; Sehgal *et al.*, 2015). Vitamin D was being used therapeutically to decrease the severity of atopic eczema as it has been proven through studies to repair the barrier and modulating the mechanism of immune system (Mutgi & Koo, 2013; Russell, 2012). Mice treated by phototherapy are being demonstrated

in a study and elevated levels of filaggrin were found, enhancing the repair of barrier (Hong *et al.*, 2008). Faulty keratinocytes differentiation seen in cti on of vitamin D on keratinocytes leading to an increment in level of calcitriol thus improving barrier function (Bikle *et al.*, 2004; Hongetal., 2008). as been shown by taking vitamin D inform of oral supplement, so for adm inistration purpose alternative methods are required. Dry skin in imulated interest in the development of emollients for xerosis treatment (Danby *et al.*, 2016).

In one study emollient cream containing 5% urea, a skin ceramide N- stearoylphosphingosine (NP) and lactate was compared with that of standard emollient (the control) (Danby *et al.*, 2016). An increase in TEWL from 11.58 to 11.94 g/m² per hour was found when the skin which was previously being treated with cream containing NP was changed to the control making it clear that investigated emollient cream had shown more improvement in the function of skin barrier than that of control as sodium lauryl sulfate having the emulsifying action was the cause of barrier damage in the control. Another factor that was considered was hydration and as compared to control the application of the ceramide NP cream showed greater hydration suggesting improvement of the stratum corneum barrier (Danby *et al.*, 2016). There is the possibility of damage if the ceramide NP cream when used with atopic eczema there are chances of damage as this cream increases pH slightly and for optimal emollient treatment for atopic eczema further studies are needed to be carried out. Synthetic elastic “second skin” which is composed of cross-linked polymer (XPL) which acts as an extra skin barrier for 24 hrs. preventing the affected areas of skin from the entry of allergens and irritants and has an anti-ageing effect removing wrinkles especially around the eyes aiming at treating the leaky skin barrier (Yu *et al.*, 2016).

However, this interesting application remains speculative, as no research has yet been conducted on this interesting application. It has recently been highlighted that damage caused to the skin barrier by *S. aureus* is being found to be reduced by increasing levels of antimicrobial peptide hβD-2 but in case of atopic eczema damage by the SspA/V8 protease cannot be prevented by the IL-1β defensive mechanism because of reduced levels of hβD-2. It was demonstrated that purified recombinant or synthesized hβD-2 could decrease skin barrier damage can be decreased by 15% and 10% respectively by using recombinant or synthesized hβD-2 which may prove as a fruitful avenue for topical treatments in future (B. Wang *et al.*, 2017). To prevent cyclic-AMP degradation in cells phosphodiesterase-4 (PDE-4) inhibitors can be administered orally which are involved in immune mechanisms of atopic eczema; however nausea and diarrhea are the common side effects related to its use (Jarnagin *et al.*, 2016).

Crisaborole, an ointment based PDE-4 inhibitor has been developed recently which it is one among the few non-

steroidal based ointments and phase 3 clinical trials are being passed by it with improvements as high as 41% in terms of severity scores of AD as compared to placebo moisturizer and it will soon be approved by the FDA for treating atopic eczema. Monoclonal antibodies which are currently being developed as a novel treatment presents the biggest opportunity to treat several different atopic diseases by targeting the inflammation and Omalizumab which is licensed for the treatment of asthma is the currently available commercially used monoclonal antibody for treatment

of atopic eczema as it acts by targeting the IgE Cε3 domain leading to decreased severity in asthma and is proven to show potential in treating atopic eczema (Landolina & Levi-Schaffer, 2016). Dupilumab, which is an anti-IL-4α receptor act by stopping the action of IL-4, is more promising monoclonal antibody treatment preventing the inflammation caused by both IL-4 and IL-13 by bringing 50% reduction in severity score of eczema in 85% patients in phase 2 trials and up to 38% patients were cleared (Landolina & Levi-Schaffer, 2016) (Beck *et al.*, 2014) and phase 3 trials (in which up to 38% of patients were cleared after 16 wk of treatment) (Simpson *et al.*, 2016). Drawbacks of this treatment are that its involvement of an injection is the drawback of this treatment as it is more invasive than the other treatments and long-term safety is currently not known (Landolina & Levi-Schaffer, 2016).

Synthetic Formulations available in the market for treatment of atopic eczema and limitations

In both children and adult for treating mild to-severe AD majorly prescribed pharmacological therapy is that of corticosteroids (Glazenburg *et al.*, 2009; Hanifin *et al.*, 2002; Nuutinen *et al.*, 2003; Peserico *et al.*, 2008). Particular drug regimen is being chosen by the health care professionals based on severity of the disease as corticosteroids have a wide potency ranging from (class 1 (super-potent) to class-7 (least-potent)). Topical calcineurin inhibitors (TCIs) been recommended for children and adult both for long term (1 year) and short term (3-12 weeks) therapy, anti-infective agents, phototherapy, anti-histamines, and vitamin-D3 analogue are classified under other pharmacologically active agents or therapies engaged in treating AD (El-Batawy *et al.*, 2009; Ho *et al.*, 2003; Kang *et al.*, 2001; Murrell *et al.*, 2007).

TCIs when applied over sensitive areas of the body (such as the face, under arms, groin area and skin folds) it was evident that they have superior action in treatment of AD than that of topical

Corticosteroids (Doss *et al.*, 2009; Draelos, 2008; Lübbe *et al.*, 2006; Zuberbier & Bräutigam, 2008). Promising efficacy have been shown by anti-infective therapy alone or in combination with other pharmacological agents in suppressing severity and progression of the disease in those patients with worsen AD due to colonization with *S. aureus* (Bath-Hextall *et al.*, 2010; Brodell *et al.*, 2011; Huang *et al.*, 2009). It was being suggested by Huang *et al.*, (Huang

et al., 2009) that sodium hypochlorite containing water if used for bathing purpose can lead to remarkable reduction in severity of AD. One of the effective and well tolerated therapy for patients with atopic dermatitis is phototherapy however this intervention has no evidence, but it has been shown in number of studies that use of phototherapy alone or in combination reduces the progression of atopic dermatitis (Grundmann-kollmann *et al.*, n.d.; Meduri *et al.*, 2007; Pacifico *et al.*, 2019; Universität & Freiburg, 2001). Moderate-to-severe AD can also be treated by using analogues of vitamin-D3 also known as second-line agents in the treatment (Nagpal *et al.*, 2012). Various other drugs of low clinical applicability because of severe side effects such as cyclosporine (Schmitt *et al.*, 2007), azathioprine (Berth-Jones *et al.*, 2002; Caufield & Tom, 2013; Hughes *et al.*, 2008) interferon-γ (T.

Chang & Stevens, 2002; Jang *et al.*, 2000), and methotrexate have also been tested for their effectiveness against AD as they come under the class of immunosuppressants (Weatherhead *et al.*, 2007),

Even though promising efficacy have been shown by various pharmacologically active agents in providing symptomatic relief, reducing severity and halting progression of this atopic diseases it cannot be neglected that they also cause several local or systemic side effects which creates a phobia and thus reduces compliance of patients. To reduce unwanted effects and to improve therapeutic outcomes and patient compliance, researchers are always in search of natural herbal medicines as alternative and complementary therapies for the treatment of AD.

During pregnancy worsening of the AD symptoms are being noticed in 52% of the females with improvements in 24% of patients. Among the various conventional medications employed for the treatment of AD, corticosteroids are used as a first line drug, but clinical applicability is being halted by the lesser evidences of safety data during pregnancy. Other agents including cyclosporine and TCIs are also not recommended for pregnant women's due to their side effects which may lead to abortion or neonatal complications. Thus, non-pharmacological approaches are being adopted for treatment purpose in pregnant women including use of moisturizers and emollients however they are not effective in treating moderate – severe form of AD (Kemmett & Tidman, 1991). After studying the efficacy of herbal drugs in males, females, children, pediatric patients, and pregnant women their safety has been proven and natural herbal medicines in the form of capsules, granules and/or decoctions of plant-derived materials, topical formulations in form of creams, ointment, solutions, and wet-wrap dressings or oral formulations can be administered to the patient.

Clinical Studies

Various clinical studies have been conducted to evaluate the effect of different natural and synthetic drugs against AD. A detail of the studies are presented in Table 1.

Conclusion

A leaky skin barrier and an immune response are being included in pathomechanisms: Both are responsible to occur and to be a cause for the other. Associated problems with atopic eczema are not only confined to skin disease and it not only affects the patient only but his whole family but it affects whole family acting as a cause for mental health problems along with the economic impact. Filaggrin encoding gene (*FLG*) undergoes mutations causing failure in effective maintenance of skin barrier and it has been regarded as an important part of the disease; immune mechanisms of the disease are also seen instead of null mutation in *FLG*. Atopic inflammation is caused by the hyper response of Th2 cell. Bacterial infection contributes to atopic eczema pathogenesis and this is potentiated via reduced antimicrobial peptides or mutations in filaggrin leads to potentiating contribution of bacterial infection to atopic dermatitis worseness via reduction in the acidic pH of skin.

Variety of treatments for atopic eczema is being proposed due to multitude of causes. Different individuals show different responses proving the treatment as effective and ineffective. The leaky skin barrier is the target of interest which needs to be repaired along with normalization of the hyper immune response and drug which fulfill the demand would be the ideal treatment for atopic eczema. In milder atopic eczema awareness is being caused by providing optimum education to the children and patients and this is the best treatment which makes them to avoid their own triggers and more knowledge improves the overall treatment. In targeting molecular mechanisms in atopic eczema novel treatments have been specified as they are hoped to be related to lesser side effects. However, to fully control this complex disease considerable amount of research is still required to develop the most effective treatment which targets both key mechanisms - dysfunctioning of skin barrier and hyper immune response.

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