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Tamarindus indica Bioactives: *In Silico* Molecular Mechanisms in Neurodegeneration

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***Abstract*: Background: Neurodegenerative diseases, characterized by progressive neuronal damage, remain a significant health burden due to their multifactorial etiology involving oxidative stress, neuroinflammation, and apoptotic dysregulation. *Tamarindus indica* fruit pulp, traditionally celebrated for its anti-inflammatory and antioxidant properties, holds promise as a source of bioactive compounds for neuroprotection. Methods: This study employs network pharmacology and molecular docking to explore the therapeutic potential of bioactive constituents of *T. indica* fruit pulp against neurodegeneration. Results: Gas Chromatography-Mass Spectrometry (GC-MS) analysis identified key phytochemicals, ADME profiling indicated the pharmacokinetic viability of the identified compounds. Network pharmacology analysis mapped the interactions between these compounds and critical targets involved in neurodegenerative pathways, followed by molecular docking studies that confirmed strong binding affinities of selected bioactives to key neuroprotective targets. The results demonstrated strong stability, minimal root-mean-square deviation (RMSD), and favorable binding free energies, supporting the potential of *T. indica* bioactives as effective neuroprotective agents. Conclusions: While computational predictions strongly support the neurotherapeutic potential of *T. indica* fruit pulp extract, further *in vivo* and clinical studies are essential to confirm its efficacy and therapeutic applications. This research bridges traditional medicinal knowledge with modern pharmacological approaches, reinforcing the relevance of plant-based compounds in developing novel interventions for neurodegeneration.**

***Keywords*: Molecular docking, Network pharmacology, Neurodegenerative diseases, Neuroinflammation, Oxidative stress, Tamarindus indica Bioactive compounds.**

1. Introduction

The slow deterioration of the structure and function of the nervous system characterizes chronic and progressive neurodegenerative illnesses. These illnesses pose serious healthcare difficulties worldwide and have grown more alarming among the elderly population [1]. Neurodegenerative diseases are associated with various biological processes, including oxidative stress, the accumulation of protein aggregates in neurons, impaired or reduced neurotransmitter production, irregular ubiquitination, mitochondrial dysfunction, neuronal excitotoxicity, blood-brain barrier (BBB) damage, and diminished neurotransmitter synthesis or availability within the synaptic cleft [2], [3]. A common feature of neurodegenerative diseases is that the central nervous system (CNS) experiences inflammation and oxidative stress due to aberrant protein aggregation [2].

Neurodegenerative disease research targets oxidative stress, making antioxidants a key treatment focus. Natural compounds, like those in galantamine and levodopa, show therapeutic potential. Africa's traditional medicine, rich in biodiversity, offers cost-effective solutions [4]. *Tamarindus indica* (tamarind) fruit pulp contains beneficial flavonoids and has strong antioxidant and anti-inflammatory properties (Ajani and Usman, 2020). Phytochemicals such as carotenoids and resveratrol protect brain structure and enhance cognition [6].

Current research on neurodegenerative diseases explores various therapeutic targets, including aggregation inhibitors, enzyme inhibitors, and receptor antagonists. Due to their capacity to alter several molecular pathways, natural compounds have recently drawn interest for their possible neuroprotective qualities. However, there is still much to learn about the probable mechanisms of the bioactive molecules found in *Tamarindus indica* fruit pulp, renowned for their potent anti-inflammatory and antioxidant effects, which can mitigate neurodegeneration. This study utilized network pharmacology, and molecular docking to assess the neuroprotective potential of flavonoids from *T. indica* fruit pulp extract, identified through GC-MS analysis.

2. Methods

A. GC-MS Analysis

GC-MS analysis of the crude extract of *T. indica* fruits was performed on a PerkinElmer Clarus 600 GC System, fitted with a Rtx-5MS capillary column (30 m x 0.25 mm inner diameter, x 0.25 µm film thickness; maximum temperature, 350 °C), coupled to a Perkin Elmer Clarus 600C MS as described by Al-Owaisi et al. [7]. The identification and characterization of chemical compounds in various crude extracts was based on GC retention time. The mass spectra were computer-matched with those of standards available in the mass spectrum libraries.

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B. Network Pharmacology

1) Identification of T. Indica Fruit Extract Constituents and their Prospective Targets

Information regarding the primary bioactive compounds in *T. indica* fruit pulp extract was gathered through GC-MS analysis. Chemical structures and Canonical Simplified Molecular Input Line Entry System (SMILES) representations of each compound were retrieved from PubChem Explore Chemistry. A virtual screening process was conducted for all identified constituents, assessing their bioavailability (OB) and drug-likeness (DL) using the Molsoft and SwissADME tools. Only compounds meeting the criteria of DL ≥ 0.18 and OB ≥ 30% were retained for further evaluation, as these parameters are essential for determining absorption, distribution, metabolism, and excretion (ADME) characteristics. Compounds failing to meet these thresholds were excluded from subsequent analyses [8], [9] as these two descriptors are positively correlated, with higher OB values often suggesting improved DL [10].

2) Identification of Targets Associated with Neurodegeneration

To identify potential targets linked to neurodegeneration, genes associated with the disease were retrieved from the OMIM (Online Mendelian Inheritance in Man, https://www.omim.org/) and GeneCards Suite (https://www.genecards.org/) databases using the keyword "neurodegenerative diseases." The identified targets were consolidated, and duplicates were removed using Microsoft Excel.

3) Acquisition of Targets Common to Disease and Active Compounds

The Venn online tool was employed to determine the overlapping genes between the predicted targets of the screened compounds and the disease-associated targets. Shared gene targets between the active compounds and the disease were identified for subsequent analysis [11].

4) Identification of the Hub Genes and Construction of the "Active Compound -Target Disease" Network Diagrams

The overlapping gene targets were uploaded into Cytoscape v3.10.3, to identify the top 15 hub genes [12]. Using the cytoHubba plug-in, topological parameters—specifically the degree—were calculated and ranked to pinpoint the most interconnected hub genes within the network. In this network, nodes represented the active compounds and their corresponding target genes, while edges depicted their interactions [13].

5) Development of the Protein-Protein Interaction (PPI) Network

Protein-protein interaction (PPI) data were retrieved from the STRING database (Search Tool for the Retrieval of Interacting Genes) with a confidence score greater than 0.4 to build a PPI network by uploading the hub genes into the database. The co-expression of the predicted key targets was also accessed through the STRING database. The resulting PPI network from STRING was further analyzed using the STITCH compound query, STRING disease query, STRING protein query, and WikiPathways within Cytoscape v3.10.3. This analysis helped identify the core regulatory genes within the PPI network, key targets, and related biological pathways [13].

6) Enrichment Analysis of Gene Ontology (GO) and Pathways

Characterizing and annotating the function of hub genes and exploring the associated signaling pathways is essential (8). The DAVID database for annotation, visualization, and integrated discovery was utilized for gene enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses [14], [15]. The list of hub genes was input into DAVID for functional annotation at three levels: cellular component (CC), molecular function (MF), and biological process (BP). DAVID, a web-based tool for functional enrichment analysis, aids researchers in understanding the bioactivity of genes.

C. Docking of Molecules

The docking of the ligands (active compounds of *T. indica*) to the hub genes and the evaluation of binding affinities were determined via PyRx. The pdbqt format of the macromolecules (genes), as well as those of the ligands (active compounds), was dragged into their respective columns, and the software was run. A cluster analysis based on Root Mean Square Deviation (RMSD) values regarding the starting geometry was then performed, and the lowest energy conformation of the more populated cluster was measured as the most trustable solution. The binding affinities of compounds for the four protein targets were recorded. The compounds were then classified by their affinity scores as described by Ishola et al. [16].

3. Results

Table 1 shows the Gas Chromatography-Mass Spectroscopy (GC-MS) result of the *T. indica* fruit pulp extract. The Table delineates the extract's bioactive profile, with kaempferol as the dominant peak. The retention times and peak areas substantiate the diversity and therapeutic relevance of identified compounds.

Table 1
GCMS analysis result of T. indica fruit pulp extract

Peak	Retention Time	% Area	Name
1.	4.033	971.0510	Beta-Amyrin
2.	4.316	523.253	Caffeic Acid
3.	5.016	9219.941	Taxifolin
4.	6.033	459.15	Catechin
5.	6.45	1266.969	Epicatechin
6.	7.15	1423.723	Isorhamnetin
7.	7.533	4546.156	Beta-Sitosterol
8.	7.816	4955.4895	Apigenin
9.	8.6	5297.694	Quercetin
10.	9.2	19589.328	Kaempferol
11.	11.016	457.698	Myricetin
12.	11.483	1217.747	Lupeol
13.	11.916	143.994	Lupanone
14.	12.55	230.539	Protocyanidin B2
15.	14.566	166.3655	Ferulic acid

This study focused on four primary bioactive compounds from *Tamarindus indica* fruit pulp extract: apigenin, catechin, epicatechin, and kaempferol. These compounds were selected based on drug-likeness, oral bioavailability, and their pharmacokinetics details. Through SwissTargetPrediction, a

comprehensive database integrating ligand-protein interactions, these compounds were mapped to potential gene targets associated with neurodegenerative conditions.

SwissTargetPrediction revealed that these compounds interact with multiple gene targets related to neurodegeneration, demonstrating significant therapeutic potential. From the GeneCards and OMIM databases, 12,384 genes associated with neurodegeneration were identified. Venn diagram analysis showed that 226 of these genes intersected with predicted targets of the active compounds, confirming a strong relevance to neurodegenerative pathways. Cytoscape v3.10.3, using the cytoHubba plug-in, analyzes overlapping gene targets to identify hub genes. By calculating degree centrality, it ranks the top 10 most interconnected genes. In this network, nodes represent active compounds and their target genes, while edges depict their interactions. This analysis pinpointed *AKT1, BCL2, EGFR,* SRC and ESR1 as the top five hub genes (figure 1) central to critical neuroprotective pathways.

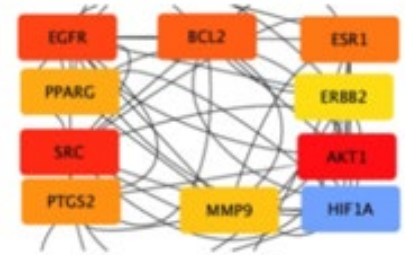

Fig. 1. The top ten (10) hub genes according to the degree topological parameter. Hub genes identification and visualization were generated using cytoscape v3.10.3, integrating cytoHubba plug-in

Enrichment analyses for the active compounds (apigenin, catechin, epicatechin, and kaempferol) in disease-specific pathways indicated significant impacts on Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis (ALS) pathways. Specifically, apigenin and kaempferol influence δ-secretase pathways implicated in Alzheimer's pathology, while catechin impacts Trop 2 regulatory signaling pathways relevant to Parkinson's disease. These findings are reinforced by visual data, including KEGG enrichment bar charts (figures 2 and 3) and bubble chart (figure 4), with a false discovery rate (FDR) of -log 10 which depict the widespread influence of these compounds on biological and molecular processes. Figures from Cytoscape (figure 5) corroborate the interconnectivity of pathways and the centrality of the identified hub genes. These findings suggest that *Tamarindus indica* compounds modulate pivotal mechanisms such as apoptosis, oxidative stress, and neuroinflammation, which are central to neurodegenerative disease progression.

Molecular docking offered a comprehensive understanding of the binding interactions between the active compounds and the selected proteins, revealing binding affinities that underscore the active compounds' specificity and strength of interaction (Table 2). Apigenin exhibited a binding affinity of -9.5 kcal/mol with AKT1, establishing stable hydrogen bonds at the ATP-binding pocket and enhancing its potential to modulate survival pathways. Catechin demonstrated an affinity of -5.5 kcal/mol with SRC, interacting through key residues responsible for tyrosine phosphorylation, critical for neuroinflammatory response modulation. Epicatechin interacted with EGFR, with a binding affinity of -7.1 kcal/mol, potentially influencing its neuroprotective signaling. Kaempferol interacted with BCL2, displaying a significant affinity of -7.4 kcal/mol, stabilizing its anti-apoptotic conformation and mitigating mitochondrial damage. Binding energy values and Root Mean Square Deviation (RMSD) suggest stable and specific interactions crucial for drug-receptor efficacy.

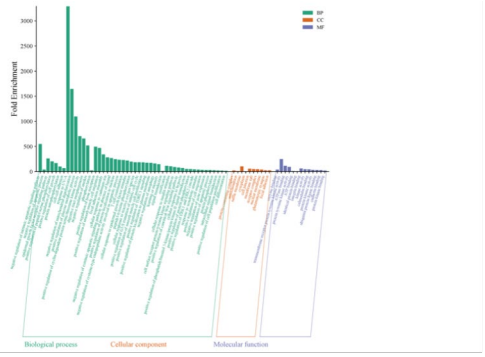

Fig. 2. KEGG pathway in a bar chart for the hub genes showing the BP, CC, and MF. KEGG pathway visualization in a bar chart was generated using the website bioinformatics.com.cn/en, integrating the 72 entries of the KEGG pathway of the hub genes generated by DAVID into the BP, CC, MF 3 in 1 function of the bioinformatics.com.cn/en website

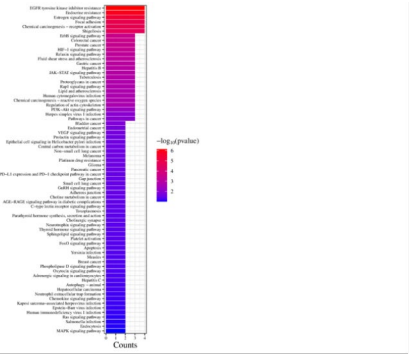

Fig. 3. KEGG enrichment bar with color. KEGG pathway visualization as an enrichment bar with color was generated using the website bioinformatics.com.cn/en, integrating the 72 entries of the KEGG pathway of the hub genes generated by DAVID into the enrichment bar with color function of the bioinformatics.com.cn/en website

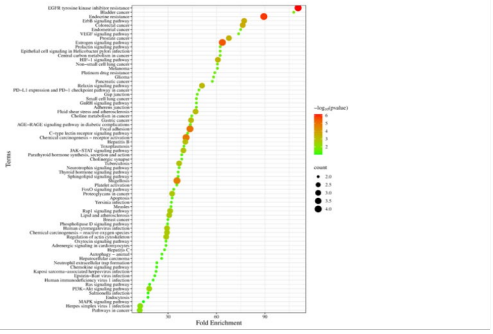

Fig. 4. KEGG enrichment bubble chart. KEGG pathway visualization as an enrichment bubble chart generated using the website bioinformatics.com.cn/en, integrating the 72 entries of the KEGG pathway of the hub genes generated by DAVID into the enrichment bubble function of the bioinformatics.com.cn/en website

Table 2
Molecular docking result of the ligands (screened and selected active compounds in Tamarindus indica fruit pulp extract) with the proteins (hub genes)

Docked Compound	Binding Affinity (kcal/mol)	RMSD Upper Bound	RMSD Lower Bound
AKT1 with Apigenin	-9.5	2.782	1.380
AKT1 with Catechin	-9.1	3.741	2.585
AKT1 with Epicatechin	-9.1	3.025	2.233
AKT1 with Kaempferol	-9.1	2.273	1.644
SRC with Apigenin	-5.8	6.556	1.542
SRC with Catechin	-5.5	3.929	2.182
SRC with Epicatechin	-5.7	6.638	3.255
SRC with Kaempferol	-5.9	6.347	1.793
EGFR with Apigenin	-7.5	3.160	1.687
EGFR with Catechin	-7.6	4.088	2.526
EGFR with Epicatechin	-7.1	1.828	1.561
EGFR with Kaempferol	-8.1	2.970	1.780
BCL2 with Apigenin	-6.9	3.031	2.106
BCL2 with Catechin	-6.1	5.330	3.500
BCL2 with Epicatechin	-6.2	6.520	1.485
BCL2 with Kaempferol	-7.4	16.544	15.111
ESR1 with Apigenin	-7.7	4.965	3.238
ESR1 with Catechin	-6.8	2.151	1.822
ESR1 with Epicatechin	-7.0	6.369	2.897
ESR1 with Kaempferol	-7.4	5.941	3.372

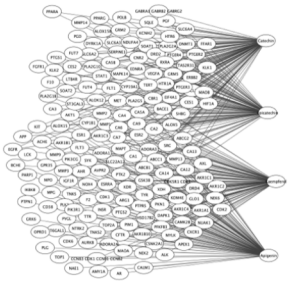

Fig. 5. The compound-gene target network between the screened active compounds of T. indica and the gene targets. The network visualization was generated using Cytoscape v3.10.3

4. Discussion

The phytochemical composition of *T. indica* fruit pulp extract underscores its potential as a multi-target therapeutic agent for neurodegeneration. Neurodegeneration is characterized by oxidative stress, mitochondrial dysfunction, neuroinflammation, and neuronal apoptosis. The phytochemicals identified in *T. indica* fruit pulp extract collectively target these pathological mechanisms. The high levels of flavonoids and phenolics and the presence of kaempferol, quercetin, and other compounds identified in this study position the extract as a potential therapeutic agent. Kaempferol has been shown to modulate oxidative stress by enhancing the activity of endogenous antioxidant enzymes, thus, protecting neurons from oxidative damage [17]. It also inhibits the activation of pro-inflammatory microglial cells, which are implicated in neurodegenerative diseases such as Parkinson's and Alzheimer's. Beta-sitosterol has been associated with stabilizing neuronal membranes and regulating cholesterol metabolism in the brain, which is critical in maintaining synaptic integrity and preventing cognitive decline [18]. Caffeic acid, epicatechin, and catechin contribute to neuroprotection through their antioxidant properties, with caffeic acid demonstrating additional potential to modulate neurotransmitter systems (Sroka and Cisowski, 2003). Quercetin is a potent antioxidant and anti-inflammatory agent that can cross the blood-brain barrier (BBB), enabling it to directly interact with neurons and glial cells to reduce oxidative stress and inflammation [20]. The presence of triterpenoids such as lupeol and beta-amyrin further enriches the neuroprotective profile of the extract. These compounds are known to reduce oxidative stress and suppress the overactivation of inflammatory signaling pathways, including the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, which is a key mediator in acrylonitrile-induced neurotoxicity (Zhao et al., 2019). These findings align with previous research on *T. indica*. Mbunde et al., (2018) also identified kaempferol, quercetin, and beta-sitosterol as dominant compounds in *T. indica* extracts, emphasizing their contributions to antioxidant and anti-inflammatory activities. Similarly, Spencer et al., (2012) reported the neuroprotective effects of caffeic acid and ferulic acid, attributing their efficacy to the modulation of oxidative stress and inflammatory pathways. However, this study provides additional insights by identifying the presence of lupanone and procyanidin B2, which have not been extensively reported in *T. indica* extracts. These compounds may offer unique contributions to the neuroprotective effects of the extract, potentially enhancing its efficacy against neurodegeneration.

This study highlights the immense therapeutic potential of *Tamarindus indica* fruit pulp bioactive compounds (apigenin, catechin, epicatechin, and kaempferol) in addressing neurodegeneration. Apigenin, catechin, epicatechin, and kaempferol were shown to interact with key neurodegenerative targets and pathways, offering multitarget mechanisms, which include antioxidant activity, modulation of apoptosis, and regulation of signaling pathways. A study by Bhattacharjee et al. found that apigenin demonstrates significant neuroprotective effects by activating the PI3K-AKT signaling pathway and inhibiting pro-inflammatory cytokines [24], this supports our findings, where apigenin showed significant interactions with AKT1 and was enriched in pathways such as PI3K-AKT and apoptosis. Likewise, catechin's capacity to neutralize free radicals and reduce oxidative stress was also observed [25],

[26], corroborating its role in the oxidative stress pathways observed in this study.

Pathway enrichment analysis highlights the influence of these compounds on critical biological processes related to neurodegeneration; this includes pathways such as PI3K-AKT signaling, AGE-RAGE signaling, and ferroptosis. The PI3K-AKT pathway plays a role in supporting neuronal survival and plasticity and is a well-documented target in neurodegenerative therapy due to its ability to mitigate apoptosis and enhance neurogenesis. Similarly, the AGE-RAGE and ferroptosis pathways address oxidative stress and inflammation, which are pivotal in Alzheimer's and Parkinson's pathologies [1]. Our study aligns with earlier research that shows the antioxidative and anti-inflammatory capabilities of plant polyphenols, including flavonoids, in modulating these pathways [27]. Additionally, the STRING network elucidates the interconnectedness of the compounds' targets, emphasizing a multi-targeted therapeutic approach.

Contemporary research also supports the interplay of these compounds with pathways involved in Alzheimer's, Parkinson's, and ALS. Kaempferol, for example, has been shown to mitigate β-amyloid toxicity in Alzheimer's models, while catechins have demonstrated the ability to stabilize α-synuclein aggregates in Parkinson's disease [28], [29]. This suggests that the *Tamarindus indica* fruit pulp extract compounds are not only theoretically relevant but also practically aligned with neurotherapeutic mechanisms documented in the literature.

Molecular docking studies reveal strong binding affinities between the compounds and key hub genes (AKT1, SRC, EGFR, and BCL2), with low binding energies showing robust interactions, favorable pharmacokinetics and indicating a potential to modulate these pathways at a molecular level. For instance, AKT1 is implicated in neuronal repair mechanisms, while SRC and EGFR are associated with synaptic health and inflammation suppression. The observed interactions align with prior molecular docking studies that have emphasized the neuroprotective roles of these proteins [30]. RMSD values further validate the stability of the docked complexes, suggesting reliable predictive models for their therapeutic potential.

While these findings are promising, they remain theoretical and reliant on computational predictions. Experimental validation in animal models is essential to confirm the bioactivities of these compounds and their efficacy in mitigating neurodegeneration.

5. Conclusion

This study highlights the potential of *Tamarindus indica* fruit pulp extract as a multitarget therapeutic agent against neurodegeneration. The phytochemical composition, rich in flavonoids, phenolics, and bioactive compounds such as kaempferol, quercetin, catechin, epicatechin, apigenin, and beta-sitosterol, underscores its capacity to mitigate oxidative stress, neuroinflammation, mitochondrial dysfunction, and neuronal apoptosis. Network pharmacology analyses show that these bioactive compounds interact with key neurodegenerative pathways, including PI3K-AKT, AGE-RAGE, ferroptosis, and NF-κB, supporting neuronal survival, synaptic integrity, and inflammation regulation.

Molecular docking further validates the pharmacokinetic advantages of these compounds, demonstrating strong binding affinities, BBB permeability, and favorable drug-likeness. The stability of interactions with critical targets such as AKT1, SRC, EGFR, BCL2, and ESR1 suggests their potential role in neuroprotection.

Since these findings are preliminary, we emphasize that any broad conclusions regarding the impact of self-control demand should be approached with caution, as further validation through alternative methodologies is necessary. Nonetheless, this study serves as a foundational step for future research for several reasons. Subsequent *in vitro* and *in vivo* studies are essential in the next phase to confirm the compound's biological activity, toxicity, and therapeutic potential. By refining these initial results, we aim to contribute progressively to the body of knowledge on natural products in neurodegeneration treatment, ultimately enhancing their recognition and application in clinical settings.

Declarations

A. Ethical Statement

No ethical approval was required as this study did not involve human participants or laboratory animals.

B. Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

C. Credit Authorship Contribution Statement

Lutfat A. Usman: Writing – original draft, Visualization, Methodology, Data curation, Conceptualization. Lutfat A. Usman and Rasheed B. Ibrahim: Resources, Investigation, & Data curation. *Emmanuel O. Ajani*: Writing – review & editing, Supervision.

D. Declaration of Competing Interest

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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