Turmeric Based Therapy in the Treatment of Psoriasis: A Clinical Trial

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Study Protocol

HAGAR NOFAL

Introduction

Psoriasis is a prevalent skin disorder. It affects around 4% of world's population. It can be disfiguring and disabling in severe cases. Psoriasis has been associated with many comorbidities e.g. increased cardiovascular risk, diabetes and metabolic syndrome **(Cai et al., 2013; Mahil et al., 2016).**

The exact cause of psoriasis is still unknown, however, in a genetically susceptible individual there is evident dysregulated immune response to an unknown stimulus **(Mitra et al., 2013; Mahil et al., 2016).** There is dysregulation of the mechanisms present in the skin to upregulate or to down regulate the immune responses when needed (**Wang et al., 2011).** Such dysregulation results in abnormal continuous inflammatory loop observed in psoriasis. In psoriasis there are specific pathways continuously activated including Th1 pathway with TNFα, IL6 and IL 12 upregulation and Th17 pathway with increased expression of IL17 and IL23. When exposed to environmental triggers, self-RNA and self-DNA released from stressed keratinocytes got complexed with / Cathelicidine (LL37). The formed complexes interact with Toll like receptors (TLRs) of plasmacytoid dendritic cells (pDCs). On their activation, pDCs produce interferon-α (IFN-α). INF-α orchestrates the maturation of monocyte derived dendritic cells (moDCs). Moreover, self-RNA / LL37 complexes and viral ssRNA directly enhance the maturation of IFN-α-primed moDCs both on phenotypical and functional levels. The moDCs maturation is further promoted by TNF-α, IL-1β, INF-γ, IL-6, secreted from stressed keratinocytes, fibroblasts, lymphocytes, natural killer T cells and macrophages. Mature IFN-α-primed moDCs migrate to draining lymph nodes, where they drive naive T cell differentiation into Th1

and/or Th17 cells through IL-12 and IL-23. These T cells migrate via lymphatic and blood vessels into psoriatic dermis and contribute to the formation of a psoriatic plaque **(Farkas & Kemény, 2012)**.

Nuclear factor κB (NF-κB) is a transcription factor that orchestrates inflammation and other complex biological processes including cellular proliferation, differentiation and apoptosis. It also controls various cytokines and chemokines production. It has a major role in psoriasis development; its activation and nuclear translocation is present in every step of the way of psoriasis starting from stressed keratinocyte release of cytokines to maturation and activation of dendritic cells to the continuous loop of T cell activation. Inducers of NF-κB include pro-inflammatory cytokines, such as TNF-α and IL-1, foreign antigens, such as carbohydrates and peptides recognized by pattern recognition molecules as TLRs **(Goldminz et al., 2013)**. Induction of NF-κB leads to its nuclear translocation with alteration of cell cycle and apoptosis in keratinocyte along with immune cell activation and cytokine release **(Tsuruta, 2009)**. NF-κB is a central point in psoriasis pathogenesis and its level is elevated in psoriatic skin (**Lizzul et al., 2005)** and is reduced with successful treatment with anti TNF- α therapies **(Lizzul et al., 2005; Avramidis et al., 2010)**. Glucocorticoids competitively inhibit NF-κB binding. NF-κB represents a potential target for antipsoriatic therapy (**Goldminz et al., 2013)**.

Curcuma longa (Linn) (turmeric) is a rhizomatous herbaceous plant. Its extract Curcumin (diferuloylmethane) has gained an increasing interest for its pro apoptotic properties inhibiting cell proliferation. So it has been tested for its anticancer efficacy in animal models of pancreatic cancer, breast cancer, colorectal cancer and skin cancer **(Kang et al., 2016)**. Turmeric

extract has also showed phosphorylase kinase inhibition activity, hence an anti-inflammatory, anti-oxidant, anti-microbial and anti-carcinogenic effects. It has inhibitory effects on NF-κB and various cytokines production **(Sun et al., 2013)**. Curcumin, the turmeric extract, inactivated NF-κB and subsequently reduced the expression of multiple proinflammatory cytokines including TNF-α, IL-1, IL- 2, IL-6, IL-8, and IL-12 **(Sugimoto et al., 2002; Camacho-Barquero et al., 2007; Sun et al., 2013)**. Curcumin also suppresses the activation of other transcriptional factors including signal transducer and activator of transcription (STAT1, STAT3, and STAT4) **(Sun et al., 2013)**. Both STAT3 & STAT4 are major contributors in T helper differentiation toward Th17 and Th1 respectively. STAT3 also regulate keratinocyte proliferation in psoriasis **(Coimbra et al., 2012)**. Curcumin also has been proved to act as a potent blocker of different types of K channels. K channels play a very important role in T cell activation and differentiation. Blockers of K channels have been under investigation for autoimmune disease management in phase I clinical study **(Kang et al., 2016)**.

The complex nature of psoriasis pathogenesis has imposed the need of many therapeutics. Each targets specific point in the disease pathogenesis. Despite the presence of various systemic and topical therapies, World Health Organization (WHO) global report on psoriasis has highlighted the psoriasis patients' need to have more treatment options **(World Health Organization (WHO), 2016)**.

Turmeric extract has been used for ages in treatment of different diseases as part of alternative medicine. Its effectiveness has been studied in different

dermatologic diseases e.g. acne, eczema, oral lichen planus and psoriasis **(Vaughn et al., 2016).**

Many other natural remedies have been tried for treatment of psoriasis and other skin disease (**Vaughn et al., 2016)**. There is a trend in patients to ask for herbal natural remedies as a safe, effective and affordable alternative or adjuvant to conventional therapeutics **(Deng et al., 2013; Talbott et al., 2015).**

Rationale

- Psoriasis is a prevalent disabling and disfiguring dermatologic condition. WHO resolution on psoriasis has recognized the inadequate treatment options psoriasis patients suffer among other problems. The available treatment options have many side effects. A lot of the effective treatment options are either expensive or not appropriate for hepatic patients who represent a large subset of Egyptian psoriatic patients. This highlights the need for inexpensive and safe alternative.

- Few reports are published on the effectiveness of Turmeric in psoriasis treatment. Having an immune modulatory effect especially as anti NFκB it is expected to be effective therapy with minimal side effect.

- Up to our knowledge this is the first study addressing the efficacy of combined turmeric and olive oil based topical therapy in psoriasis treatment.

Research question

What is the efficacy of Turmeric based topical therapy in the treatment of psoriasis?

Hypothesis

- Turmeric based therapy effectively treat psoriasis through reduction of NFκB expression in psoriatic skin.

Aim

The aim of this study is to verify the efficacy of Turmeric based therapy alone and combined with olive oil in the treatment of psoriasis.

Objectives

1- To evaluate the effectiveness of Turmeric extract based topical therapy for psoriasis

2- To compare the effectiveness of Turmeric extract based therapy and combined Turmeric/Olive oil based therapy.

3- To identify the effect of Turmeric based therapy of NFκB expression in psoriasis.

Subjects and methods

Technical design

- **Setting:** Dermatology, Venereology & Andrology Department, Faculty of Medicine Zagazig University, Pathology Department, Faculty of Medicine Zagazig University.

Study design:

- **Type of study:**

Clinical trial

- **Sample size:**

The sample size is calculated using OpenEpi with PASI score of the control group is 3.3 ± 2 and of the Turmeric treated group is 1.4 ± 1.1. So at power of study 80 % and CI 95% the sample size is calculated to be 40 with 10 subjects in each group.

- **Inclusion criteria**

All participants must be willing to sign informed consent.

The study will include

For the patients group:

1- Patients with mild to moderate psoriasis vulgaris of any age & gender.
2- Patient didn't receive any systemic or topical therapy for psoriasis the last 4 weeks.

For the control group:

1- Psoriasis vulgaris patients (mild to moderate) of matching age and gender.
2- Patients didn't receive any systemic or topical therapy for psoriasis the last 4 weeks

- **Exclusion criteria**

1. Patients previously received topical or systemic therapy for psoriasis in the past 4 weeks.
2. Patients with pustular or erythrodermic psoriasis.
3. Patients with other dermatological diseases.

4. Patients have hypersensitivity from the active ingredients of the therapy.

- **Study groups**

Four groups will be included in the study

Group 1: 10 psoriatic patients will receive Turmeric extract based topical therapy for at least 4 weeks up to 12 weeks.

Group 2: 10 psoriatic patients will receive Turmeric and Olive oil based topical therapy for at least 4 weeks up to 12 weeks.

Group 3: 10 psoriatic patients will receive only the base topical therapy for at least 4 weeks up to 12 weeks.

Group 4: 10 psoriatic patients will receive 2 sessions of NB-UVB every week for at least 4 weeks up to 12 weeks.

Group 5: 10 psoriatic patients will receive daily Betamethasone or Calcipotriol every week for at least 4 weeks up to 12 weeks.

Steps of study:

- All study subjects will be subjected to:

I. *History Taking:* Detailed history will be taken from patients regarding name, age, duration of disease, arthropathy, family history of the disease, other dermatologic conditions, other systemic diseases and drug history

II. *Clinical evaluation*: Assessment of the psoriasis using PASI score.

III. *Dermoscopic evaluation*: The psoriatic plaques will be assessed using dermoscope. The dermsoccopic criteria of psoriasis includes dotted vessels regulary distributed on light red background with white silvery scales homogenously distributed on the erythematous background.

IV. *Histopathologic assessment*: 5 ml punch Skin biopsies will be obtained and immersed in 10% formalin then embedded in paraffin wax and processed for H&E staining. The diagnosis of psoriasis will be histologically confirmed.

V. *Immunohistochemical analysis*: NFκB expression in the psoriatic skin will be evaluated before and after treatment using immunohistochemical stain.

Administrative design

All patients included in the study will provide written informed consent after being informed about the study steps, the possible complications and their capability to withdraw at any time after approval of Institutional Review Board Of Faculty of Medicine, Zagazig University.

Results

The collected data will be presented in tables and suitable graphs and the appropriate statistical methods will be applied.

Discussion

The obtained results will be discussed and compared to the available relevant literature and published scientific researches to explain them.

Conclusion and recommendations

Conclusion and recommendations derived from the results of the study will be presented.

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