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Persea Americana's Extract Could Offer Effective Treatment for Amyotrophic Lateral Sclerosis: A Hypothesis

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ABSTRACT

Background: Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease characterized by the degeneration of upper and lower motor neurons in the central and peripheral nervous systems. Several pathological conditions, including neuroinflammation, oxidative stress, and mitochondrial dysfunction, contribute to the degeneration of motor neurons. Despite extensive research, no current drug therapies have proven effective in treating ALS.

Purpose: This study explores the therapeutic potential of Persea americana (PA) Mill, commonly known as avocado, in the treatment of ALS.

Methods: The review draws on pre-clinical and clinical studies that have demonstrated the neuroprotective effects of PA extracts (PAE) in diseases such as Alzheimer's and Parkinson's, highlighting the potential mechanisms that may be relevant to ALS.

Results: Although no studies have directly investigated the effects of PA on ALS, the bioactive compounds in PA have shown promising results in mitigating neurodegenerative processes through their diverse biological activities.

Conclusion: Based on existing evidence from related neurodegenerative conditions and the mechanisms involved in ALS pathology, it is hypothesized that PA extracts may offer a novel therapeutic avenue for ALS. Further research is required to validate the efficacy of PAE in managing ALS symptoms and slowing disease progression.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is classified under neurodegenerative disease (NDs). ALS is also called Lou Gehrig's disease, Charcot's disease, and motor neuron disease (Evans *et al.*, 2013). It is a paralytic condition in which degeneration of motor neurons occurs in the central nervous system (CNS). ALS affects the body's physiology such as muscle twitching, stiff muscles, weakness of hands and legs, problems in swallowing, chewing, and speaking. Sometimes patients with ALS also suffer from an abnormality in cognitive and psychotic functions. Moreover, due to respiratory paralysis patients' death may occur in nearly 3 to 5 years (Brown & Al-Chalabi, 2017; Rowland, 2010). The pathophysiology of ALS is very broad and many genetic as well as cellular changes can be responsible for the degeneration of upper and lower motor neurons. Neuroinflammation (McGeer & McGeer, 2002), oxidative stress (Robberecht, 2000), mitochondrial dysfunction (Shi *et al.*, 2010) and some genetic changes (C9ORF72 repeat expansion) are mentioned by several authors in previous studies (Byrne *et al.*, 2012; Cooper-Knock *et al.*, 2014). Mutation in inflammatory mediators (IMs) in CNS can affect neurons and is responsible for several NDs (Chen *et al.*, 2016; Guzman-Martinez *et al.*, 2019). IMs such as Tumour necrosis factor alpha (TNF-α), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Interleukin $(IL)_{6 \text{ and } 8}$ produce inhibitory response to brain cell and these are also responsible for the intracellular inflammation that may lead to apoptosis of neuronal cells.

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2. The Proposed Hypothesis

Persea Americana Mill (PA) is commonly known as avocado, alligator pear, and butter fruit. It belongs to the Lauraceae family. The fruit's extract contains various chemical constitutes such as vitamin A, B_2, C, E, K, folic acid, glycosylated abscisic acid, cellulose, polygalacto urease, polyuronoids, volatile oils, lutein, coumarin, zeaxanthin, linoleic, oleic, palmitic, stearic, linolenic, capric, myristic acids, coenzyme Q10 and beta-carotene. PA's seeds, peels, pulp, leaves and oil contain various other therapeutically active chemical constituents (Table 1). Various literatures reported that PA extract (PAE) has very good antioxidant, anti-inflammatory, anti-apoptosis, antiplatelet, antithrombotic (Rodriguez-Sanchez *et al.*, 2015), anti-cancer (Lara-Márquez *et al.*, 2020) and free radical scavenging activity (Alkhalaf *et al.*, 2019). It has also shown potential against some NDs such as Alzheimer, Huntington and Parkinson's disease in preclinical trials (Ameer, 2016). The PA fruit extract also has potency to minimise mitochondrial dysfunctions (Ortega-Arellano *et al.*, 2019; Silva-Platas *et al.*, 2012) (Table 1). PAE has numerous potential activities and it also possesses neuroprotective activities. Based on aforementioned pharmacological activities of PAE obtained from different parts of PA, it can be anticipated that PAE can be helpful in minimizing the symptoms of ALS in patients suffering from it.

Table 1: Chemical constituents and medical uses of various parts of PA

Extract of different parts of PA	Chemical constituents	Medicinal use	References
Seed and endocarp	Phytosterols, triterpenes, fatty acids, and abscisic acid.	Antioxidants, antimicrobial, anticancer, immunity booster, antioxidant, antihypertensive, hypolipidemic, larvicidal, fungicidal, amoebicidal, and giardicidal.	(Alkhalaf *et al.*, 2019; Bhuyan *et al.*, 2019; Ejiofor *et al.*, 2018; Padilla-Camberos *et al.*, 2013; Rodríguez-Carpena *et al.*, 2011)
Peels (exocarp)	Phenolic compounds, flavonoids, linoleic, oleic, palmitic, stearic, linolenic, capric, and myristic acids.	Antioxidants, antimicrobial, and anticancer.	(Bhuyan *et al.*, 2019; Rodríguez-Carpena *et al.*, 2011)
Pulp (mesocarp)	Carbohydrates, fat, proteins, fibers, sterols, alcohols, tocopherols, and carotenoids.	Antioxidants, antimicrobial, anticancer, anti-inflammatory and useful for the treatments of diabetes and cardiovascular disease.	(Bhuyan *et al.*, 2019; Mooz *et al.*, 2012)
Leaves	Coumarin, scopoletin, catechin and epicatechin.	Produces action against neurodegenerative disease, cancer, and skin diseases. It also controls cholesterol.	(Yasir *et al.*, 2010)
Oil	Polyunsaturated fatty acids, tocopherols, polyphenols, and phytosterols. Saturated fatty acids, predominance of palmitic acid. Monounsaturated fatty acids, predominance of oleic acid.	Enhances mitochondrial functions, minimizes free radical production, and oxidative stress. It also has anticancer and anti-inflammatory effects. In low dose, it diminishes insulin resistance and glucose tolerance while in high dose, it reduces the body weight.	(Del Toro-Equihua *et al.*, 2016; Flores *et al.*, 2019; Ortiz-Avila *et al.*, 2015)

3. Justification of Proposed Hypothesis

3.1. Anti-inflammatory Activity

It has been reported that several genetic factors, such as TANK Binding Kinase 1 (TBK1), Optineurin (OPTN), and Sequestosome-1-p62 (SQSTM/p62) are responsible for the mutation of proteins. This may lead to inflammation of neuronal cells (Brown & Al-Chalabi, 2017). In addition to this, inflammatory mediators such as TNF-α, NF-κB, $IL_{6 \text{ and } 8}$ can also enhance neuroinflammation, which may lead to degeneration of the motor neuron (Brown & Al-Chalabi, 2017). Adeyemi *et al.* (2002) have reported that aqueous

extract of leaves of PA has analgesic and anti-inflammatory properties. PAE has shown significant analgesic and anti-inflammatory activity in a dose dependent manner as compared to acetylsalicylic acid and morphine (Adeyemi *et al.*, 2002). As per Hong *et al.* (2019) ethanolic extract of PA has shown a positive response against colitis by inhibiting protein and mRNA expression levels of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and pro-inflammatory mediators such as TNF-α, interleukin (IL)-6, and IL-1β. This study has reported that ethanolic extract of PA suppresses dextran sulfate sodium (DSS)-induced colitic mice. In addition, ethanolic extract of PA is also reported to inhibit NF-κB, signal transducer and activator of transcription 3 (STAT3) (Hong *et al.*, 2019). PA seed extract contains a rich number of chemical constituents which have very good anti-inflammatory effect. In cell line study, seeds of PA have been reported to reduce the production of IL-6, IL1β and TNFα. PAE is also reported to reduce NF-κB in nuclear translocation pathways (Dabas *et al.*, 2019). In one of the recent studies, aqueous leaf extract of PA is reported to reduce the symptoms of fatty liver through its anti-inflammatory property (Brai *et al.*, 2020).

3.2. Anti-oxidant Activity

Oxidative stress causes occurrence of several diseases into the body. It is very much responsible for progression of NDs and many literature reported that oxidative stress is also responsible for the ALS. Various studies proven that PAE has very good antioxidant activity, which reduces free radical production into body. 90% of ethanolic extract of PA leaf contains good amounts of flavonoids, saponins, tannins, triterpenoids, and steroids. These phytochemicals have the super antioxidant property and can be used for averting some diseases associated with oxidative stress (Rahman & Dewi, 2018). PA plant contains diverse polyphenolic compounds with strong antioxidant effects which have potency to treat many disease (Castro-López *et al.*, 2019). Amado *et al.* (2019) determined the antioxidant and antibacterial properties of four varieties (Quintal, Fortuna, Margarida, and Hass) of PA peel, pulp, and seed. They found that ethanolic extract of Quintal variety peel has the greatest antioxidant and antibacterial activity as compared to others. Bhuyan *et al.* (2019) reported antioxidant effects of PA's seed, and leaves. They also reported that due to the antioxidant effect, PA can produce positive effects against different types of cancers. In one of the studies, PA's fruit extract has shown antioxidant effect by inhibiting peroxidase, catalase, superoxide dismutase (SOD) and L-ascorbate peroxidase(Zhang *et al.*, 2013). The antioxidant mechanism of PAE are presented in Figure 1.

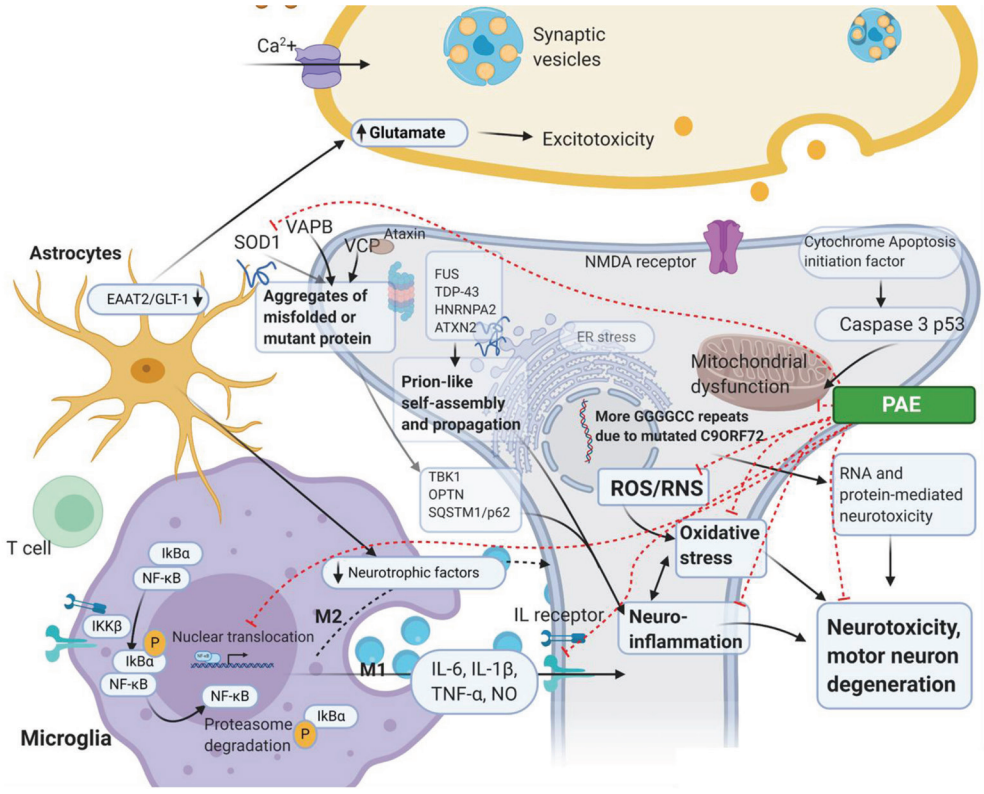

Figure 1: Possible role of PAE against ALS.

Molecular pathways are the leading causes of ALS pathogenesis. Increased levels of ROS/RNS, oxidative stress, mitochondrial dysfunctions, excitotoxicity and neuroinflammation are responsible for the neurotoxicity and degeneration of motor neurons. Many misfolded or mutated proteins and inflammatory mediators such as IL6, IL1β, TNFα, and NO directly and indirectly increase the neuroinflammation. This leads to the apoptosis of motor neurons. Moreover, these inflammatory mediators also activate the NF-κB nuclear translocation signaling pathways which enhance neuroinflammation. Apart from this some genetic changes such as mutation in C9ORF72 due to multiple repeats of GGGGCC nucleotide increases RNA and protein mediated neurotoxicity. PAE loaded SNEDDS may produce neuroprotective effects in CNS due to enhanced absorption of bioactives present in it which are further anticipated to get permeated through BBB due to their nano size. Upon reaching to brain it may produce antioxidant and anti-inflammatory effects as well as it may enhance mitochondrial functions. In addition to this, PAE may directly target IL6, IL1β, TNFα, and NF-κB and thus reduces neuroinflammation.

3.3. Enhance Mitochondrial Function

PAE have chemical constituents which are very nutritious as well as good for health. In the previous literature, the presence of chemical constituents such as lutein has been reported, which have protective effects on mitochondrial membrane potential ($\Delta\Psi m$) and mitochondrial respiration (Dreher & Davenport, 2013; Ortiz-Avila *et al.*, 2015). It also reduces the mitochondrial oxidative stress due to its antioxidant effect by diminishing ROS level and lipid peroxidation and enhances adequate mitochondrial functions in brain by maintaining mitochondrial redox state (Ortiz-Avila *et al.*, 2015).

3.4. Other Possible Mechanism

Fruit extract of PA are reported to contain α-linolenic acid which has neuroprotective effect. Moreover, it is reported to improve cognitive functions. It also contains fatty acids which enhance membrane fluidity and level of polyunsaturated fatty acids. The polyunsaturated fatty acids help in the formation of phospholipids in the membranes of the neurons and thus it may directly improve neuronal function, neuroprotection and synaptic plasticity by signaling cascades in neuronal cells (Ameer, 2016; Kapoor *et al.*, 2018; Vishwas *et al.*, 2020a; Vishwas *et al.*, 2020b).

4. Conclusion

There are many pathological pathways associated with ALS but none of the drugs has shown complete relief against the disease. Herbal medicines are very much effective from the ancient time throughout the world due to presence of many phytochemicals that can work through multiple pathways. In addition to that, they are considerably non-toxic as compared to synthetic drugs. PAE contains various active phytochemicals which have antioxidant, anti-inflammatory and anti-apoptosis properties as well as they also enhance mitochondrial functions effects. Owing to these many pharmacological activities it is anticipated that PAE could offer neuroprotective effect for treating ALS.

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Authorship Contribution

Sukriti Vishwas: Methodology, data curation, and writing – original draft; Bushra Bashir: Methodology; Nikhil B. Khandale: Methodology; Uma Devi: Methodology; Sachin Kumar Singh: Conceptualization, validation, supervision, and writing – review & editing.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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