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ECHINACEA USE AND AUTOIMMUNE DISEASE ONSET OR FLARE: A REVIEW

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Abstract :-

Background: Echinacea is an immunostimulating phytotherapy substance commonly used to prevent and treat colds and urinary infections. However, there are a few descriptions of It Being associated with autoimmune disease flares or onse.

Aim: To systematically review the use of Echinacea and autoimmune disease onset or flare.

Methods: PubMed/MEDLINE was screened for articles on Echinacea and autoimune until September 2024.

Results: The search found 7 articles with 7 cases reported. The age varied from 25 to 63 years old, and 4/7 were male gender. The diseases studied were acute demyelinating encephalomyelitis (ADEM), cholestatic autoimmune hepatitis, erythema nodosum, Sjögren's syndrome, and pemphigus. The Echinacea dosage varied from 45mg to 1,500mg/day. The studies showed ADEM, cholestatic autoimmune hepatitis, and Sjögren's syndrome, erythema nodosum. A flare of this disease was observed after Echinacia contact in the pemphigus case. Regarding treatment, all patients with Echinacea were excluded. Steroid pulse therapy was done in ADEM; prednisone, intravenous immunoglobulin, plasma exchange azathioprine, mycophenolate mofetil,

dapsone, and hydroxychloroquine were used. In 6/7 cases, the diseases improved or were cured after Echinacea withdrawal and/or immunosuppressive drugs [4-6]. In 1/7, the outcome was bad, and patients died after 2 years.

Conclusion: This systematic review shows that Echinacea may induce autoimmune diseases, such as ADEM, autoimmune hepatitis, Sjögren's syndrome, and pemphigus flares.

Keywords: Echinacea, toxicity, autoimmune diseases, autoimmunity.

Running title: Echianmce and autoimmune diseases onset/flare.

Introduction

Echinacea (Echinacea purpurea, Echinacea angustifolia, and Echinacea pallida) are widely recognized medicinal plants commonly employed in the prevention and treatment of the common cold, influenza, and upper respiratory tract infections [1]. The purported immune-enhancing effects of Echinacea are primarily attributed to its ability to stimulate nonspecific immune mechanisms, including enhanced phagocytic activity, macrophage activation, and the stimulation of natural killer (NK) cell activity. These immunomodulatory effects have been substantiated through both in vitro studies and animal models, particularly with the use of expressed juice from the aerial parts of the plant and alcoholic extracts from the roots [1].

In addition to the ongoing investigation into their efficacy, there is an increasing emphasis on the safety profile of Echinacea. Reports of adverse events associated with Echinacea consumption are varied and include allergic reactions, thrombocytopenia,

leukopenia, eosinophilia, erythema nodosum, and exanthema, among others. Of particular concern are reports documenting the exacerbation of pre-existing autoimmune diseases or, in some cases, the onset of new autoimmune disorders following the ingestion of Echinacea [2]. This growing body of evidence raises significant questions about the safety of Echinacea, especially in individuals predisposed to or currently managing autoimmune conditions.

Given the increasing use of Echinacea in complementary and alternative medicine, it is crucial to assess the potential immunological risks associated with its consumption rigorously.

This article seeks to provide a comprehensive review of the current literature on the ingestion of Echinacea and its potential role in modulating autoimmune diseases. It explores both the mechanistic pathways involved and the clinical implications for patient safety.

Methods

Literature review: We carried out a systematic search of publications in PubMed/MEDLINE until September 2024. The search was based on specific MeSH entry terms, which included: "Echibnacea" AND "autoimmune diseases," OR "rheumatologic" OR "rheumatic" OR “rheumatoid arthritis” OR “systemic lupus erythematosus” OR “Sjogren syndrome” OR “vasculitis” OR “systemic sclerosis” OR “myositis” OR "myocarditis" OR “pericarditis" OR "thyroiditis" OR "hypophysitis" OR "diabetes" OR

"pancreatitis" OR "uveitis" OR "autoimmune hepatitis" OR "primary biliary cholangitis" OR "celiac disease" were used. There were no language restrictions. The lists of references of the selected publications were analyzed to identify additional publications.

The two authors (AL and JFC) initially searched the literature and independently selected the included studies' abstracts. In the second step, the two authors independently read the full-text publications chosen based on the abstracts. PRISMA guidelines [4] were again followed. Finally, We designed a standardized form for extracting the following information from the relevant publications: authors, publication year, country, patient numbers, demographics, disease duration, follow-up, Echinacea dosage, clinical features, treatment, and outcome.

Results

Table 1 summarizes all published cases of Echinacea use and autoimmune diseases.

The search found 7 articles with 7 cases reported [3-9]. The countries in which the cases were reported were the United States (n=3), Canada (n=1), Cyprus (n=1), Germany (n=1), and Turkey (n=1). The age varied from 25 to 63 years old, and 4/7 were male gender. The diseases studied were acute demyelinating encephalomyelitis (ADEM) (n=3), followed by cholestatic autoimmune hepatitis (n=1), erythema nodosum (n=1), Sjögren's syndrome (n=1), and pemphigus (n=1). The Echinacea dosage varied from 45mg to 1,500mg/day, but this information was not available in 3/7 reports. One of them [ref] used intramuscular Echinacea, and the other 6/7 used oral ingestion. The time

between Echinacea use and autoimmune onset/flare they were varied from 3 days to 3 weeks. In 5/7 studies, patients used concomitantly other substances (described in Table 1).

The clinical and laboratory alterations were: progressive muscle weakness, and hypoesthesias in patients with ADEM. Furthermore, the MRI was altered and compatible with demyelinating diseases. In some cases, cerebrospinal fluid was abnormal [3,5,9]. In autoimmune hepatitis, the patient develops ictericia and fatigue, increases levels of transaminases, and develops cholestatic enzymes [6]. In the erythema nodosum case, patients had several episodes of this dermatological condition, always after Echinacea ingestion [8]. In the pemphigus case, a flare of this disease was observed after Echinacia contact [7]. Lastly, a patient developed rapid muscle weakness secondary to hypocalcemia and profound metabolic acidosis; the investigation determined a distal tubular acidosis secondary to Sjögren's syndrome [4].

Regarding treatment, all patients with Echinacea were excluded. Methylprednisolone pulse therapy was done in 3/7 cases (all ADEM) [3,5,9], intravenous immunoglobulin and plasma exchange in 1/7 (ADEM) [5], prednisone in 2/7 [7,8], and azathioprine, followed by mycophenolate mofetil and dapsone in 1/7 [7]. The Sjögren's syndrome patient received hydroxychloroquine, bicarbonate, and potassium supplementation [4].

In 6/7 cases, the diseases improved or were cured after Echinacea withdrawal and/or immunosuppressive drugs [4-6]. In 1/7, the outcome was bad, and patients died after 2 years [5].

Discussion

This review systematically analyzed published cases that associate Echinacea consumption with the onset or exacerbation of autoimmune diseases. The findings suggest a potential link between Echinacea intake and the development or worsening of various autoimmune conditions, including ADEM, cholestatic autoimmune hepatitis, erythema nodosum, Sjögren's syndrome, and pemphigus. These cases highlight the need for caution when recommending Echinacea, particularly for individuals with a predisposition to autoimmune disorders.

The immunostimulatory properties of Echinacea, which are often sought after for their supposed benefits in enhancing immune function, may paradoxically trigger or exacerbate autoimmune reactions in susceptible individuals. This aligns with the hypothesis that the same mechanisms that bolster nonspecific immune responses—such as macrophage activation and enhanced phagocytic activity—might also drive aberrant immune responses, leading to autoimmunity. For instance, the activation of macrophages and other immune cells by Echinacea could theoretically enhance the presentation of self-antigens to autoreactive T cells, thereby precipitating an autoimmune response.

The diversity of autoimmune conditions observed in the reviewed cases underscores the broad immunomodulatory effects of Echinacea, which may impact various tissues and organ systems. In particular, the cases of ADEM reported by Kaymakamzade et al. and Schwarz et al. [3,9] illustrate the neurological risks associated with Echinacea, with patients developing severe demyelinating disease following its use.

The involvement of the central nervous system (CNS) in these cases raises significant concerns, given the limited capacity for CNS repair and the potential for lasting neurological deficits.

However, several limitations must be acknowledged. The small number of cases and the lack of detailed information on Echinacea dosage in most reports hinder the ability to draw definitive conclusions about the risk magnitude. Furthermore, many of the cases involved the concomitant use of other herbal supplements or medications, which complicates the attribution of causality to Echinacea alone. Despite these limitations, the consistent temporal relationship between Echinacea use and the onset of autoimmune symptoms across multiple cases provides compelling, though not conclusive, evidence of a potential link.

The implications of these findings are particularly pertinent given the widespread use of Echinacea in complementary and alternative medicine. Healthcare providers should be aware of these risks and exercise caution when recommending Echinacea to patients, especially those with existing autoimmune conditions or those at high risk for developing such diseases. Prospective studies are urgently needed to better understand the safety profile of Echinacea, particularly in populations vulnerable to autoimmune diseases. These studies aim to elucidate the mechanisms underlying Echinacea-induced autoimmunity and to identify any genetic or environmental factors that may predispose individuals to these adverse effects.

The limitations of this study were: 1. the small number of cases described; 2. the dosages of Echinacea are not available in most cases, and 3. most cases used concomitantly with other phytotherapeutic drugs.

In conclusion, while Echinacea is widely used for its perceived benefits in enhancing immune function, the potential for triggering or exacerbating autoimmune diseases must be considered. This review highlights the need for heightened awareness and further research to ensure the safe use of Echinacea, particularly in populations at risk for autoimmune disorders.

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JFC: Conception, analysis, writing, interpretation, revision, submission

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Table 1. Studies on Echinacea ingestion and autoimmune disease onset or flare.

Author, year, reference	Study design	Country	N, age, gender	Disease	Echinacea dosage	Concomitant drugs	Time to disease onset/flare	Clinical, CSF, and MRI features	Treatment	Outcome

Kaymakamzade et al., 2016 [3]	Case report	Cyprus	1, 25 yo, Male	Acute Disseminated Encephalomyelitis (ADEM)	Unknown. Thrice a day for 2 weeks.	Carthamus tinctorius s, pollen, stinging nettle, fennelflower, ginger, galingale, Myristica frangrans, vitamin C, betaglucan	2 weeks	Bilateral central facial palsy, severe quadriparesis, and leftsided hemihypoestesia. Brain MRI: ovoid T2 hyperintense lesions in the left pontocerebellar area, the right corona radiata, and bilateral asymmetry in parietal lobes with contrast enhancement. Blood	7 doses of methylprednisolone 1g pulse therapy.	He was able to walk and use his left upper extremity at the end of the pulse therapy. Complete recovery after 3 weeks. MRI after 1 month: T2 hyperintense lesions persisted while contrast enhancement disappeared, and no additional lesion was detected. No exacerbation during 4 years.

								and CSF were normal.		
Logan & Ahmed, 2013 [4]	Case report	United States	1, 36 yo, Female	Sjogren's syndrome with tubular renal acidosis	Unknown	St John's Wort, and kava	3 weeks	Severe generalized muscle weakness due to K 1.3 mEq/L and pH 7.15.	Echinacea withdrawn. Hydroxychloroquine 200mg/day. 1200 mEq of NaHCO3 and 400 mEq of KCl given over 4 days of hospitalization	Improved

Kostianovsky et al., 2011 [5]	Case report	United States	1, 63 yo, Female	Acute Disseminated Encephalomyelitis (ADEM)	Echinacea purpurea 45 mg	Uncaria tomentosa 37.5 mg, Tabebuia avellanedae and Plantago maritima 30 mg.	7 days	Asthenia, postural instability and falls. Left-eye horizontal nystagmus, mild dysarthria, and mild right arm weakness together with both axial and appendicular ataxia.	3 doses of methylprednisolone 1g pulse therapy. 5 plasma exchange sessions and 120 g intravenous immunoglobulin.	She was quadriparetic, and required help on daily Activities. Her level of consciousness was impaired, and she was barely able to connect with her family members. A follow-up brain MRI at 8 months showed atrophy and scarring; no new

								MRI: pseudonodular, subcortical, and periventricular bilateral white matter lesions. CSF: protein Concentration of 60 mg/dl (n.: ≤45 mg/dl)		lesions had occurred. Two years later, the patient died of septic shock.

Kocaman et al., 2007 [6]	Case report	Turkey	1, 45 yo, Male	Cholestatic autoimmune hepatitis	1,500 mg/day for 3 days	No	3 days	Fatigue and jaundice. Alanine aminotransferase 1260 IU/L (normal: <55 IU/L), aspartate aminotransferase 840 IU/L (n.: <34 IU/L), alkaline phosphatase 984 IU/L (n.: <150 IU/	Echinacea withdrawal.	Everything normalized after 1 month, except positivity for anti-smooth muscle antibodies.

								L), gammaglutamyl transferase 672 IU/L (n.: <b64 IU/L), total bilirubin 2.8 mg/dL (n.: <1 mg/dL), A liver biopsy revealed an interface hepatitis, prominent cholestasis, and portal lymphoplas mocytic and eosinophilic granulocyte infiltration		

Lee & Werth, 2004 [7]	Case series	United States	1 out of 3, 57 yo Male	Pemphigus flare	Unknown	No	7-10 days	A pemphigus flare was verified with a worse clinical picture that resolved	Echinacea stopping. Prednisone and azathioprine, mycophenolate mofetil. And dapsone.	Partial disease control, but never complete remission, was achieved with prednisone, azathioprine mycophenolate

								after 2 weeks of stopping Spiruline and using prednisone. One week after this flare cleared, a second worse flare was observed.		mofetil, and dapsone

Soon & Crawford, 2001 [8]	Case report	Canada	1 41 yo Male	Erythema nodosum	Intermittently for the past 18 months	St John's wort, and loratadine.	ND	4 episodes of clinically erythema nodosum, with myalgias, arthralgias, fever, headache, malaise, and sore throat.	Echinacea stopping and prednisone.	Cured.
Schwarz et al., 2000 [9]	Case series	Germany	1 out of 2 49 yo	Acute Disseminated Encephalomyelitis (ADEM)	Echinacea angustifolia D2 1.1 ml Intramuscular	Aconitum D4 0.3 ml, and Lachesis	5 days	Progressive numbness and	5 doses of methylprednisolone (500mg) pulse therapy.	The symptoms improved rapidly.

			Female		twice a week for 7 weeks.	D8 0.3 ml intramuscular		weakness in the right arm. CSF: 0.24 g protein/l and 11 leucocytes/µl (>90 % lymphocytes), and IgG (47 mg/l). Positive oligoclonal bands. MRI: 2 distinct hyperintense lesions in the left parietal paraventricular deep white matter, enhancing		7 months later, the patient had minimal residual coordination difficulties in the right hand. New MRI: a residual paraventricular, left parietal, small hyperintense lesion.

								after contrast.		

CSF: cerebrospinal fluid; MRI: magnetic resonance imaging; N: number; ND: not described; yo: years old.