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Review of the Use of Fumaric Acid Esters in Dermatology

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Abstract

Background: Fumaric acid esters (FAE) have been used as a drug since 1959. The therapeutic preparation containing FAE has been one of the prominent drugs used for the systemic treatment of psoriasis since 1994 in Germany. FAE have been used in the treatment of sarcoidosis, granuloma annulare, necrobiosis lipoidica, cheilitis granulomatosa, annular elastotic giant cell granuloma, malignant melanoma, pityriasis rubra pilaris, alopecia areata, hidradenitis suppurativa, and lupus erythematosus with different success rates.

The results obtained from research articles, case reports or case series of the used FAE of dermatological diseases were revised in this article. FAE can be an effective and safe first-line treatment alternative in the treatment of psoriasis. It also can be beneficial to granulomatous skin diseases, lupus erythematosus, malignant melanoma, pityriasis rubra pilaris, alopecia areata, and hidradenitis suppurativa in patients unresponsive to first line therapies.

Introduction

Fumaric acid (FA) is a simple organic dicarbonic acid with a simple structure widely used in the food, agriculture, pharmaceutical and chemical industries today [1]. In humans, it plays a role in an important step of the citric acid cycle. It has been also in use as a drug since 1959 when it was discovered to be effective in the treatment of psoriasis. *Schweckendiek*, a German chemist, suggested that the lack of FA may play a role in the etiopathogenesis of psoriasis. Using an oral mixture made of FA esters (FAE) he developed himself, *Schweckendiek* has cured his own psoriatic lesions and shown the efficacy of the FAEs in psoriasis [2, 3].

When administered through the oral route, the bioavailability of FA is not satisfactory and it may cause gastrointestinal irritation. Therefore, the FAE used for treatment is manufactured in the form of enteric-coated tablets. There are three types of FAE, namely dimethyl fumarate (DMF), methyl hydrogen fumarate (MHF) and ethyl hydrogen fumarate (EHF) [2]. The therapeutic preparation containing FAEs have been one of the prominent drugs used for the systemic treatment of psoriasis since 1994 in Germany. The preparation includes DMF and a blend of the three monoethyl fumarate (MEF) salts (**Table 1**). Under the brand name Fumaderm®, it is presented in two different strengths including a low-dose starting treatment and a high-dose tablet. The active ingredient effective for the treatment is DMF [3].

Table 1. The Contents of The Preparation of Fumaric Acid Esters

	Dimethylfumarate (mg)	Mono-ethylfumarate Ca-salt (mg)	Mono-ethylfumarate Mg-salt (mg)	Mono-ethylfumarate Zn-salt (mg)
Fumaderm Initial	30	67	5	3
Fumaderm	120	87	5	3

Pharmacokinetics

Following the oral administration, FAE is almost completely absorbed through the small intestine. From the enteric-coated tablets, the DMF is released in the small intestine and a portion of it is hydrolysed to MMF in the alkaline pH environment of the intestines. In the pH 7.4 environment consistent with the human serum, DMF is rapidly hydrolysed to its active metabolite monomethyl fumarate (MMF). This hydrolysis does not occur in an acidic environment [**3, 4**]. The half-life of DMF is 12 minutes and it is not detectable in the plasma. Following the oral intake, its metabolite MMF is detected in the plasma [**5**]. The plasma concentrations of DMF and fumaric acid are negligible. In a study conducted on the pharmacokinetics of FAEs on healthy volunteers, the postprandial pharmacokinetics of a single tablet containing 120 mg DMF and 95 mg calcium monoethyl fumarate was observed to greatly vary between individuals. Therefore, fumarate doses were recommended to be taken before meals [**6**]. Following the oral intake, the peak plasma MMF levels are reached within 5-6 hours. In the serum, 50% of MMF is bound to proteins and its half life is 36 hours. No teratogenicity was observed in the therapeutic doses in animal studies. MMF enters the citrate cycle and is metabolised to carbondioxide and water. It main route of excretion is through respiration. A small fraction is excreted through the urine and faeces [**7**].

Mechanism of Action

The mechanism of action of the FAEs has not been fully understood. Their effects on various cells have been demonstrated in patients with psoriasis. They are suggested to play their role through their effect on the keratinocytes, T-lymphocytes, dermal fibroblasts, mast cells, endothelial cells, dendritic cells and other antigen presenting cells.

Effects on the T-lymphocytes

FAE has been reported to exert strong effects on the T-lymphocytes. During the treatment of 16 patients with severe psoriasis using FAE, leukocytopenia was observed in 94% of the patients. In the study where a 26.6% mean reduction in the leukocyte count was observed, CD4+ T lymphocytes were decreased by 45.4% and the CD8+ T-cells were decreased by 44.5% [2]. In psoriatic patients without concurrent disease or infection and treated with FAE, a significant reduction was observed in the CD3+, CD4+ and CD19+ lymphocyte counts. However, the citric acid cycle and the intracellular ATP levels were shown to be unaffected by the FAE [**8, 9**].

The reduction in the T-lymphocyte count in the peripheral blood goes parallel to the reduction of the T-lymphocytes on the skin of the patients with psoriasis lesions [**2**].

The common point of the mechanism of action of FAE in psoriasis and multiple sclerosis has been investigated. Studies have shown that the type 2 dendritic cells producing IL-10 are increased through FAE. The stimulation of the type 2 dendritic cells inhibits the T helper 1 and T helper 17 cells producing IL-12 and IL-23, while the T helper 2 cells producing IL-4 are induced. This effect has been suggested to bring about the action of FAE in psoriasis and multiple sclerosis [**10, 11**].

Effects on the Epidermal Keratinocytes

In cultured human keratocytes, production of the chemokins and cytokins such as IL-8, IL-20, CXCL1, CXCL8, CXCL9, CXCL10 and

CXCL11 is observed to be strongly suppressed in the presence of DMF [**12, 13**]. In the skin biopsies of the psoriatic patients treated with FAE, acanthosis was observed to be rapidly reduced at the beginning while the effect slowed down in time [**14**]. In the keratinocyte cell cultures incubated with DMF, the mitogen-activated protein kinase (MAPK) 1 and 2 activation, which is thought to play a role in the pathogenesis of psoriasis, was observed to be suppressed. Thus, the gene transcription induced by the NF-kappa B transactivated MAPK 1 and 2 is also inhibited [**15**].

Inhibition of the Angiogenesis

Angiogenesis is a factor playing an important role in chronic inflammatory conditions and tumour formation. DMF exerts its antipsoriatic and antitumorigenic activity through the inhibition of angiogenesis. FAE leads to the inhibition of angiogenesis both in the in vitro and in vivo environments by affecting various steps of angiogenesis [**16**]. A major part of its angiogenetic effect is realised through the inhibition of the endothelial VEGFR-2 expression. Thus, it also inhibits the development of the capillary-like structures induced by VEGF [**17**].

Induction of Apoptosis

The nuclear transcription factor, production of the NF-kappaB1 inflammatory cytokins and cell differentiation play a major role in apoptosis. DMF has been shown to be a potent inhibitor for NF-kappaB1 and to lead apoptosis in various cells through this inhibition [**18**]. The induction of the apoptosis of the T-lymphocytes has been suggested as a mechanism of action in psoriasis [**19**]. In recent years, DMF was shown to cause apoptosis in mast cells and the mast cell apoptosis has been reported to contribute to the curative effect in psoriasis and MS [**20**].

Effects on Oxidative Stress

The effects of DMF on the intracellular thiol depend on time. In case of long term exposure to DMF, the interaction with the intracellular thiols has been reported to lead to an increase in the glutation levels. Increased levels of glutation inhibit the redox-sensitive kinases, reducing the oxidative stress [**2**].

Within the cell, DMF and MMF rapidly react with glutation (GSH) and are transformed into S-glutation forms. In vivo, the GSH-adducts are catalysed into mercapturic acids through enzymatic reactions and are excreted through urine. DMF is thought to cause the apoptosis of the cell through the repletion of the intracellular GSH. The reduction of the intracellular GSH leads to the downregulation of the Th 1 cytokins. Consequently, one of the effect mechanisms of FAE may be the release of the anti-inflammatory cytokins from the immune cells and/or the induction of apoptosis due to the depletion of the intracellular GSH [**21**].

The Clinical Uses of FAEs in Dermatology (**Table 2**)

Psoriasis:

For more than fifty years, FAE has been in use as a safe and effective treatment for psoriasis in Western European countries including primarily Germany and the Netherlands. It has been shown to exert its effect in the treatment of psoriasis through its immunomodulatory, antiproliferative and anti-inflammatory effects and apoptosis in the active T-cells [**22**].

The first placebo-controlled, double-blind, randomised clinical efficiency study on FAE was conducted by *Nugteren-Huying* et al [**23**]. In this study where 39 psoriatic were treated for 16 weeks, the combination of DMF and MEF salts were observed to lead to a significantly greater improvement compared to placebo. The subsequent first multi-centre, double-blind, placebo-controlled study by *Altmeyer* et al. has demonstrated that FAE is significantly more effective than placebo in the treatment of psoriasis [**24**].

In a multi-centred and prospective study, *Mrowietz* et al. [**25**] have investigated the efficiency and safety of FAEs and observed an 80% decrease in the PASI values in comparison to the baseline values in the patients who have completed the four months treatment period. Side effects were observed in 69% of the patients who participated in the study. In general, a reduction in the lymphocyte count was observed in all the patients during the

Table 2. Diseases of the Fumaric Acid Ester is Indicated

Approved indications	**Psoriasis vulgaris**
Off-Label indications	**Granulomatous diseases**
	Sarcoidosis (42, 43, 44)
	Granuloma annulare (45, 46, 47, 48, 49)
	Necrobiosis lipoidica (50, 51, 52)
	Cheilitis granulomatosa (61)
	Annular elastotic giant cell granuloma (61)
	Other Skin diseases
	Malign melanoma (53, 54, 55, 56)
	Lupus erythematosus (57, 58, 59)
	Pityriasis rubra pilaris (60)
	Alopecia areata (62)
	Hidradenitis suppurativa (63)

course of the treatment. The most commonly observed side effect were complaints related to the gastrointestinal system and flushing, which were generally observed to be dose-dependent. In 1999, *Mrowietz* et al. [**26**] have published a guideline reporting that FAEs are an effective and safe treatment alternative in the treatment of psoriasis.

Studies focussing on the effects of the FAEs in the treatment of psoriasis have also been conducted in countries outside Germany. It has been reported that 58.6- 71.0% of the patients treated with FAEs in Ireland had good or excellent outcomes. In this study, one fifth of the patients could not tolerate the drug [**22, 27**]. In a retrospective study from the United Kingdom where 55 patients with severe psoriasis were evaluated, improvement was observed in 55% of the patients whereas 28% showed no response and the condition was worsened in16% [**28**]. Similarly to the other countries, also in Italy, partial or complete healing was reported in 82.5% of the patients with severe psoriasis treated with FAE [**29**]. All the studies reported that FAE is an effective and safe alternative in the first line systemic treatment of psoriasis.

The effects of FAE have been compared with the other systemic treatments for psoriasis. Both in retrospective and prospective randomised and controlled studies, FAE was observed to have a similar effect with methotrexate in the treatment of psoriasis. Discontinuation rates of the therapy due to side effects were also reportedly similar [**30, 31**]. FAE has been used concurrently with another antipsoriatic treatment in the patients with plaque-type refractory psoriasis. In this study, 36% of the patients have discontinued and 25% have reduced the dose of the other antipsoriatic drug at the end of the 3 month treatment period [**32**]. FAE has also been found effective when used in combination with methotrexate, cyclosporine, acitretin and hydroxyurea and no significant drug interaction has been observed. Thus, in case of a lack of a response to the other systemic treatments or side effects, FAE can be added to the therapy and the side effects of the other drug can be reduced by a dose adjustment. Still, it must be borne in mind that the experience with combination therapy is limited and care must be taken during the treatment [**33**].

When used as monotherapy in palmoplantar pustular psoriasis, a higher dose was required and the treatment was found to be less effective compared to the other types of psoriasis [**34**]. Successful results were reported in nail psoriasis unresponsive to the other therapies [**35**]. It is not recommended to be used in psoriatic arthritis due to its lack of effect [**5, 22**].

The onset of the response to FAE treatment is observed within 5-6 weeks and complete

is usually achieved in 15 months [**28**]. The long term efficacy and safety of FAE was investigated in a multi-centred, retrospective study conducted on 984 patients for a mean treatment period of 44 months. At the end of 6 months 67%, at the end of 24 months 78%, and at the end of 36 months 82% healing was observed. Among the patients, 90% did not show any significant side effects necessitating a change in the therapy [**36**]. In recent years, studies have been conducted on the use of FAE in pediatric psoriatic patients. FAE was generally well tolerated in children and only 2 children discontinued the treatment due to side effects [**37**]. In a prospective study including 6 pediatric psoriatic patients, a PASI 100 response was observed in 3 children, PASI 90 was observed in one child and PASI 75 was observed in 2 children at the 12th week [**38**]. These studies have reported that FAE can be a treatment alternative in pediatric patients.

In a large-scale, multi-centred, prospective study on the use of Fumaderm®, a 75% DQLI reduction was observed in adult psoriatic patients at the end of the 12 month treatment period. This improvement in the DQLI has been found comparable to biological treatments [**39**]. In a retrospective study, the mean duration of the medication in 249 patients treated with FAE was 64 months. The ratio of the patients who continued the treatment for four years was 60%, while this ratio was 40% for etanercept and 70% for infliximab [**40**]. In conclusion, FAE can be an effective and safe first-line treatment alternative in the treatment of psoriasis.

Granulomatous Diseases:

Non-infectious granulomatous diseases are chronic diseases of unknown etiology. Experience on FAE in the treatment of granulomatous diseases is limited with case reports or case series.

Sarcoidosis:

Between1998 and 2014, FAE was used in a total of 20 patients with sarcoidosis reported either in case reports or patient series. Among these patients, 6 had cutaneous sarcoidosis and 14 had pulmonary and cutaneous sarcoidosis. Standard doses used in psoriasis treatment were used in the treatment of sarcoidosis with FAE. In 10 patients in the literature, in terms of complete healing in cutaneous sarcoidosis, 5 had a partial response while no response could be achieved in 5 patients [**41**]. *Nowack* et al. [**42**] have observed full remission with FAE in 3 female patients with sarcoidosis unresponsive to treatment with chlorokin and corticosteroids. Full remission was achieved between 4 and 12 months of therapy.

In patients with pulmonary involvement treated with FAE for the cutaneous lesions, the pulmonary changes were improved in parallel to the skin symptoms and the serum angiotensin converting enzyme levels returned to normal. The cutaneous and pulmonary changes were observed after 11-12 months of therapy [**43, 44**].

Granuloma Annulare:

Disseminated granuloma annulare (DGA) tends to be more chronic and refractory to treatment than localised granuloma annulare. It is usually unresponsive to topical treatments. Patients with DGA unresponsive to other therapies have been treated with FAE and cases with successful outcome have been reported. In these patients, FAE was used in the standard dose used for psoriasis [**45, 46, 47**]. Older lesions have been reported to require longer healing periods than newer lesions [**46**]. *Weber* et al. [**48**] have investigated the efficacy and safety of the treatment with low-dose FAE in 8 patients with DGA. Significant improvement was achieved in approximately 63% of the patients using low-dose fumarate treatment. Low-dose FAE used in the treatment of DGA had much less side effects than high-dose therapy and was better tolerated.

Wollina et al. [**49**] have compared the efficacy of the combination of FAE + PUVA against PUVA monotherapy in patients with DGA. In the group treated with FAE plus PUVA , the cumulative dose of PUVA was significantly lower and the complete healing rate was higher. The combination of PUVA with low-dose FAE has been reported to be beneficial in patients unresponsive to PUVA therapy.

Necrobiosis Lipoidica:

Necrobiosis lipoidica (NL) is an idiopathic skin disease observed usually concurrently with diabetes mellitus. More than one third of the lesions lead to ulcerations. While non-ulcerative NL causes dysesthesia and cosmetic problems, ulcerated lesions cause severe pain and morbidity. *Gambichler* et al. [**50**] observed complete clearance after a 6-month treatment with FAEin a 50-year-old female patient with a 15-year history of recalcitrant NL of the pretibial skin on the leg. *Kreuter* et al. [**51**] have investigated the results of the FAE treatment in NL patients unresponsive to the other treatments. In 15 patients who used DMF at the doses used in standard psoriasis treatment for a minimum of 6 months, the clinical results were satisfactory both for the physician and the patients. The clinical improvement was also verified histopathologically and using 20 M-Hz ultrasound. No progression was observed in the lesions during the 6-month follow up after the treatment was discontinued.

FAE has been used in a female patient with long-term, bilateral ulcerative NL in which no improvement was achieved through topical corticosteroids and tacrolimus, systemic corticosteroids and phototherapy. After six months of DMF treatment, the ulcers were healed and the pain and dysesthesia were improved. It has been suggested that the anti-inflammatory effect brought about by FAE in the endothelial cells may contribute to the healing in the treatment of NL [**52**].

Malignant Melanoma:

DMF's antiangiogenic activity is also thought to have antitumoral and antimetastatic effects besides its antipsoriatic activity. Therefore, it may be a potential therapeutic agent in case of malignancies where angiogenesis plays a role [**16**]. Although there is no data obtained from humans, DMF was investigated for the treatment of malignant melanoma in animals.

Loewe et al. [**53**] have studied the potential antitumorigenic activity of DMF on a mouse model. DMF administered three times the standard dose used in the treatment of psoriasis was found to delay the growth of nodular melanoma and the slow down the lymphogenic tumour dissemination in metastatic melanoma. DMF stopped the cell cycle at G2-M boundary. The proapoptotic effect of DMF was also shown in this study and its antiproliferative and proapoptotic features are thought to be effective in delaying tumour growth and metastases. In another study, DMF was shown to inhibit the NF-kappaB, which plays a role in tumour progression, cell invasion and metastasis; and the metastasis of the melanoma cells through the suppression of the activity and expression of matrix metalloproteinases. Therefore, it has been suggested to be beneficial as a metastasis preventive agent in the treatment of malignant melanoma [**54**]. For this purpose, *Valero* et al. [**55**] have investigated the effects of dacarbazine plus FAE compared to dacarbazine monotherapy on a severe combined immune deficiency (SCID) mouse model. In mice xenografted with human melanoma cells metastasized to the sentinel lymph nodes, the sentinel lymph node metastases were significantly delayed in the group treated with FAE + dacarbazine compared to the dacarbazine monotherapy group. Also, the density of the lymph vessel in the primary tumour was observed to be significantly reduced with the combination of FAE and dacarbazine.

In spite of the successful results obtained from animal studies and cell cultures, malignant melanoma has been reported to develop in 2 patients treated with FAE due to psoriasis [**56**]. However, it is unclear if these tumours are coincidental or therapy-related. A greater number of case reports and studies on the immunologic effects may shed light to this question.

Other Dermatological Diseases:

Positive results have been reported with FAE in patients with different types of lupus erythematosus unresponsive to other treatment methods. A female patient with severe discoid lupus erythematosus (DLE), in which treatment with topical corticosteroids, topical tacrolimus, klorokin, hydroxychloroquin and alitretinoin was ineffective, was successfully treated with low-dose Fumaderm over 6 months [**57**]. Another patient with chronic DLE was treated with FAE and hydroxychloroquin for 73 months and the disease remai-

ned stable [**58**]. In lupus erythematosus tumidus, complete healing was reported after a 3-month therapy with FAE at a psoriasis dose. In systemic lupus erythematosus unresponsive to systemic prednisolone, hydroxychloroquin ad cyclosporine therapy, FAE was used in combination with 10 mg/day of prednisolone and healing was achieved after a 3 month therapy [**59**]. These case reports demonstrate that the healing period with FAE in lupus erythematosus may be dose-dependent.

In a 15-year old male patient with atypical juvenile pityriasis rubra pilaris unresponsive to classical treatments, the FAE dose used in psoriasis was used and his lesions were improved, although relapse was observed after the discontinuation of the treatment [**60**].

FAE was used in 3 patients with annular elastolytic giant cell granuloma and good treatment response was observed in two patients, although one remained unresponsive. No healing was achieved in a patient with granulomatous cheilitis after 5 months of treatment [**61**].

FAE was used for 6 months in 10 patients with refractory alopecia areata. Full remission was achieved in three patients, while good response was observed in one patients and partial response was achieved in two patients. The remaining four patients showed no improvement [**62**].

Recently , the effectiveness and short-term tolerability of fumarates in patients with moderate to severe hidradenitis suppurativa who were refractory to conventional hidradenitis suppurativa therapies were assessed in a prospective, single-centre, open-label pilot study. It was shown that fumarates induced clinically meaningful improvement in three out of seven patients with recalcitrant moderate to severe hidradenitis suppurativa in the study [**63**].

A hand creme containing 5% Fumaric acid used twice daily was compared to a creme containing 0.1% triamcinolone used twice daily in hand eczema and was found to be less effective than the 0.1% triamcinolone creme. This result may be explained with the poor absorption of FA and the low concentration of 5% [**64**].

Side Effects:

Side effects with FAE are frequent but mild. Organ toxicity is lower than the licensed products such as methotrexate or cyclosporine [**32, 65**]. The frequency of side effects in studies was reported as 52-74% [**22, 32, 66**]. Side effects are most frequently observed during the first months of the therapy and approximately 30-40% of the patients have to discontinue treatment due to side effects [**22, 32, 65**]. The most frequently observed side effects are complaints related to the gastrointestinal system and flushing. Flushing and gastrointestinal side effects are more common among the patients with good treatment response [**5, 7, 65**]. Gastrointestinal side effects are observed in two-thirds of the patients and comprise abdominal pain, increased frequency of stool and tenesmus, bloating, diarrhea and nausea. The other reported side effects include headaches, malaise, fatigue, hair loss, exacerbation of the disease and palpitations [**28**].

A significant decrease in lymphocyte count is observed in 94% of the patients and necessitates a dose adjustment in 3.1% of the patients. Lymphopenia is also parallel to the efficacy of the drug and reduces both the T and B cells [**7, 13**]. Approximately half of the patients develop temporary eosinophilia. Elevations in the liver enzymes were observed in psoriatic patients under long-term treatment [**7**].

Acute kidney failure was reported in patients under treatment with FAE. Kidney failure is more frequent in female patients and was associated with high doses [**67**].

Method of Administration and Dose:

In order to minimize the side effects, standard treatment with FAE is stared at low doses and increased stepwise to the therapeutic dose [**28**]. The first week, therapy is initiated with Fumaderm initial® once a day and the treatment is continued with Fumaderm initial® twice a day through the second and third weeks. On the fourth week, Fumaderm® tablet is administered once a day and the dose increased to Fumaderm® tablet twice a day during the fifth week and three times a day in the sixth week. The dose is recommended to

be increased at weekly intervals. The maximum dose is 1.2g/day (6 strength tablets). After the treatment response is achieved, the dose is adjusted according to the individual [**5, 7**].

Patients under treatment with FAE should be followed up through monthly laboratory tests during the first 6 months and tests should be repeated every two months after this period. The routine hematology tests including serum creatinine, blood urea nitrogen, alanine and aspartate aminotransferases, gamma glutamyl transferase and the white blood count a complete urine test are among the parameters to be examined during the follow up visits. If the leukocyte count is below 3x109/L, lymphocyte count is 0.5x109/L and the eosinophil count is above 25%, the serum creatinine is 30% above the baseline value and proteinurea is observed, the dose should be reduced. If abnormal laboratory parameters prevail after the dose adjustment, the treatment should be discontinued [**7**].

No evidence of teratogenicity or mutagenicity was found in the toxicology studies with FAE. Still, since the data at hand is limited, it should not be prescribed during gestation and the lactation period. No metabolic interaction is known with another agent. Nevertheless, it is not recommended to be used concurrently with the drugs with an impact on the kidney function [**5, 7**].

References

1. Xu Q, Li S, Huang H, Wen J. Key technologies for the industrial production of fumaric acid by fermentation. Biotechnol Adv 2012; 30: 1685-1696. PMID: 22940403
2. Mrowietz U, Asadullah K. Dimethylfumarate for psoriasis: more than a dietary curiosity. Trends Mol Med 2005; 11: 43-48. PMID: 15649822
3. Rostami Yazdi M, Mrowietz U. Fumaric acid esters. Clin Dermatol 2008; 26: 522-526. PMID:18755371
4. Litjens NH, van Strijen E, van Gulpen C, Mattie H, van Dissel JT, Thio HB, Nibbering PH.In vitro pharmacokinetics of anti-psoriatic fumaric acid esters. BMC Pharmacol 2004; 12: 22. PMID: 15479475
5. Wollina U. Fumaric acid esters in dermatology. Indian Dermatol Online J 2011; 2: 111-119. PMID: 23130241
6. Litjens NH, Burggraaf J, van Strijen E, van Gulpen C, Mattie H, Schoemaker RC, van Dissel JT, Thio HB, Nibbering PH. Pharmacokinetics of oral fumarates in healthy subjects. Br J Clin Pharmacol 2004; 58: 429-432. PMID: 15373936
7. Mrowietz U, Christophers E, Altmeyer P. Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. The German Fumaric Acid Ester Consensus Conference. Br J Dermatol 1999; 141: 424-429. PMID: 10584060
8. Gambichler T, Scola N, Rotterdam S, Höxtermann S, Haghikia A, Faissner S, Kreuter A, Bechara FG, Altmeyer P, Chan A. Monitoring peripheral blood CD4(+) intracellular adenosine triphosphate concentration in patients with psoriasis treated with fumaric acid esters. Acta Derm Venereol 2012; 92: 364-366. PMID: 22294455
9. Rostami-Yazdi M, Clement B, Mrowietz U. Pharmacokinetics of anti-psoriatic fumaric acid esters in psoriasis patients. Arch Dermatol Res 2010; 302: 531-538. PMID: 20574745
10. De Jong P, Bezemer AC, Zomerdijk TPL, Van de Pouw-Kraan T, Ottenhoff THM & Nibbering PH. Selective stimulation of T helper 2 cytokine responses by the anti-psoriasis agent monomethylfumarate. Eur J Immunol 1996; 26: 2067-2074. PMID: 8814248
11. Ghoreschi K, Brück J, Kellerer C, Deng C, Peng H, Rothfuss O, Hussain RZ, Gocke AR, Respa A, Glocova I, Valtcheva N, Alexander E, Feil S, Feil R, Schulze-Osthoff K, Rupec RA, Lovett-Racke AE, Dringen R, Racke MK, Röcken M. Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells. J Exp Med 2011; 208: 2291-2303. PMID: 21987655
12. Stoof TJ, Flier J, Sampat S, Nieboer C, Tensen CP, Boorsma DM. The antipsoriatic drug dimethylfumarate strongly suppresses chemokine production in human keratinocytes and peripheral blood mononuclear cells. Br J Dermatol 2001; 144: 1114-1120. PMID: 11422029
13. Meissner M, Valesky EM, Kippenberger S, Kaufmann R. Dimethyl fumarate – only an anti-psoriatic medication? J Dtsch Dermatol Ges 2012; 10: 793-801. PMID: 22897153
14. Bacharach-Buhles M, Röchling A, el Gammal S, Altmeyer P. The effect of fumaric acid esters and dithranol on acanthosis and hyperproliferation in paoriasis vulgaris. Acta Derm Venereol 1996; 76: 190-193. PMID: 8800297
15. Gesser B, Johansen C, Rasmussen MK, Funding AT, Otkjaer K, Kjellerup RB, Kragballe K, Iversen L. Dimethylfumarate specifically inhibits the mitogen and stress-activated kinases 1 and 2 (MSK1/2): Possible role for its anti-psoriatic effect. J Invest Dermatol 2007; 127: 2129-2137. PMID: 17495961
16. Garcia-Caballero M, Mari-Beffa M, Medina MA, Quesada AR. Dimethylfumarate inhibits angiogenesis in vitro and in vivo: A possible role for its antipsoriatic effect? J Invest Dermatol 2011; 131: 1347-1355. PMID: 21289642
17. Meissner M, Doll M, Hrgovic I, Reichenbach G, König V, Hailemariam-Jahn T, Gille J, Kaufmann R. Suppression of VEGFR2 expression in human endothelial cells by dimethylfumarate treatment: evidence for

anti-angiogenic action. J Invest Dermatol 2011; 131: 1356-1364. PMID: 21430706

18. Gerdes S, Shakery K, Mrowietz U. Dimethylfumarate inhibits nuclear binding of nuclear factor kappaB but not of nuclear factor of activated T cells and CCAAT/enhancer binding protein beta in activated human T cells. Br J Dermatol 2007; 156: 838-842. PMID: 17381463
19. Treumer F, Zhu K, Gläser R, Mrowietz U. Dimethylfumarate is a potent inducer of apoptosis in human T cells. J Invest Dermatol 2003; 121: 1383-1388. PMID: 14675187
20. Förster A, Preussner LM, Seeger JM, Rabenhorst A, Kashkar H, Mrowietz U, Hartmann K. Dimethylfumarate induces apoptosis in human mast cells. Exp Dermatol 2013; 22: 719-724. PMID: 24112621
21. Rostami-Yazdi M, Clement B, Schmidt TJ, Schinor D, Mrowietz U. Detection of Metabolites of fumaric acid esters in human urine: Implications for their mode of action. J Invest Dermatol 2009; 129: 231-234. PMID: 18704112
22. Heelan K, Markham T. Fumaric acid esters as a suitable ?rst-line treatment for severe psoriasis: an Irish experience. Clin Exp Dermatol 2012; 37: 793-795. PMID: 22548419
23. Nugteren-Huying WM, van der Schroeff JG, Hermans J, Suurmond D. Fumaric acid therapy in psoriasis; A double-blind, placebo-controlled study. Ned Tijdschr Geneeskd 1990; 134: 2387-2391. PMID: 2263264
24. Altmeyer PJ, Matthes U, Pawlak F, Hoffmann K, Frosch PJ, Ruppert P, Wassilew SW, Horn T, Kreysel HW, Lutz G, et al. Antipsoriatic effect of fumaric acid derivatives. Results of a multicenter double-blind study in 100 patients. J Am Acad Dermatol 1994; 30: 977-981. PMID: 8188891
25. Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. Br J Dermatol 1998; 138: 456-460. PMID: 9580799
26. Mrowietz U, Christophers E, Altmeyer P. Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. The German Fumaric Acid Ester Consensus Conference. Br J Dermatol 1999; 141: 424-429. PMID: 10584060
27. Brewer L, Rogers S. Fumaric acid esters in the management of severe psoriasis. Clin Exp Dermatol 2007; 32: 246-249. PMID: 17362235
28. Harries MJ, Chalmers RJ, Griffiths CE. Fumaric acid esters for severe psoriasis: a retrospective review of 58 cases. Br J Dermatol 2005; 153: 549-551. PMID: 16120141
29. Carboni I, De Felice C, De Simoni I, Soda R, Chimenti S. Fumaric acid esters in the treatment of psoriasis: an Italian experience. J Dermatolog Treat 2004; 15: 23-26. PMID: 14754645
30. Fallah Arani S, Neumann H, Hop WC, Thio HB. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multi- centre prospective randomized controlled clinical trial. Br J Dermatol 2011; 164: 855-861. PMID: 21175564
31. Inzinger M, Weger W, Heschl B, Salmhofer W, Quehenberger F, Wolf P. Methotrexate vs. fumaric acid esters in moderate-to-severe chronic plaque psoriasis: data registry report on the efficacy under daily life conditions. J Eur Acad Dermatol Venereol 2013; 27: 861-866. PMID: 22672248
32. Wain EM, Darling MI, Pleass RD, Barker JN, Smith CH. Treatment of severe, recalcitrant, chronic plaque psoriasis with fumaric acid esters: a prospective study. Br J Dermatol 2010; 162: 427-434. PMID: 19519838
33. Balasubramaniam P, Stevenson O, Berth-Jones J. Fumaric acid esters in severe psoriasis, including experience of use in combination with other systemic modalities. Br J Dermatol 2004; 150: 741-746. PMID: 15099371
34. Ständer H, Stadelmann A, Luger T, Traupe H. Efficacy of fumaric acid ester monotherapy in psoriasis pustulosa palmoplantaris. Br J Dermatol 2003; 149: 220-222. PMID: 1289023
35. Vlachou C, Berth-Jones J. Nail psoriasis improvement in a patient treated with fumaric acid esters. J Dermatol Treatment 2007; 18: 175-177. PMID: 17538807
36. Reich K, Thaci D, Mrowietz U, Kamps A, Neureither M, Luger T. Efficacy and safety of fumaric acid esters in the long-term treatment of psoriasis--a retrospective study (FUTURE). J Dtsch Dermatol Ges 2009; 7: 603-611. PMID:19459898
37. Balak DM, Oostveen AM, Bousema MT, Venema AW, Arnold WP, Seyger MM, Thio HB. Effectiveness and safety of fumaric acid esters in children with psoriasis: a retrospective analysis of 14 patients from the Netherlands. Br J Dermatol 2013; 168: 1343-1347. PMID: 23738641
38. Steinz K, Gerdes S, Domm S, Mrowietz U. Systemic Treatment with Fumaric Acid Esters in Six Paediatric Patients with Psoriasis in a Psoriasis Centre. Dermatology 2014; 229: 199-204. PMID: 25247273
39. Walker F, Adamczyk A, Kellerer C, Belge K, Brück J, Berner T, Merten K, Núnez Gómez N, Neureither M, Röcken M, Ghoreschi K. "Fumaderm® in daily practice for psoriasis: dosing, efficacy and quality of life. Br J Dermatol 2014; 171: 1197-205. PMID: 24813676
40. Ismail N, Collins P, Rogers S, Kirby B, Lally A. Drug survival of fumaric acid esters for psoriasis: a retrospective study. Br J Dermatol 2014; 171: 397-402. PMID: 24471408
41. Zouboulis CC, Lippert U, Karagiannidis I.Multi-Organ Sarcoidosis Treatment with Fumaric Acid Esters: A Case Report and Review of the Literature. Dermatology 2014; 228: 202-206. PMID: 24686198
42. Nowack U, Gambichler T, Hanefeld C, Kastner U, Altmeyer P. Successful treatment of recalcitrant cutaneous sarcoidosis with fumaric acid esters. BMC Dermatol 2002; 2: 15. PMID: 12498617
43. Wolter A, Müller M, Völker B, Gehring M, Caldarone F, Kapp A, Werfel T, Raap U. Cutaneous and pulmonary sarcoidosis. Successful therapy with fumaric acid esters. Hautarzt 2012; 63: 808-811. PMID: 22552842

44. Gutzmer R, Kapp A, Werfel T. Successful treatment of skin and lung sarcoidosis with fumaric acid ester. Hautarzt 2004; 55: 553-557. PMID: 15098093

45. Eberlein-König B, Mempel M, Stahlecker J, Forer I, Ring J, Abeck D. Disseminated granuloma annulare--treatment with fumaric acid esters. Dermatology 2005; 210: 223-226. PMID: 15785051

46. Acharya U. Successful treatment of disseminated granuloma annulare with oral fumaric acid esters.Int J Dermatol 2013; 52: 633-634. PMID: 23590379

47. Wollina U. Granuloma annulare disseminatum responding to fumaric acid esters. Dermatol Online J 2008; 14: 12. PMID: 19265625

48. Weber HO, Borelli C, Röcken M, Schaller M. Treatment of disseminated granuloma annulare with low-dose fumaric acid. Acta Derm Venereol 2009; 89: 295-298. PMID: 19479130

49. Wollina U, Langner D.Treatment of disseminated granuloma annulare recalcitrant to topical therapy: a retrospective 10-year analysis with comparison of photochemotherapy alone versus photochemotherapy plus oral fumaric acid esters. J Eur Acad Dermatol Venereol 2012; 26: 1319-1321. PMID: 22035266

50. Gambichler T, Kreuter A, Freitag M, Pawlak FM, Brockmeyer NH, Altmeyer P. Clearance of necrobiosis lipoidica with fumaric acid esters. Dermatology 2003; 207: 422-424. PMID: 14657645

51. Kreuter A, Knierim C, Stücker M, Pawlak F, Rotterdam S, Altmeyer P, Gambichler T. Fumaric acid esters in necrobiosis lipoidica: results of a prospective noncontrolled study. Br J Dermatol 2005; 153: 802-807. PMID: 16181464

52. Eberle FC, Ghoreschi K, Hertl M. Fumaric acid esters in severe ulcerative necrobiosis lipoidica: a case report and evaluation of current therapies. Acta Derm Venereol 2010; 90: 104-106. PMID: 20107745

53. Loewe R, Valero T, Kremling S, Pratscher B, Kunstfeld R, Pehamberger H, Petzelbauer P. Dimethylfumarate impairs melanoma growth and metastasis. Cancer Res 2006; 66: 11888-11896. PMID: 17178886

54. Yamazoe Y, Tsubaki M, Matsuoka H, Satou T, Itoh T, Kusunoki T, Kidera Y, Tanimori Y, Shoji K, Nakamura H, Ogaki M, Nishiura S, Nishida S. Dimethylfumarate inhibits tumor cell invasion and metastasis by suppressing the expression and activities of matrix metalloproteinases in melanoma cells. Cell Biol Int 2009; 33: 1087-1094. PMID: 19595779

55. Valero T, Steele S, Neumüller K, Bracher A, Niederleithner H, Pehamberger H, Petzelbauer P, Loewe R. Combination of dacarbazine and dimethylfumarate efficiently reduces melanoma lymph node metastasis. J Invest Dermatol 2010; 130: 1087-1094. PMID: 19940857

56. Barth D, Simon JC, Wetzig T. Malignant melanoma during treatment with fumaric acid esters - coincidence or treatment-related? J Dtsch Dermatol Ges 2011; 9: 223-225. PMID: 20678147

57. Tsianakas A, Herzog S, Landmann A, Patsinakidis N, Perusquía Ortiz AM, Bonsmann G, Luger TA, Kuhn A. Successful treatment of discoid lupus erythematosus with fumaric acid esters. J Am Acad Dermatol 2014; 71: e15-e17. PMID: 24947703

58. Klein A, Coras B, Landthaler M, Babilas P. Off-label use of fumarate therapy for granulomatous and inflammatory skin diseases other than psoriasis vulgaris: a retrospective study. J Eur Acad Dermatol Venereol 2012; 26: 1400-1406. PMID: 22007931

59. Balak DMW, Thio HB. Treatment of lupus erythematosus with fumaric acid ester derivatives: two case-reports. Journal of Translational Medicine 2011 9 (Suppl 2): P15.

60. Coras B, Vogt TH, Ulrich H, Landthaler M, Hohenleutner U. Fumaric acid esters therapy: a new treatment modality in pityriasis rubra pilaris? Br J Dermatol 2005; 152: 388-389. PMID: 15727670

61. Breuer K, Gutzmer R, Völker B, Kapp A, Werfel T. Therapy of noninfectious granulomatous skin diseases with fumaric acid esters. Br J Dermatol 2005; 152: 1290-1295. PMID: 15948995

62. Venten I, Hess N, Hirschmüller A, Altmeyer P, Brockmeyer N. Treatment of therapy-resistant Alopecia areata with fumaric acid esters. Eur J Med Res 2006; 11: 300-305. PMID: 16899425

63. Deckers IE, van der Zee HH, Balak DM, Prens EP. Fumarates, a new treatment option for therapy resistant hidradenitis suppurativa: a prospective open-label pilot study. Br J Dermatol 2015; 172: 828-829. PMID: 25123023

64. Jowkar F, Saki N, Mokhtarpour A, Saki MR. Comparison of fumaric acid 5% cream versus triamcinolone 0.1% cream in the treatment of hand eczema. Acta Med Iran 2014; 52: 528-531. PMID: 25135262

65. Anstey AV. Fumaric acid esters in the treatment of psoriasis. Br J Dermatol 2010; 162: 237-238. PMID: 20374246

66. Kokelj F, Plozzer C, Avian A, Trevisan G. Fumaric acid and its derivatives in the treatment of psoriasis vulgaris: our experience in forty-one patients. Acta Dermatovenerol Croat 2009; 17: 170-175. PMID: 19818215

67. Häring N, Mähr HS, Mündle M, Strohal R, Lhotta K. Early detection of renal damage caused by fumaric acid ester therapy by determination of urinary ?2-microglobulin. Br J Dermatol 2011; 164: 648-651. PMID: 21143462