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Review Article

Mechanistic Role of Phytophenolic Acids in the Management of Alzheimer's Disease: A Comprehensive Review

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ABSTRACT

Alzheimer's Disease (AD) or dementia, is a brain illness, which is chronic and non-reversible and is related to advanced memory loss, cognitive decline and altered behaviour. Current treatments including synthetic agents mostly have an effect of only providing relief to the patient without treating the root cause of disease. Though synthetic drugs available for the treatment but are only few and are associated side effects. A better alternate will be the traditionally used herbal drugs in the treatment of neurodegenerative diseases. Phenolic acids are secondary metabolites in plants and current evidence indicates that they can be useful in the treatment of AD because of their antioxidant, anti-inflammatory and neuroprotective. The present review explores the multifaceted functions of phenolic acid which include neutralizing Reacting Oxygen Species (ROS), preventing amyloid-beta aggregation, reducing hyperphosphorylation of tau protein and modulating neuro-inflammation. Several phenolic acids such as gallic acid, ellagic acid, caffeic acid, ferulic acid, coumaric acid, etc. Have demonstrated significant neuroprotective effects in various preclinical studies. The mode of action phenolic acids can be identified to produce better and more attuned treatments. Similarly, the synergistic effect exerted by phenolic acid when combined with other medical agents will enhance the potential efficacy of other drugs. In conclusion, the present review is an attempt at extensive and elaborated information regarding phytophenolic acids, with significant promise in fighting AD based on their antioxidant, anti-inflammatory and neuroprotective properties as a multi-faceted approach to the complex pathology in AD.

Keywords: Alzheimer's disease, Amyloid-beta, Cognitive decline, Neuroprotection, Phenolic acids, Tau protein.

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INTRODUCTION

Phenolics

Vascular plants create a wide range of organic compounds called secondary metabolites, which serve vital structural support functions while also protecting the plant. Which are among the most effective and abundant in the plant kingdom.[1] Phenolic acids are classified as natural and synthetic and contain a phenolic ring carrying at least one carboxylic acid functional group. Phenolic acids play important functions not only as a defence mechanism for the plant but also aid in the color, flavor and nutrition of most foods derived from plants. To date, over 8000 phenolic compounds have been identified from natural sources, which are broadly categorized into classes like flavonoids, lignans, coumarins, stilbenes, and tannins. Phenolic acids are also internal physiological regulators that control plant growth and therefore are essential for the development and survival of plants.[2,3] In general, most phenolic compounds in plants are formed by the shikimic acid pathway followed by the synthesis of phenylalanine, which acts as a precursor to most of the phenolic compounds. Such phenolics are further modified through various enzymatic conversions to yield the extensive array of phenolics found in plants.[4]

Classification of Phenolics

Phenolic and polyphenolic chemicals are categorized into several groups that include flavonoids, stibenes, coumarins, lignans

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and tannins. They are more specifically present in many natural matrices such as grains, legumes and nuts. These acids build bridges with macromolecules like as cellulose derivatives, which aid in the development of cell wall matrices resulting in compact and structurally rigid cell walls.[5] Phenolic acids generally contain a phenolic ring and one or more carboxylic acid groups. They may be of natural and synthetic origin.

Natural

Natural phenolic acids are a group of naturally occurring substances that can be found in different traditionally used plants, fruits and vegetables. Generally, they are categorized into two groups: benzoic acid and cinnamic acid derivatives. The detail information about the names of the cinnamic acid and benzoic acid derivatives, their structures, sources and therapeutical applications are given in Tables 1 and 2.[6]

Synthetic phenolic acids

Although phenolic acids and their derivatives are proven to be therapeutically potent in the treatment of various illnesses, isolation and identification of them is a tedious process involving high cost and longer duration. Hence an alternative will be the synthesis of the same in the laboratory that has been proven to be cost effective and faster. Synthetic phenolic acids prepared in laboratories can be utilised for various industrial applications or to mimic natural phenolic acids. These compounds are found to be equally potent and of high purity.[2,7]

Phenolic acids are classified synthetically into two main categories based on their structure hydroxybenzoic acids and hydroxycinnamic acids.

Hydroxybenzoic Acids

These compounds have a benzoic acid core structure (C6-C1), where a (-OH) is linked to the aromatic ring. Examples include,[8,9] Para-hydroxybenzoic acid, Protocatechuic acid (3,4-dihydroxybenzoic acid), Gallic acid (3,4,5-trihydroxybenzoic acid), Vanillic acid (4-hydroxy-3-methoxybenzoic acid).

Hydroxycinnamic Acids

These are derived from cinnamic acid, characterized by a three-carbon chain linked to the aromatic ring. Examples include Caffeic acid (3,4-dihydroxycinnamic acid), *P*-Coumaric acid (4-hydroxycinnamic acid), ferulic acid (4-hydroxy-3-methoxycinnamic acid), sinapic acid (3,5-dimethoxy-4-hydroxycinnamic acid).

Alzheimer's Disease (AD)

Overview

AD is a progressive illness of the brain which affects memory, thinking and behavior. It accounts for over 60% of all cases of dementia in elderly people and millions of people are suffering from this ailment. The pathogenesis of AD involves multiple factors, including genetic, environmental, lifestyle, age, gender, infections, head injuries, etc., Mutations in genes such as APP (Amyloid Precursor Protein), PSEN1 (Presenilin 1) and PSEN2 (Presenilin 2) are associated with early-onset familial AD, while the APOE ε4 allele is a major genetic risk factor for late-onset sporadic AD. Environmental factors such as diet, physical activity and exposure to toxins also contribute to the development and progression of AD.[10,11]

In its pathological manifestations, features that define AD include amyloid-beta plaques and neurofibrillary tangles that is, hyperphosphorylated tau proteins that cause neuronal damage and brain atrophy. That is why, besides the aggregation of Aβ, oxidative stress, neuroinflammation and cholinergic dysfunction stand as key mechanisms contributing to the progression of the disease.[12,13] Until now, the source of Alzheimer has not been effectively identified but there are many theories on this issue. Despite this, currently available medications do not cure AD but just help in managing the symptoms.[14]

MATERIALS AND METHODS

In this review we explored the mechanistic role of phytophenolic acids in the management of AD. Including the various method for identification, quantification and therapeutical role of the phenolic acids. The study includes Amyloid-beta Peptides, Tau Proteins, Neurofilament Light Chain, Oxidative stress, Inflammatory Cytokines and future directions and challenges. The data was collected by comprehensively searching various scientific search engines i.e., PubMed, Google Scholar, Web of Science, Science Direct, MDPI, etc.

Methods of Identification and Quantification

Various identification methods are employed to identify polyphenolic compounds, including ferric chloride test, shinoda test, gelatin test, etc. along with quantitative tests like total phenolic, flavonoid and tannin content determinations. Additionally, various sophisticated methods are introduced for isolation, identify qualitatively and quantify of phenolic acids present in the extracts, fractions and various herbal formulations that include: Chromatographic techniques: HPLC, HPTLC and GC are commonly used for the isolation, identification and quantification of phenolic acids.[15] Spectroscopic techniques: UV-visible spectroscopy,[16] MS[17] and NMR[18] techniques are employed for identification based on unique absorption, mass and magnetic properties of phenolic acids. Electrophoretic Techniques: The Capillary Electrophoresis (CE) method is also used in order to separate and evaluate the phenolic acids with a difference in charge and in size.[5,19]

Therapeutical Role of Phenolic Acids

Phenolic acids have been extensively studied in relation to their medicinal applications are antioxidant, anti-inflammatory, anticancer, antimicrobial, neuroprotective and anti-diabetic activities (Tables 1 and 2, Figure 1). With these properties, phenolic acids seem to be great hopeful precursors for developing natural therapeutic reagents.

Antioxidant activity

Phenolic acids are known for their strong antioxidant activity. Free radicals and ROS are associated with the pathogenesis of many diseases, including AD.[20] The antioxidant capacity of phenolic acids is attributed to their capability to donate hydrogen atoms or release electrons. It also tends to form chelate complexes with metal ions and tends to bind to cell components and protect them from oxidative damage by damaging lipids, proteins and DNA.[2]

Anti-inflammatory activity

Inhibitions of inflammation are manifested through a decrease in the severity of pro-inflammatory and enzymes like COX-2 and LOX.[21] Such an anti-inflammatory effect could be very relevant to neuroinflammatory conditions like AD. It may even fight from destructions that result from chronic inflammation in the brain and hence bring about a decrease in inflammation.[22]

Anticancer properties

Some phenolic acids have exhibited anticancer activities through promoting apoptosis and suppressing cell proliferation and metastasis.[23] These properties characterize them as candidate drugs for cancer therapy as such effects are linked to modification of several signalling pathways and gene expressions that pertain to the regulation of cell cycle and apoptosis.[4]

Antimicrobial activity

Antimicrobial effects of phenolic acids are demonstrated against a broad spectrum of pathogens, encompassing bacteria, fungi, and viruses. This makes them useful in the development of natural antimicrobial agents.[24] Even their capacity to rupture microbial cell membranes, interfere with microbial enzyme activities that lead to the inhibition of the growth and reproduction of microbial pathogens.[3]

Neuro-protective activity

Phenolic acids exhibit neuroprotective effects.[25] These have resulted in the abolition of stress-induced oxidation as well as inflammation, both of which are believed to be significant contributors to neurodegenerative diseases like AD and Parkinson's. However, major phenolic acids include gallic acid, ferulic acid and caffeic acid.[26] which has been shown to minimize oxidative damage and the aggregation of amyloid-beta and tau proteins. Neuroprotection remains the main potential therapeutic use of their neuroprotective activities.[27]

Anti-diabetic activity

Plant-based phenolic acids are a class of bioactive chemicals that show promise in the treatment of diabetes.[28] These acids, like caffeic acid, ferulic acid and chlorogenic acid, have been reported to maintain blood glucose levels by their action on improving insulin sensitivity, attenuation of oxidative stress and inhibition of other key enzymes in the system, such as α-glucosidase and α-amylase, which participate in carbohydrate metabolism.[29]

BIOMARKERS IN ALZHEIMER'S DISEASE

Biomarkers, often known as "biological markers," are medical signals that may be precisely assessed from outside the patient. Biological markers are basically any form of substance, structure, or process.[30] The National Institute of Health (NIH) created the Biomarkers Consortium to speed up the development of innovative health technologies, medications and therapies aimed at improving early detection, prevention, diagnosis, prognosis and treatment of various diseases.[31] It represents the physiological state and how it is influenced by a disease or other pathological condition.[32] This could be assessed in/outside the body and may affect any changes in the body and the likely prevalence of any disease in the human body. Biomarkers play a crucial role in the diagnosis and progression monitoring of AD and it includes amyloid-beta, tau proteins and Neurofilament Light chain (NFL), oxidative Stress markers and, inflammatory cytokines. Imaging biomarkers using the advanced techniques like Positron Emission Tomography (PET) scans and Magnetic Resonance Imaging (MRI) helps to assess the extent of brain changes associated with AD.[13,14]

Formation and role of Amyloid-beta in Alzheimer disease

Amyloid Beta (Aβ) is a small protein that comes from a larger protein called APP which is found in the brain and helps with signalling between cells. The APP stretches across the cell membrane, with parts inside the cell, through the membrane and outside. It was acted upon by two enzymes working one after the other: Beta-Secretase (BACE1) and gamma-secretase. BACE1 cuts APP into two pieces: a soluble fragment and another piece known as C99. Then, gamma-secretase comes in to make another cut on the C99 piece, producing amyloid-beta peptides, mainly Aβ40 and Aβ42. Among these two, Aβ42 is the main type that forms plaques in AD and some plaques are entirely made up of Aβ42.[33]

Aggregation of Amyloid-beta Peptides

In (AD), Aβ levels disrupted, leading to its buildup and the formation of plaques. These plaques contribute to cognitive impairments.[34] The Aβ peptides can form oligomers, protofibrils

and fibrils. Initial oligomers are thought to be extremely hazardous and related with neurotoxicity. They can then combine into insoluble fibrillar structures, which create amyloid plaques in the brain.[35] The insoluble Amyloid Beta (Aβ) is collected because the brain fails to achieve a balance in the production and clearance of it. This imbalance brings about the formation of plaques that forms a basis of AD disease. These plaques surrounded by deteriorating neurons and glial cells are damaging to neurons and are one of the features of Alzheimer's pathology. Amyloid-beta peptides aggregate, leading to synaptic dysfunction thus ends up in neurodegeneration with cognitive loss in AD.[36,37] The most common type of sporadic AD is responsible for the suffering of more than 15 million worldwide and typically results from the failure of the brain to clear Aβ adequately, a process that is often inextricably linked with aging and a complicated mixture of genetic and ecological factors.[38] Familial AD is much less common and typically starts at a younger age. Familial AD has been known to exhibit strong heredity. It has been linked to mutations of certain genes involved in the metabolism of Aβ, such as APP and presenilin. Phenolic acids and amyloid beta aggregation: Phenolic acids prevent amyloid-beta aggregation, which helps to lower amyloid burden and protect neurons from amyloid-beta-induced toxicity.[22] The detail information about the potential phenolic acids and the dose at which they exhibit the inhibition of aggregation of amyloid-beta peptides is given in the (Table 3). One of the best phenolic acids like gallic acid has been shown to decrease in amyloid-beta plaque formation, a characteristic of AD. It accomplishes this by attaching to amyloid-beta peptides and inhibiting their aggregation. It's capacity to pass through the blood-brain barrier makes it a promising therapeutic agent, as it can directly affect the brain.[12] In addition to inhibition of amyloid-beta aggregation, it is also reported to reduces oxidative stress, antioxidant activity[39] metal chelation,[40] and anti-inflammatory actions by controlling cytokine production.[24] Caffeic acid, found in coffee, apples, rosemary, barley, wheat and pears plays a role in treating AD by lowering amyloid-beta levels, safeguarding neurons from oxidative stress and regulating inflammation. It decreases amyloid-beta by inhibiting the enzymes involved in its production.[2-4]

Tau Proteins and their role in Alzheimer disease

Tau proteins are essential for maintaining microtubule stability in neurons, can undergo pathological alterations in neurodegenerative conditions.[41] Tau proteins are synthesized within the neurons, mainly in the axons and are known as Microtubule-Associated Proteins (MPA) that stabilize microtubules. These may be considered critical components of the neuron structure and intracellular transport.[42] Tau proteins are phosphorylated at some sites, by which they interact with microtubules. However, upon hyperphosphorylation (too many phosphate groups are added) during neurodegenerative conditions reduces its ability to bind with microtubules causing it to detach. This leads to destabilization of microtubules and impairment of cellular functions. If these tau proteins are free, they misfold and assemble into soluble oligomers, eventually forming Paired Helical Filaments (PHFs).[43] These PHFs are twisted structures that consist of two strands of misfolded Tau proteins further aggregate into larger insoluble structures known as Neurofibrillary Tangles (NFTs) that accumulate in neurons.[44] The accumulation of NFTs disrupts intracellular transport, leading to neuronal dysfunction, synaptic loss and ultimately cell death. This abnormal tau aggregation is characteristic of other tauopathies such as frontotemporal dementia.[45] Tau aggregates are suspected to spread from AD one cell to another, spreading pathology throughout the brain. This appears to be by extracellular vesicles and exosomes or cell-to-cell contact.[46] Due to NFT formation and spread, neurodegeneration spreads widely in disorders such as AD, frontotemporal dementia and other tauopathies.[47] Details of phytoconstituents with the treatment ability in AD is given in (Table 3) Ellagic acid is one of the best phenolic acids shown promising results in the treatment of AD by inhibiting the hyperphosphorylation of tau proteins, minimizing oxidative damage and reducing inflammation. It protects neurons by lowering ROS production and boosting endogenous antioxidant defence.[22]

Role of Neurofilament Light Chain (NfL) in Alzheimer Biomarker

Neurofilament is an important component of myelinated axon of a neuron, and it is composed of NfL. It is a structural protein found in neurons and its levels in the blood and CSF rise with neuronal loss or degeneration, which is common in neurodegenerative illnesses mainly in AD. NfL is emerging as a potential biomarker for AD. Elevated NfL levels in Alzheimer's patients with axonal damage and have been linked to disease severity, cognitive impairment and brain atrophy.[48] NfL can be found in both the initial and final phase of AD, making it valuable for diagnosing and tracking disease development. Its presence in blood also makes it a less invasive biomarker than typical CSF tests. As a result, NfL has significant potential in clinical settings for early identification, prognosis and assessing treatment responses in AD. The most promising phenolic acids in the treatment of AD are caffeic acid, ellagic acid, ferulic acid and *p*-coumaric acid. Caffeic acid present in coffee and various fruits and vegetables, has neuroprotective effects that help reduce neuronal damage. It decreases amyloid-beta levels, protects neurons from oxidative stress and modulates inflammatory responses, which collectively contribute to lowering NfL levels. By maintaining neuronal integrity and reducing axonal damage, caffeic acid helps slow the progression of neurodegenerative processes [5,22,10] Caffeic acid also suppresses the activation of microglia and limits pro-inflammatory cytokines, thus reducing neuroinflammation. Animal studies have shown its potential to enhance cognitive function and alleviate inflammation in AD models.[12]

Oxidative stress and Alzheimer disease

Oxidative stress markers indicate the presence of oxidative damage in cells, which is a significant factor in the development of AD. Elevated levels of ROS mention in Table 3 are are commonly reported in patients with Alzheimer's diseases.[2,3] Huge number of scientific publications are published every year explaining the role of phenolic compounds with antioxidant activities. Ferulic acid, gallic acid, ellagic acid, caffeic acid, coumaric acid, etc. are found potential agents in the treatment of AD through antioxidant mechanism. Among these, ferulic acid has shown promise in the treatment of AD. It is found in seeds and leaves of various plants, particularly cereals, grains, and provides therapeutic benefits for AD through multiple mechanisms. It has strong antioxidant features enable it to eliminate free radicals and mitigate oxidative stress.[22]

Role of Inflammatory Cytokines as Alzheimer Biomarker

Inflammatory cytokines are signalling molecules that mediate inflammation. Chronic neuroinflammation, marked by elevated levels of pro-inflammatory cytokines including (Table 3) is a key feature of AD and contributes to neuronal injury and disease progression.[12] Few potential phenolic acids include coumaric acid, ferulic acid, gallic acid, ellagic acid, caffeic acid, etc. are shown beneficial effect in the management of AD by inhibiting the inflammatory cytokines. Coumaric acid is present in rich amounts in peanuts, tomatoes, carrots and basil and supports in the management of AD through several mechanisms. It inhibits acetylcholinesterase, that degrades acetylcholine, a neurotransmitter that is commonly inadequate in Alzheimer's patients. By blocking this enzyme, it also helps to increase acetylcholine levels, which can enhance cognitive function. Additionally, it reduces inflammation by inhibiting the synthesis of pro-inflammatory cytokines. The combined antioxidant, anti-inflammatory and acetylcholinesterase-inhibiting properties of coumaric acid make it a promising candidate for AD treatment.[13,14] Additionally, ferulic acid supports cognitive function by enhancing synaptic plasticity and promoting neuronal survival. It also helps reduce neuroinflammation by modulating microglial activity and decreasing the generation of cytokines that stimulate inflammation. Clinical studies suggest that ferulic acid may improve cognitive performance in individuals with mild impaired cognitive function, highlighting its potential as a treatment for AD.[10]

FUTURE DIRECTIONS AND CHALLENGES

Clinical Trials and Therapeutic Development

The outcome of various preclinical studies suggest that phenolic acids hold promising treatment for AD but research studies are necessary for establishing both safety and effectiveness in humans. Hence, future studies need to be focused on well-designed clinical trials that investigate the therapeutical benefits of the phenolic compounds in AD patients.[22] The translation of preclinical findings into clinical applications depend on large-scale human tests. Clinical trials should be conducted with the aim of studying the efficacy, safety and pharmacokinetics of phenolic acids among Alzheimer's patients.[49] These studies must include choosing the best dosage with least side effects and expected therapeutic effects to administer and the right duration of therapy. Furthermore, clinical trials should contain a broad patient population to account for differences in genetic background, illness development and responsiveness to therapy.[50] Researchers can employ through clinical trials to determine the therapeutic potential and safety of various phytophenolic acids.[10]

Bioavailability and Pharmacokinetics

Bioavailability and pharmacokinetics are the most important components of pharmacology to understand the therapeutical efficacy of phenolic acids. Generally, phenolic acids show poor absorption and are largely metabolized with quick elimination from the organ. Further studies should focus on enhancing bioavailability through novel drug delivery systems and formulation strategies.[22] Improving phenolic acid bioavailability entails improving their ADME properties.[51] This can be achieved through various tactics, such as nanoparticles, liposomes and other drug delivery systems that enhance the solubility and stability of phenolic acids. Additionally, formulation strategies such as the use of prodrugs, enzyme inhibitors and bioenhancers can improve the pharmacokinetics of phenolic acids.[52] By addressing the challenges of bioavailability and pharmacokinetics, researchers can enhance the therapeutic efficacy of phenolic acids and improve their clinical outcomes.[10] Attempts must also be made to study the structural activity relationship to prepare the semisynthetic or synthetic phenolic acid derivatives are used to modify the potency of the phenolic acids or to reduce their toxic side effects.

Synergistic Effects with Other Therapies

The combination of phenolic acids with other therapies will exert synergistic effects and assures that the total effect is greater than the sum of their individual effects. This may improve therapeutic potency, decrease the required dose and reduce side effects.[53] Phenolic acids may complement synergistically in combination therapies in the treatments for AD. Future studies should put more emphasis on the combination of phenolic acids with other pharmaceutical drugs, lifestyle interventions and other natural compounds for increased therapeutic efficacy.[12] The addition of phenolic acids to a treatment regimen of AD that contains cholinesterase inhibitors, anti-inflammatory drugs and antioxidants may have a multi-targeted approach to treating AD. Beyond this, such lifestyle interventions like diet, exercise and cognitive training may also be capable of adding some synergy of effects. Thus, there is further scope for the development of

Table 1: Structure, source and therapeutical uses of cinnamic acid derivatives.

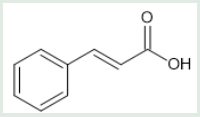
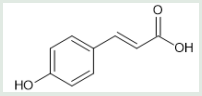
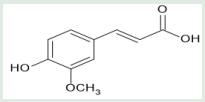
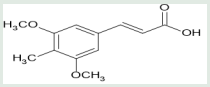
Sl. No.	Name	Structure	Rich sources	Therapeutical uses
01.	Cinnamic acid		Cinnamon,[55] balsam of Peru, tomatoes,[56] honey[57] and grape.[58]	Antioxidant, anti-inflammatory[59] and to treat neurological disorders.[60]
02.	Coumaric acid		Coffee, tomatoes, Carrots,[61] Strawberries and Peanuts.[62]	Antioxidant, anti-inflammatory, anticancer[63] and, antimicrobial agent.[64]
03.	Ferulic acid		Wheat bran, oranges, spinach,[65] flaxseeds and turmeric.[66]	Anti-diabetic, anticancer,[67] and neuroprotective agent.[68]
04.	Sinapic acid		Mustard seeds, broccoli, apples and beans.[69]	Anti-diabetic, anticancer,[70] and, neuroprotective agent.[64]

Table 2: Structure, source and therapeutical uses of benzoic acid derivatives.

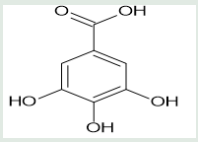
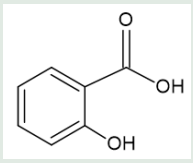
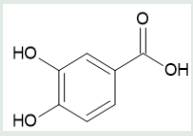
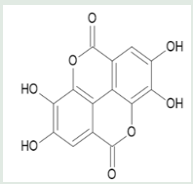
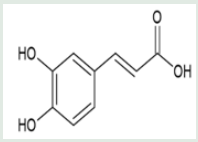
Sl. No.	Name	Structure	Rich source	Therapeutical uses
01.	Gallic acid		Tea, grapes, berries,[71] gallnuts, walnuts and witch hazel.[72]	Anti-oxidant, anticancer[73] and neuroprotective agent.[74]
02.	Salicylic acid		Blueberries, raspberries, broccoli and spinach.[75]	Anti-inflammatory, analgesic, anti-oxidant[76] and neuroprotective agent.[77]
03.	Protocatechuic acid		Green tea, cloves. olives, Cocoa,[78] tomatoes and berries.[79]	Antioxidant, anti-inflammatory, antihyperglycemic,[80] antimicrobial and, neuroprotective agent.[81]
04.	Ellagic acid		Strawberries, raspberries, nuts and walnuts.[82]	Anti-inflammatory, anti-oxidant, anticancer[83] and Neuroprotective agent.[84]
05.	Caffeic acid		Coffee, apples, rosemary, barley,[85] wheat and pears.[86]	Antioxidant, anti-inflammatory, antimicrobial,[87] anticancer and, Neuroprotective agent.[88]

Table 3: Phenolic acids and their effects on Alzheimer's biomarkers.

Sl. No.	Alzheimer biomarkers	Phenolic acids, doses and % inhibition values
1	Amyloid-beta	Gallic acid 50 µM (80%)[89] Ferulic acid 50 µM (70%)[90] Caffeic acid 50 µM (50%)[91] *p*-Coumaric acid 60 µM (50%)[92]
2	Tau Proteins	Ellagic acid 50 µM (70%)[93] Gallic acid 20 µM (40%)[94] Ferulic acid 50 µM (60%)[94] Caffeic acid 50 µM (60%)[95]
3	Neurofilament Light Chain (NfL)	Caffeic acid 75 µM (60%)[96] Ellagic acid 50 µM (60%)[97] Ferulic acid 100 µM (25%)[98] *p*-Coumaric acid 50 µM (45%)[99]
4	Oxidative Stress Markers 1. (ROS) and (MDA) 2. (ROS) 3. (MDA) 4.(H_2O_2)	Ferulic acid 50 µM (70%)[100] Gallic acid 50 µM (55%)[101] Ellagic acid 50 µM (55%)[102] Caffeic acid 75 µM (55%)[103]
5	Inflammatory Cytokines 1.IL-1β 2.TNF-α, IL-1*β*, 3.IL-6 4. IL-1*β*	*p*-Coumaric acid 50 µM (70%)[104] Gallic acid 50 µM (60%)[105] Ellagic acid 50 µM (55%)[106] Caffeic acid 75 µM (60%)[107]

MDA: Malondialdehyde; H_2O_2: Hydrogen peroxide; IL-6: Interleukin; IL-1*β*: Interleukin-1 beta; TNF-*α*: Tumour Necrosis Factor-alpha.

treatment strategies for AD based on the aspects of synergistic effects.[22] However; the drug-drug interaction study must be conducted prior to include these phenolic acids as a medication in the therapy of AD.

Understanding Mechanisms of Action

More research is needed to determine how each phenolic acid used to treat AD works. Especially the targets as well as the signalling pathways and cellular processes that account for neuroprotective and therapeutic actions. Such understanding would provide an avenue to further targeted and efficient treatments in AD. This will also avoid the drug-drug interactions as well as associated adverse effects.[14] Additionally, understanding the exact mechanism ensures the dose and the frequency of the drug to be administered as well as the form in which the phenolic acid compounds must be administered to obtain the expected outcome. There seems to be more complexity regarding the mechanisms of action of phenolic acids, which involve multiple molecular targets and signalling pathways. Therefore, the work in this field may first investigate the specific enzymes, receptors and proteins that interact with phenolic acids to elicit their overall effects. Docking studies of these phenolic acids also provide information about the binding of the compounds with targeted molecules in the treatment of AD. In addition, other downstream signalling pathways and cellular processes such as apoptosis, autophagy, or synaptic plasticity might be required for further exploration of the mechanisms that are to be incorporated into the development of treatments that would have more targeted and effective interventions in the pathophysiology of Alzheimer's.[10] Despite their interesting properties, the therapeutic utilities of phytophenolics are very limited because of low bioavailability,

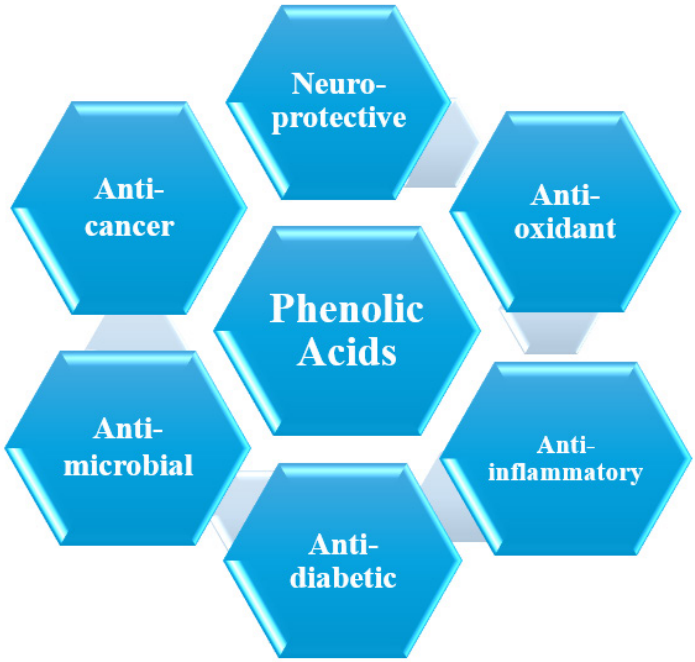


Figure 1: Different types of activities of phenolic acids.

rapid metabolism and rapid elimination. Therefore, in the future research, the main aim should be to enhance these parameters using innovative delivery systems and formulation strategies.[54]

CONCLUSION

Phenolic acids are secondary plant metabolites, the type of structurally diverse compounds that are generally known for their potential therapeutic applications in the treatment of AD. Other than being generally distributed in a broad range of plant-based foods, these compounds have a wide range of biological activities necessary to combat the complex pathophysiology of AD. Due to their antioxidant, anti-inflammatory and neuroprotective properties, they are very useful in the acts of being taken that could find some effective treatments for this devastating neurodegenerative disorder. AD is a kind of dementia that progresses over time, cognitively incapacitates the patient although memory loss comes first and culminates with personality changes. The amyloid-β plaques and paired helical filaments made of hyperphosphorylated tau proteins with dead neurons scattered throughout the cortex. Oxidative stress, chronic neuroinflammation and cholinergic antagonism are instrumental in aggravating the disease process. The therapies currently in use do more to ease the symptoms rather than tackling the problem of Alzheimer's ailments as the disease causes. Gallic acid inhibits amyloid-β aggregation, thereby preventing plaque formation and reducing neurotoxicity. Ellagic acid decreases the excessive phosphorylation of tau proteins, which reduces the growth of tangles in neurons. Ferulic acid scavenges free radicals, enhances cognitive function and inhibits neuroinflammation protects neurons from oxidative stress, Coumaric acid modulates inflammatory response and caffeic acid inhibiting the NFL levels, by reducing the axonal damage.

These include neuroprotection as well as enhancement of synaptic plasticity. Ferulic acid and other phenolic compounds optimize survival in neurons, which ensures the optimization of synaptic plasticity considered as an event critical for maintaining such cognitive functions as learning and memory. Through the optimization of neuronal health as well as synaptic connectivity, phenolic acids lead to better outcomes regarding cognition in patients affected by AD.

Upcoming research will focus on proving the effectiveness of phenolic acids in individuals with AD. Such trials will be developed by the most accurate method to ensure the suitable dosage, duration and route of administration. The other approach is to explore the synergistic effects of phenolic acids when combined with other therapeutic agents. Co-administration of such acids with other anti-inflammatory, antioxidants, or cholinesterase inhibitors may provide a more significant therapeutic effect. In conclusion, phenolic acids would provide the next promising frontier in fighting AD. So, future research inputs should encompass overcoming the problem of bioavailability, thorough clinical trials and synergy in treatments. In this way, we can develop the knowledge and application of phenolic acids to improve our ability toward therapies that offer a satisfactory quality of life among Alzheimer's patients. Further research of these compounds in preclinical and clinical settings could result in the development of novel therapeutic strategies that may alter this paradigm in AD treatment and prevention.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AD: Alzheimer's disease; **ROS:** Reacting oxygen species; **APP:** Amyloid Precursor Protein; **PSEN1:** Presenilin 1; **PSEN2:** Presenilin 2; **APOE ε4:** Apolipoprotein E epsilon 4; **HPLC:** High-Performance Liquid Chromatography; **HPTLC:** High-Performance Thin-Layer Chromatography; **GC:** Gas Chromatography; **MS:** Mass Spectrometry; **NMR:** Nuclear Magnetic Resonance; **CE:** Capillary electrophoresis; **COX-2:** Cyclooxygenase-2; **LOX:** Lipoxygenase; **NIH:** National Institute of Health; **NFL:** Neurofilament light chain; **PET:** Positron emission tomography; **MRI:** Magnetic resonance imaging; **Aβ:** Amyloid beta; **BACE1:** Beta-Site Amyloid Precursor Protein Cleaving Enzyme 1; **MPA:** Microtubule-associated proteins; **PHFs:** Paired helical filaments; **NFTs:** Neurofibrillary tangles; **NfL:** Neurofilament Light Chain; **CSF:** Cerebrospinal Fluid; **ADME:** Absorption, Distribution, Metabolism and Excretion; **Aβ40:** Amyloid Beta 40; **Aβ42:** Amyloid Beta 42; **μM:** Micromolar; **MDA:** Malondialdehyde; **H_2O_2:** Hydrogen peroxide; **IL-6:** Interleukin; **IL-1β:** Interleukin-1 beta; **TNF-α:** Tumor Necrosis Factor-alpha.

ETHICAL STATEMENTS

This study did not involve any human or animal subjects requiring ethical approval.

SUMMARY

Alzheimer's Disease (AD) is a chronic irreversible neurodegenerative disorder characterized by memory loss, cognitive decline and behavioral changes. Phenolic acids, plant-derived secondary metabolites, show promise as alternative therapies due to their antioxidant, anti-inflammatory and neuroprotective properties.

They will be beneficial in enhancing the effect of current therapies through synergistic actions and may provide a holistic approach when taken with a diet rich in phenolic acids. The review highlights the potential of phenolic acids as a multi-faceted strategy for managing and preventing AD, improving long-term brain health. It counteracts ROS, prevents the aggregation of amyloid-beta peptides, reduces tau protein hyperphosphorylation and modifies neuroinflammation. A few well-known examples of phenolic acids include gallic acid, ellagic acid, caffeic acid, ferulic acid and coumaric acid, where preclinical studies have presented neuroprotective activity.

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