



## PHARMACOLOGICAL ACTIVITIES OF AZELAIC ACID: A RECENT UPDATE

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### Abstract

Azelaic acid (AA) is occurring asdicarboxylic acid naturally that is produced by *Malassezia furfur*, found in rye, barley, grains and animals. It is a complex molecule with many diverse activities. It includes anti-inflammatory, anti-bacterial, keratolytic, comedolytic, and anti-oxidant activity. AA has an anti-inflammatory action by scavenging action of free oxygen radical. Azelaic acid is used topically to reduce inflammation due to acne and rosacea. The physiological effect of this acid produced by decreasing protein synthesis and sebaceous gland activity. There has been record of it being used as antineoplastic agent (the one that prevents tumour) but its mechanism of action is still unknown. This wonderful acid is also known to have its role in treatment of schizophrenia. In this review, we reviewed the neurological effects of azelaic acid and the new approaches in the area.

**Keywords:** Azelaic acid, Pharmacological activities, Treatments.

### Introduction

Natural molecules are always the first choice for the treatment of several diseases. The researchers have explored therapeutic potential of various natural compounds in in-vitro and in-vivo studies. Therapeutic activities of phytochemicals were observed by using PASS software (Kumar *et al.*, 2018; Kumar *et al.*, 2018). The plant extracted compounds are basically phenolic compounds or standardized extracts of particular plant like: Hesperidine (Habibyar *et al.*, 2016), Boswellic acid (Mehta *et al.*, 2018), INM-176 (Kumar *et al.*, 2017), Betain (Kaur *et al.*, 2019), Fisetin (Kumar *et al.*, 2019), Gallic acid (Manshare *et al.*, 2018), Sinomenium (Gupta *et al.*, 2019), Dioscoriavillosa (Satija *et al.*, 2018), Psidiumguajava (Mehta *et al.*, 2018), podophylotoxin and kaempferol (Dar *et al.*, 2017), epigallocatechingallate (Anand *et al.*, 2017), *Oscimuntenuiflorum* (Sharma *et al.*, 2017), *Crataevanurvala bark* (Kaur *et al.*, 2017), *Sida cardifolia* (Khurana *et al.*, 2016), herbal drugs (Bawa *et al.*, 2019), *Sphaeranthus indicus* Linn leaves extract (Mansoori *et al.*, 2018), *Piper betle* L. (Betel leaf) (Sarma *et al.*, 2018), extracts of pumpkin (Sharma *et al.*, 2020), bioactive compounds (Dhiman *et al.*, 2020), role of Biochanin A and Genistein with 9 Omega-3-fatty Acids (Rao *et al.*, 2020), extracts obtained from floral spikes of *Prunella vulgaris* L. (Ahmad *et al.*, 2020), *Artemisia indica* (Nahid *et al.*, 2017), *Paris polyphylla* (Mayirnao *et al.*, 2017), *Heracleum afghanicum* Kitamura leaves (Amini *et al.*, 2017), antifungal potential of ethanol extracts of *Allium sativum* and *Allium ampeloprasum* (Khan *et al.*, 2017), extraction of oleaginous flaxseed constituents (Sharma *et al.*, 2019), berberine (Feng *et al.*, 2019) and the plant extracts of *Mimosa pudica* L. (Kaur *et al.*, 2011). AA is a saturated dicarboxylic acid analogue. It is obtained in wheat, rice, barley and in small amounts in human body. It is formed from "*Malassezia furfur*", also known as *Pityrosporumovale*; a species of fungus basically originated on human dermis. AA is a very weak acid, much weaker than vinegar with plasma levels

ranging from 20-80ng/kg. It is found to have *in vitro* antimycotic properties, antimicrobial and keratinization normalizing properties which is why 20% AA cream is used in the treatment of acne vulgaris. Whereas, evidences, it's working out with other drugs have been established as effective. The twenty percentazelaic acid ointmentis reported effective as monotherapy in moderate pimple when comparable to benzoyl peroxide (5%); tretinoin (0.05%) and tropical erythromycin (2%). AA has excellent local tolerability, inhibit the growth of acne causing bacteria and keep skin pores clear. Some studies exhibit that AA manifests its effect by inhibiting protein synthesis in anaerobic bacteria particularly *Staphylococcus epidermidis* and *Proionibacterium*. In such cases of aerobic bacteria, it reversibly inhibits several oxido-reductive enzymes such as enzyme tyrosinase; mitochondrial enzyme of respiratory chain; thioredoxinreductase and DNA polymerases. In anaerobic bacteria, it impedes glycolysis. It is effective against both inflamed and non-inflamed lesions. It's mostly expelled in urine which endures of  $\beta$ -oxidation to shorter chain of dicarboxylic acids. Although, there is not much information on the acid's role in neurological disorders, it is found that AA has role in the treatment of multiple sclerosis (Ahumada-Pascual *et al.*, 2019).

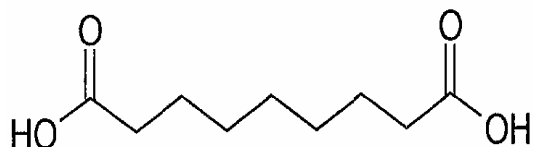
### Source

It is found in wheat, rice, barley, animal products and in small amounts in human body. AA is obtained from *Malassezia furfur* which is known as *Pityrosporumovale*. AA is a species of fungus normally originate on dermis of human(Schallreuter and Wood, 1990).

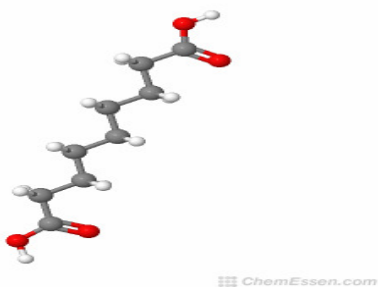
### Synonyms

Nonanedioic acid (IUPAC), Anchoic acid, Azelex, Finacea(Schallreuter and Wood, 1990).

## Structure



**Fig.1** : Structure of Azelaic acid  
(Schallreuter and Wood, 1990)



**Fig. 2** : 3D Structure of Azelaic acid  
(Schallreuter and Wood, 1990)

## Formula and Molecular weight

**Formula:** C<sub>9</sub>H<sub>16</sub>O<sub>4</sub> (Schallreuter and Wood, 1990)

**Molecular weight:** 188.22 g/mol (Schallreuter and Wood, 1990)

## Therapeutic effects

### 2.4.1 AA in facial acne

The pilosebaceous unit acknowledged to acne which is a common, chronic and inflammatory disease. It has a substantial impact on quality life of patients, particularly when lacerations happen on cosmetic sensitive portion. The chemical flaking is a term used in the cure of acne vulgaris. In some cases, it is recognized nearby AZ peels. In one of the research outcomes, AA was reported in reducing the amount of secreted sebum, and decreasing lesions of pimples. In a clinical study, about 35 women having face acne lesions were participated for clinical study of AA. At least six treatment at every two weeks were given to all subjects volunteers. As per the clinical study, 20% AA cream was applied twice daily for six months. In this clinical observation lentigomaligna was considered as its parameter that were recognised by the slowly reduction in pigmentation as well as lesion shrinkage. AA has a therapeutic effect against the phototoxic hyper pigmentation. Where, it was observed a significant reduction of secreted sebum. The severity of the disease was measured. In this study, reduction of sebum is speculated that observed results in patients can be stable (Szymańska *et al.*, 2019).

Organic molecules are going to very popularized options as cosmetic agents in many products. Organic molecules derived from the plants was found effective in melanin synthesis by various mode of actions. In most of the studies, it was found that 15 to 20% AA was administered twice daily for three to twelve months, in which the efficacy of AA was considered with the 2% and 4% hydroquinone cream, in attenuation hyper pigmentation and lesion shrinkage. These molecules are widely used as an anti-aging and antioxidants. This is known about the formulation and growth of organic molecules that have a desire therapeutic effects without any adverse effect (Zaid and Al Ramahi, 2019).

It has been established that AA was observed as practical as intragastric tetracycline in the cure of vulgaris pimples. In an evaluation of effects of anti-acne drugs, AA was found to be alone as effective as both benzoyl peroxide (5%) and clindamycin (2%) when treated for a span of 4 months. As far as toxicity of AA is concerned, oral LD<sub>50</sub> in rat is more than 5g/kg (Aprianiet *al.*, 2019).

## AA in Rosacea

AA in Rosacea was utilized to design a non-conventional and prospective design. A trial was conducted in the United State; first the patient's recruitment information was advertised for the greater or equal age of 18 years. The Equal and higher to 18 years old patient were recruited The patients were recruited as per criteria selection. The 54 patients were met the eligibility criteria of selection in which all patients were belong of age 26 to 63 years. The inform consent was given to all patients who are going for the topical treatment of rosacea. After all these, online survey tool was used for survey regarding the treatment of rosacea. During this survey, Rosacea related questions were asked from the patients. The trial result of Rosacea was in favour about 74.1% patients have no concern with this treatment. The 59.3% patients were found to have mild symptoms. Furthermore research on this Rosacea is require to compare the results of the two studies (Williamson *et al.*, 2019).

## Role of AA in various diseases

### In treatment of hyper pigmentation

A study aimed to developing nanoemulsion of AA with hyaluronic acid (HA) that can give double targeting strategy. This nanoemulsion loaded AA with HA can enhance the drug retention and tyrosinase blocking action. From the various research papers, this was extracted that the study was industrialized of o/w nanoemulsion. Then nanoemulsion was evaluated by using the several parameters such as droplet size distribution, zeta potential, pH value, drug content, encapsulation efficiency, stability, spectroscopic characteristics, and morphology. After all these parameters evaluation, the nanoemulsion was observed to have characteristics within the nanoscale. This was reported that it absorbed in the deeper layers of the derma, and also observed to have significant effect as tyrosinase blocker *in vitro* study. Therefore, this could be a promising treatment of the skin (Jacobus Berlitz *et al.*, 2019).

## Novel approaches

AA nanocrystals and its dermal uses performance study of in situ hydrogels

Hydrogel have improved solubility and dissolution rate. It was found that the topical application of AA nanocrystal (hydrogels) was self-possessed Pluronic. In a study, this was considered that the mixture can transfer the stratum corneum and deeper to the dermis layers. As per this study, it evaluated the effects of polysorbate 60. Polysorbate 60 is used *in situ* gelation agent and hyaluronic acid. A drug release was governed that define the connection between the penetration and the rheological properties of the gels of AA. It composed hydrogels to reveal pseudoplastic flow behaviour with enhance Pluronic level. Therefore, hydrogel loaded nanocrystal of AA was found to have a beneficial effect and considered as a novel approach (Tomić *et al.*, 2019).

## Neurological disorders related to AA

### PD risk in patients with rosacea

AA is used as an anti-inflammatory skin treatment conditions. This conditions are grown due Rosacea. The Rosacea is well known by basics evere skin inflammation that is characterized by transient erythema. The Parkinson's disease is well characterised by the motor symptoms. The neuroinflammation and loss of neuron and dopamine level occur in PD. *In vivo* study, it was found that MMP-3 gene leads to greater promoter action associated with the higher risk of neurode generation in patients with Rosacea. As per the several research papers, it has been postulated that the greater rate PD in Rosacea patients were found, noted by Fischer in 2001. This study resolve the overlaps investigating the concomitant occurrence of PD. PD is associated with the seborrheic skin inflammation. The sensitivity was analysed in patients with Rosacea. In this study, tetracycline was considered to decrease the risk of PD patients with Rosacea (Wingo, 2016); (Egeberg *et al.*, 2016).

### In treatment of Multiple Sclerosis

A research study was conducted on multiple sclerosis (MS). As per this study, it was concluded that MS is a greater frequency neurological disorder in young adults. Moreover, there are some genetic and environmental factors that have been identified to relate the onset of the disease. Now days, it is not quite possible to say, that MS can neither be prevented nor its symptom effectively treated due to heterogeneity of disease. Therefore, to fill out this research gap in MS, The most of the research of prognostic factors and new therapeutic compounds are going on among clinicians and researchers. In a research article, it was reported that GEMSP consists of functional constituents mixture. The GEMSP compound is emerging drug for MS treatment. In a clinical study of GEMSP, an open clinical trial was conducted on humans' volunteers who found the effective consequence in MS. A biochemical characterization of main constituents of GEMSP was performed which include fatty acids as oleic acid; linoleic acid; or azelaic acid; the antioxidants "alpha-tocopherol"; and ascorbic acid provided in order to understand their proved therapeutic effects. It was found to be effective in case of MS. In one of the study, patients with MS were observed to form the antibody against endogenous AA (Ahumada-Pascualet *et al.*, 2019).

An antioxidant level in blood and catecholamine metabolites level in urine patients with beta-thalassemia

The most of study suggested that iron overload in  $\beta$ -thalassemia leads to enhance generation of reactive oxygen species. A study was conducted over on 17 males and 31 females of age 11-22 year with the  $\beta$ -thalassaemic patients. In this intervention, plasma and lymphocyte levels were checked. The level of vitamin E, ubiquinol, and ubiquinone were observed in plasma. Literature research postulated that the urine sample at 24 hours was collected routinely. The sample were properly analysed in laboratory and simultaneously the blood sample were collected to analyses. After statistical calculation, it was considered a significant correlation between vitamin E and non-transferrin-bound iron. This also can have a harmful effects on the development of the disorder (De Luca *et al.*, 1999).

### The photochemical hyper pigmentation and Malignant Melanoma

In a study, it was claimed that 20% AA topical application for up to 4 month treatment was reported to have satisfactory consequence in hyper pigmentation. Therefore, 20% AA has no depigmentation effect on normal dermis pigmentation. As per the research study, AA also has no effect on pigmentation later exposure of UVA; UVB and visible light. Recently, sufficient information from the clinical research study is not available to explain the proper role of AA to cure malignant melanoma. In a study, the 69 year old person with malignant lesion was observed to get relief after applying 20% AA cream. Three months later, biopsy was performed which showed the attenuation in number of atypical melanocytes. From these studies, it was concluded that AA should not be used as initial treatment (Nguyen and BUI, 1995).

## Summary and Conclusion

AA is a very common ingredient used in treatment of acne and mostly available as a topical medication. Not much of the role of AA in neurological diseases is known till date but it has role in diseases like PD and MS. PD and other neurological diseases displayed increment of loss of neuron. From the above reported studies, it recognized that the hyperhidrosis and facial flushing are generally considered manifestations of autonomic deregulation. Therefore, rosacea is very common in patients with PD. Also risk of PD subjects with rosacea is higher. AA is used as a first line therapy for the treatment of rosacea. It has been reported in various research that a serious relationship to both MMPs and peptides in rosacea dermis. This can supplementary excite to inflammation. The matrix metalloproteinases were observed to have an implication in the pathogenesis of PD and other neurodegenerative disorders. As per the various experimental models of PD; the MMP-3 and MMP-9 levels are enhanced with loss of dopaminergic neuron. The GEMSP consists constituents such as lipids, free radical scavengers and amino acids. This is linked individually to poly-L-Lysine (PL), for emerging as a promising drug in MS treatment. In a study, GEMSP was described with various constituents that are fatty acids as oleic acid; linoleic acid; or azelaic acid and the antioxidants "alpha-tocopherol". It was given in order to understand their demonstrated therapeutic effects which have proved to be effective in case of MS.

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