

Aloe-Emodin in Aloe Vera Extract for Beneficial Effects on Brain Health with Mild Dementia and Cognitive Impairment in Alzheimer's Disease

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Abstract

Introduction: Primary Immune Deficiencies (PID) of rare, under-determined diseases particularly in sub-Saharan Africa. Our aim was to share the results of the follow-up of these patients.

Patients and Methods: We conducted a descriptive and analytical cross-sectional study at the Albert Royer National Children's Hospital in Dakar, in collaboration with other pediatric departments and the Immunology laboratory of the National Blood Transfusion Center. We included all patients received with suspected PID, from 2014 to 2021, after ruling out HIV infection. The diagnostic criteria were the recommendations of the Moroccan Society of Immunology. We did not include patients with incomplete data. A complete blood count was performed in all patients. Further explorations were carried out depending on the orientation. The data was analyzed with Excel 10.

Results: Out of 32 patients registered, 16 were included in a follow-up consultation (50%). The sex ratio was 0.6 and the mean age at diagnosis was 51.1 months. Inbreeding was observed in half of the patients (8/16). The warning signs were mainly infectious (11/16). The other symptoms were dermatological, such as eczema and warts (3/16), but also neurological, type ataxia (3/16). Anemia was observed in 12/16 children, lymphopenia in 4/16 children. Protein electrophoresis was performed in 10/16 children, immunoglobulin weight determination in 4/16 children and lymphocyte immunophenotyping in 10/16 patients. The main PIDs diagnosed were congenital neutropenia (3/16), severe combined immune deficiencies or SCID (3/16), telangiectasia ataxia (3/16), hypogammaglobulinemia (2/16), verruciform epidermodysplasia (2/16), Wiskott-Aldrich syndrome (1/16), chronic septic granulomatosis (1/16), Evans syndrome (1/16). The course was marked by relapses-remissions in 6/16 patients and discontinuation of follow-up in (5/16 patients). Bronchiectasis was observed in 2 patients, with secondary bacterial and fungal infections and digital hypocratism. 100% mortality was observed in carriers of SCID and Telangiectasia ataxia.

Conclusion: PIDs are suspected based on atypical clinical signs. Confirmation is difficult in low income countries. The development is marked by a risk of complications or death, hence the need to strengthen clinical-biological collaboration.

Keywords: Primary Immune Deficiencies; Sub-Saharan Africa

Introduction

Barbaloin in Aloe vera extract is decomposed quickly at high temperatures and under neutral basic conditions.

Additives and metal ions can change the transformation, and degradations of barbaloin are iso-barbaloin, aloe emodin, 10-hydroxaloin B were main products. Aloe emodin may have greater toxicity hazards and potential safety risks [1]. The Aloe vera extract has demonstrated a neuroprotective effect and was founded to decrease blood brain barrier (BBB) permeability and increase neurological scores in male rats after traumatic brain injury. The potential mechanism of action for Aloe vera extract involves reducing the levels of oxidizing agents, such as protein carbonyl (PC) and malondialdehyde (MDA), in both the brain and serum, while simultaneously increasing antioxidant agents like total antioxidant capacity [2]. Aloe vera extract has a neuroprotective effect induced by reducing brain edema. The probable mechanism particularly for high dose of Aloe vera extract is decreasing levels of proinflammatory cytokines such as TGF- β , INF- α , IL-6 and IL-1 β [3].

Aloe vera extract (AV) is a succulent plant with numerous health benefits, including antioxidant, immune-boosting, and antidepressant properties. Increased-brain indolamine 2,3-dioxygenase (IDO) activity due to proinflammatory cytokines contribute as to serotonin depression. The study investigates how Aloe vera extract affects brain IDO activity and liver antioxidant status in rats subjected to the forced swim test (FST). Albino Wistar rats were assigned to control and AV treated groups (n = 12/group). The test group received an aqueous extract of Aloe vera orally at 0.2 g/ml/kg, while the control groups received tap water for fourteen days. Behavioral analysis showed AV' anxiolytic properties in mice subjected to an elevated plus maze (EPM) test, with a significant reduction in total locomotor activity and exploratory behavior in open field test. Antidepressant effect was indicated by decreased (P < 0.05) immobility time in FST and decreased brain IDO activity in AV-tested rats. Moreover, the significant anti-oxidant activity of AV extract was reflected in elevated catalase and reduced glutathione levels, along with considerable depletion in Malondialdehyde (MDA) levels when compared to unstressed controls. Together, these findings suggest AV extract possess antioxidant and anxiolytic properties mitigating stress-induced depressive states by decreasing brain IDO activity, thereby increasing tryptophan availability for serotonin synthesis [4]. After 8th weeks of intervention, the mean depression score in the 500 mg Aloe vera (A1 500) group decrease significantly (P = 0.033). Aloe vera extract powders (A1 500) considerably alleviated depression mean score in patient during an eight weeks period [5]. The use of Aloe vera extract in pre-diabetic, could revert impaired blood glucose within four weeks, but after 8 weeks the Aloe vera A1500 (p < 0.001, and p = 0.004) could alleviate their abnormal lipid profile [6]. The effect of an aloe polymannose multi-nutrient complex on cognitive and immune functioning in Alzheimer's disease: The results showed improvement's in both clinical and physiological outcomes for a disease that otherwise has no standard ameliorative remedy [7].

Experimental results by Yulu Wang showed that Aloe emodin can activate mitophagy through AMPK/PGC-1 α /SIRT3 signaling pathway, alleviate cognitive dysfunction in Alzheimer's disease (AD), and reduce damage to hippocampal neurons [8].

As a background of his study: Impaired mitophagy results in the accumulation of defective mitochondria that are unable to be cleared effectively in AD. Aloe emodin (AE), a key compound of the traditional Chinese's Rhubarb, a metabolite of AE in rats and human, rhein, exhibits neuroprotective effect against AD. Through the underlying mechanism unclear, studying aloe emodin's role in enhancing mitophagy is vital for improving cognitive function and reducing neuronal damage in AD. Aloe emodin (AE), an anthraquinone from Aloe vera acts as an anti-aggregate agent to the thermally aggregated hemoglobin. Aggregation of protein is a physiological process which contributes to the pathophysiology of several maladies including diabetes mellitus, Huntington's and Alzheimer's disease. It has been reported that AE, an anthraquinone, which is one of the active components of the Aloe vera plant, acts as an inhibitor hemoglobin (Hb) aggregation. Hb thermally aggregated at 60°C for four days as evident by increased this flavin T and ANS fluorescence, subjected Congo red absorbance appearance of sheet structure, increase in turbidity and presence appearance of β sheet structure, increase in turbidity and presence of

oligomeric aggregates, increasing concentration of AE partially reverse the aggregation of the model heme protein (hemoglobin). The maximum effect of AE was observed at 100 μM followed by saturation at 125 μM . The results were confirmed by UV-visible spectrometry, intrinsic fluorescence, TnT, ANS, Congo red assay as well as transmission electron microscopy (TEM). These results were also supported by Fourier transform infrared spectroscopy (FTIR) and circular dichroism (CD) which show the disappearance of β -sheet structure and appearance of α helices. The study serves as the base-line for translating research and the revers development of AE based therapeutics for diseases attributed to protein aggregation [9].

Conjugation aloe emodin aldehyde and hemoglobin

An *in vitro* reaction between aloe emodin (AE) aldehyde and hemoglobin would most likely proceed via the formation of a Schiff base, a type of covalent adduct. However, no specific studies were found detailing this exact conjugation, though literature exist on the broader interaction of aggregation of protein is a physical-biological process which contributes to the pathophysiology of several maladies including diabetes mellitus, Huntington's and Alzheimer's disease. By Furkan's study [10] the authors have reported that AE which is one of the active components of Aloe vera plant, acts as an inhibitor hemoglobin (Hb) aggregation. Hb thermally aggregated at 60°C for four days as evident by increased thioflavin T and ANS fluorescence, shifted Congo red absorbance appearance of β -sheet structure, increase in turbidity and presence of oligomeric aggregates.

Comments

Conjugation aloe emodin aldehyde and hemoglobin

- Structure of AE aldehyde:** Specific structure for "Aloe emodin aldehyde" was identified by Furkan's group as an anti-aggregatory agent to the thermally aggregated hemoglobin [10]. The addition of aldehyde functional group(-CHO) would make it susceptible to a Schiff base reaction.
- Functional groups on hemoglobin:** Hemoglobin is rich in potential reaction sites including.
- Schiff base formation:** The overall reaction is presented as follows: $\text{R-CHO} + \text{R}'\text{-NH}_2 \leftrightarrow \text{R-CH=NR}'$ (Schiff-base) and H_2O .

Analogy to similar reactions

Proposed conjugation mechanism is supported by documented reactions involving other aldehydes and hemoglobin.

Glucose and hemoglobin

Formation of HbAc1c in diabetics a well-known example of a Schiff base reaction. Glucose forms an unstable Schiff base with then-terminal valine of hemoglobin, which then undergoes a slow, in-reversible rearrangement to form a more stable keto-amine adduct.

Lipid peroxidation aldehydes and hemoglobin

Aldehydes formed during lipid peroxidation (such as malondialdehyde and croton aldehyde) have been shown to react with hemoglobin to form adducts (Schiff base formulation).

A 2017 study found that AE can inhibit the aggregation of hemoglobin, suggesting a direct reaction, though the mechanism is non-covalent and distinct from adduct formation (Schiff base formation).

Comments in total

Aloe emodin in Aloe vera extract for beneficial effects on brain health with mild dementia and cognitive improvement in Alzheimer's disease, decreased attributed to protein aggregation by Schiff base formation: keto/amine adduct: C=O NH_2 to C=N- .

Schiff base formation of Aloe emodin aldehyde with valine amine group in hemoglobin through non-covalent and distinct from adduct formation.

Conclusion

Schiff base formation of Aloe emodin aldehyde with valine amino group in hemoglobin through non-covalent and distinct from adduct formation was demonstrated by Furkan group.

Aloe emodin aldehyde has a neuroprotective effect by addressing mitochondria dysfunction and is effective in a treating AD. This provides modern evidence for the clinical application of traditional Chinese medicine, Rhubarb, in which Aloe emodin is expressed as one of the components.

Aloe emodin (AE) in Aloe vera extract can activate mitophagy through AMPK/PGE-Id/SIRT3 pathway alleviate cognitive dysfunction in Alzheimer's disease, and reduce damage to hippocampal neurons. The researches by Furkan group [10] were resulted in AE based therapeutics for diseases attributed to protein, hemoglobin aggregation.

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