Colegio de Postgraduados

Phenols as an alternative, neuroprotective, and preventive strategy for Alzheimer's disease: (mini-review and bibliometric analysis)

Iñiguez-Luna, María Isabel[1]; Suárez-Medellín, Jorge A.[1*]; Vidal-Limon, Abraham[2*]

[1] Universidad Veracruzana, Instituto de Investigaciones Cerebrales. Dr. Castelazo Ayala s/n Industrial Animas, Xalapa-Enríquez, Veracruz, México. C.P. 91190.
[2] Instituto de Ecología AC, Laboratorio de Ecología Química, Red de Estudios Moleculares Avanzados, Clúster Científico y Tecnológico BioMimic®, Xalapa, Veracruz, México. Carretera antigua a Coatepec 351, El Haya, Xalapa-Enríquez, Veracruz, México, CP. 91073.
* Correspondence: abraham.vidal@inecol.mx; josuarez@uv.mx

ABSTRACT

Objective: This study aimed to perform a bibliometric review focused on secondary metabolites of phenolic origin in the context of Alzheimer's disease. Analyzing the research trend in this field during the last two decades, highlighting the chemical-computational (*in silico*) perspective.

Design/methodology/approach: Publications from the last two decades (2001-2023) were examined using the academic search engine Dimensions. The focus of our analysis was on identifying co-occurrence networks of terms present in the titles and abstracts of these publications, setting a minimum threshold of 100 co-occurrences for inclusion in the study (VOSviewer v. 1.6.19,2023).

Results: The literature consulted suggests phenolic compounds as metabolites with preventive capacity, derived from their antioxidant, anti-inflammatory, and neuroprotective properties.

Limitations on study/implications: However, it is essential to highlight the limitations observed in each area so that an integral vision is encouraged in future research.

Findings/conclusions: The integration of epidemiological studies, *in vitro* investigations, *in silico* analysis, and *in vivo* experiments will advance the development of therapeutic strategies based on phenolic compounds for the care of multifactorial Alzheimer's disease.

Keywords: Alzheimer; bibliometric analysis; *in silico*; Phenols.

Citation: Iñiguez-Luna, M.I., Suárez-Medellín, J.A., & Vidal-Limon, A. (2023). Phenols as an alternative, neuroprotective, and preventive strategy for Alzheimer's disease: (mini-review and bibliometric analysis). *Agro Productividad*. https://doi.org/ 10.32854/agrop.v16i9.2716

Academic Editors: Jorge Cadena Iñiguez and Lucero del Mar Ruiz Posadas

Received: October 14, 2023.
Accepted: November 01, 2023.
Published on-line: November 03, 2023.

Agro Productividad, 16(9). September. 2023. pp: 113-132.

INTRODUCTION

Secondary metabolites (MeS) represent a diverse group of biomolecules derived from natural sources, including plants, bacteria, fungi, and algae. These substance's roles complement primary or essential metabolism (nucleic acid and protein synthesis) with functions such as interspecies interactions, quorum sensing, and tissue differentiation. Moreover, MeS are involved in several critical functions, such as defense mechanisms against predators, adaptation to stress conditions (either biotic or abiotic), but also growth regulation, pollination, interspecies competition, and act as chemical messengers enabling intra- and interspecific communication (Böttger *et al.*, 2017; Garcia-Mier *et al.*, 2018).

The diversity of mechanisms involving MeS is directly due to its wide chemical range. In plants, for instance, there are more than 200,000 different MeS reported (Rasmann *et al.*, 2012). These molecules are synthesized and distributed at various levels, tissues, or phenological stages, being present in a limited way between taxonomic groups and representing 1% of the total weight of their organisms. (Akula & Ravishankar, 2011; Caretto *et al.*, 2015). Moreover, the diversity of biological activities exhibited by secondary

metabolites (Gibney *et al.*, 2019; Kim *et al.*, 2021) underscores the significance of research on the chemistry of MeS, such as phenols, triterpenoids, flavonoids, among others.

The phenolic compounds are widely distributed in the cell walls of plants, forming part of polymers such as p-hydroxybenzoic acid, suberin, and lignin. In the case of lignin, a cross-arrangement of phenols is observed, with diverse spatial and structural distributions, adopting ortho-, meta- and para-positions (Li *et al.*, 2023). This structural variability is due to the susceptibility of the benzene ring in phenols to be modified by hydroxyl groups (Hithamani *et al.*, 2022). Such modifications lead to the formation of different phenolic compounds, each with its own distinct bioactivities. The phenolic compounds possess a versatility that makes them indispensable in our daily lives and essential both in scientific research and in different industries, including food, agriculture, cosmetics, and pharmaceuticals (Silva *et al.*, 2020; Bondam *et al.*, 2022). Hence, the importance of the identification of phenolic compounds as active principles in herbal drugs due to their medicinal and pharmacological properties (Sá *et al.*, 2017; Xu *et al.*, 2022).

With increasing life expectancy and the growing concern to address multimorbidity with more effective pharmacological strategies, there has been an increasing focus on the development of drugs with diverse biological properties (Zhang *et al.*, 2017; Elansary *et al.*, 2019; Foscolou *et al.*, 2021). These include antioxidant capacity, antiproliferative effects, vasodilators, and enzyme modulators that are progressively relevant in the context of healthy aging toward addressing age-associated and chronic-degenerative diseases. (Zhang *et al.*, 2017; Elansary *et al.*, 2019). Among these diseases are heart disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, and Alzheimer's dementia (AD) (Kovacic, 2017; Luna-Guevara *et al.*, 2018).

Alzheimer's disease, the most common form of dementia worldwide with approximately 55 million cases, is listed as the third most costly disease according to data recorded by the Alzheimer's Association and the International Classification of Diseases (Gauthier *et al.*, 2021; ICD-11, 2023). The reported incidence in Mexico is 27.3 persons per thousand inhabitants yearly (Arrieta-Cruz & Gutiérrez-Robledo, 2015). Moreover, the number of cases is estimated to triple in the next 30 years (Hernández-Reyes *et al.*, 2012; Mejía-Arango *et al.*, 2020). This dementia is a progressive multisystemic terminal neurodegenerative disease of unknown etiology. It is mainly characterized by memory loss, language impairment, decreased motor coordination, and gradual intellectual decline (Sherman *et al.*, 2021).

Concerning pharmacotherapy, medications approved by the Food Drug Administration (FDA) offer temporary symptomatic relief tailored to clinical needs at different progressive stages of dementia. During the initial therapeutic approach, acetylcholinesterase inhibitors, monoclonal antibodies, and NMDA receptor antagonists are administered. In more advanced stages of the disease, a combination therapy incorporating antidepressants, anxiolytics, and antipsychotics is usually chosen (Gustavsson *et al.*, 2022; Cammisuli *et al.*, 2022). These therapies often lead to adverse effects such as confusion, edema, and microhemorrhages, in addition to showing reduced efficacy (Huang *et al.*, 2020; Alhazmi & Albratty, 2022). It has been observed that naturally occurring molecules of phenolic origin present a bioactive potential in neurodegenerative diseases, which can be exploited in the search for new strategies for the treatment of Alzheimer's disease (Rojas-García *et al.*,

2023). This study aims to conduct a bibliometric review focused on secondary metabolites of phenolic origin in the context of Alzheimer's disease. The trend of research in this field during the last two decades will be analyzed, highlighting the chemical-computational (in silico) perspective.

MATERIALS AND METHODS

The aim of this research is to conduct a bibliometric review of studies related to Alzheimer's disease with particular emphasis on in silico studies concerning bioactive phenolics that might be useful as lead compounds in diverse drug development stages.

Construction of a bibliographic database

The database was obtained using the next-generation academic search engine Dimensions. It indexes more than 10 million datasets from more than 1000 repositories, including sources such as multidisciplinary publications, scientific, grants, datasets, clinical trials, patents, and policy documents (https://app.dimensions.ai) (Van Eck & Waltman, 2010; Arruda *et al.*, 2022).

The systematic search for publications was performed by enriching the thesaurus "Alzheimer," "phenols," "*in silico* analysis," and "computer-designed drugs." The Boolean operators used were "AND" and "OR". All publications in a time interval of the last two decades (2001-2023), were considered valid hits. The information obtained was classified, with special curation of unrelated topics to the study.

Bibliometric analysis

For the bibliometric analysis, the software tool VOSviewer version 1.6.19,2023 was used. The software tool allows the construction and visualization of bibliometric networks based on queries in databases such as Web of Science, PubMed, Scopus, and Dimensions. In this work, our aim was to analyze the components of the bibliometric network generated by VOSviewer. The generated networks derived from the analysis of the co-occurrence of terms found in the titles and abstracts of the documents, with a minimum threshold of co-occurrences set at 100. Nodes and links represent the semantic elements of the network. In this representation, nodes correspond to terms that co-occur, while links represent the relationships between these terms (Van Eck & Waltman, 2010; Arruda *et al.*, 2022). The node size within the network reflects the frequency with which term appears, the distance between nodes indicates proximity, and colors group terms into independent clusters within the network.

RESULTS AND DISCUSSION

Chemotaxonomy of secondary metabolites

The biosynthesis of secondary metabolites (MeS) is a complex and diverse process involving distinct metabolic pathways that sometimes become species-specific. However, several authors describe MeS biogenesis through four main pathways: 1) The mevalonic acid pathway used by plants, bacteria, fungi, and animals for isoprenoid synthesis (Bach & Weber, 1989; Thompson *et al.*, 2018). 2) The methylerythritol phosphate pathway

used by archaea, protozoa, plants, and algae in the synthesis of terpenoids (González-Cabanelas *et al.*, 2016; Rodriguez-Concepcion, 2016). 3) The acetate-malonate pathway mainly employed by bacteria, fungi, and algae to synthesize polyketides (Niu *et al.*, 2019). 4) The shikimic acid pathway mainly used in plants to synthesize aromatic compounds such as alkaloids and phenols (Santos-Sánchez *et al.*, 2019). Furthermore, these secondary metabolites are classified into four main groups: alkaloids, terpenes, cyanogenic glycosides, and phenolic compounds (Chomel *et al.*, 2016). It is relevant to mention that phenols are the most prevalent secondary metabolites found in plants, with more than 8,000 molecules reported (Bhuyan & Basu, 2017). Phenols are classified according to their molecular weight, *i.e.* low molecular weight or simple phenols and high molecular weight phenols, also known as complex phenols (Chomel *et al.*, 2016; Carregosa *et al.*, 2022). Both can be subclassified based on their constituent carbon structure (Table 1). This classification provides a swift approximation to understand the diversity and mechanisms of action of these compounds in the plant kingdom as well as their potential use in biomedicine.

The structural diversity of phenolic compounds can explain, in part, the heterogeneous biological activities that these compounds can display, suggesting their role as potential bioactive agents. Several clinical and preclinical studies have shown that phenols can help from the prevention to the treatment of neurodegenerative diseases, such as Parkinson's and Alzheimer's. Therefore, as progress is made in natural products as alternative therapies in treating chronic degenerative diseases, current challenges are addressed, and future perspectives for using phenols in neurodegenerative diseases are outlined.

Phenols and their therapeutic potential in chronic degenerative diseases

Due to their quasi-ubiquitous presence in different organisms, phenols play an essential role in developing cosmetic additives, herbal products, functional foods, and active ingredients in pharmaceutical treatments (Ammar *et al.*, 2020). The therapeutic activity of phenols was evidenced in various diseases (Rigacci & Stefani, 2015; Essa *et al.*, 2016), where different metabolites, such as anthocyanins, flavanols, procyanidins, flavanols hydroxycinnamates and ellagitannins exhibited antiplatelet aggregation actions, oxidation

Table 1. Classification of phenolic compounds according to molecular weight and carbon structure.

Molecular weight	carbon skeleton
Low molecular weight less than 500 Da (LMW)	Benzoquinones (C_6) Phenolic acids (C_6C_1) Acetophenones and phenylacetic acids (C_6C_2) Coumarins and hydroxycinnamic acids (C_6C_3) Naphthoquinones (C_6C_4) Xanthones ($C_6C_1C_6$) Stebilenes and anthraquinones ($C_6C_2C_6$) Flavonoids ($C_6C_3C_6$)
High molecular weight from 500 to 3000Da (HMW)	Lignans $(C_6C_3)^2$ Lignins $(C_6C_3)^n$ Catecholamines $(C_6)^n$ Tannins $(C_6C_3C_6)^n$

Lattazio, 2013; Jawal *et al.*, 2018.

of low-density lipoproteins, decrease in blood pressure, as well as, a lower association of mortality in cardiovascular diseases (Rodriguez-Mateos *et al.*, 2014; Behl *et al.*, 2020; Vetrani *et al.*, 2020). Meanwhile, in respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), phenols have stood out for their antioxidant, anti-inflammatory, immunomodulatory, and bronchodilator effects (Sagar *et al.*, 2020; Beigoli *et al.*, 2021).

Regarding diabetes mellitus, resveratrol, and anthocyanins showed reduced blood glycemic index and improved functions in pancreatic βcells (Asgar, 2013; de Paulo Farias, 2021). Clinical studies in humans suggest that phenols present in grapes, such as catechin, epicatechin, anthocyanidin, and quercetin, after prolonged ingestion, tend to accumulate in the brain and show the ability to cross the blood-brain barrier, modifying the modulation of cell signaling and neutralization of the redox state in aged brains, and improve the cognitive activity. In addition, another study revealed that a diet rich in flavonoids, combined with physical activity, was associated with a lower risk of developing Alzheimer's disease (Luna Guevara *et al.*, 2018; Devi & Chamoli, 2020; Shishtar *et al.*, 2020). This evidence proposes phenols as bioactive molecules with a broad pharmacological potential in neurodegenerative-type diseases.

Epidemiological studies

Epidemiological studies focused on Alzheimer's disease (AD) have provided information on geographical prevalence (countries), age (dependent on aging rates), incidence (increases after 65 years), and risk factors (smoking, insomnia, stress, diet, and sedentary lifestyle in others). There are strategies designed for healthy mental aging (Yamada et al., 2015; Shahidi & Yeo, 2018), highlighting the adoption of healthy habits and incorporation of social, physical and cognitive activities (Makrakis *et al.*, 2022), which, in conjunction with an anti-inflammatory diet high in phenols, can lead to a lower incidence of AD (Tobias *et al.*, 2014; Gao *et al.*, 2019; Bermejo-Pareja *et al.*, 2016; Fernandez *et al.*, 2018.; Azar *et al.*, 2021; Chu *et al.*, 2023). Some phenol-rich foods, such as olive oil, red wine, coffee, tea, cocoa-derived products, a variety of fruits, culinary herbs, and vegetables, have been identified as important sources of polyphenols (Angeloni *et al.*, 2017; Holland *et al.*, 2020; Pintać *et al.*, 2022; Rivero-Pino *et al.*, 2023).

These foods contain phenols, such as resveratrol, curcumin, apigenin, caffeic acid, ferulic acid, chlorogenic acid, quercetin, and other compounds. These substances add flavor and color to foods and have shown health benefits, including possible preventive effects for Alzheimer's disease (Khan *et al.*, 2019; Dhingra & Chopra, 2023). However, these associative studies highlighting the beneficial properties attributed to phenols lack scientific validation to understand the mechanisms of action of these metabolites in AD.

***In vitro* and *in vivo* studies**

Due to the above, *in vitro*, and *in vivo* studies seek tangible evidence of the attributes ascribed to phenols in AD. In this regard, the research conducted by Vargas-Restrepo and coworkers (2018) suggests quercetin can act as an anti-inflammatory agent in AD, based on results obtained from a transgenic mice (3xTg-AD) animal model,

identifying the decrease of reactive microglia as well as fluorescent intensity of Aβ aggregates, GFAP (glial fibrillary acidic protein), iNOS (nitric oxide synthase) and COX-2 (cyclooxygenase-2) immunoreactivity in the hippocampal area. All of them are factors associated with neuroinflammation present in AD brains. Phan *et al.* (2019), using an electrochemical approach, identified that the characteristics of aromatic rings and hydroxyl groups present in flavonoid-type polyphenols (gallocatechin gallate and theaflavin) and stilbene (resveratrol and piceid), allow interaction with Aβfibrils, leading to inhibition in structured aggregation of the same. On the other hand, in vivo studies were performed in the organism Caenorhabditis elegans as an AD model, through the generation of oxidative stress induced by AAPH (2,2'-azobis (2- methylpropionamidine dichlorohydrate) and then applying honey extracts from avocado multiflora (Romero-Márquez *et al.*, 2023), which is rich in phenols such as cafeic acid, ferulic acid, and protocatechuic acid (Zhang *et al.*, 2018). This research identified a positive regulation of the daf-16 gene associated with the oxidative stress response, effectively decreasing the accumulation of reactive oxygen species (ROS). There is also some clinical evidence in humans, regarding the beneficial effects of these phenols in treating dementia (Quinn *et al.*, 2004; Kovacic, 2017).

One of the most recent and extensive works was focused on 921 older adults with a mean age of 81.2 years. These individuals were subjected to a diet enriched with flavonoids, including kaempferol, quercetin, myricetin, and isorhamnetin. The results obtained after one year of treatment revealed that only 23.89% (220 cases) developed Alzheimer's disease, pointing to a significant correlation between phenol intake and reduction in the incidence of AD. However, the mechanisms of action of phenols as an alternative treatment for Alzheimer's disease are not yet fully understood, nor whether this preventive effect lasts in the long term (Hollan *et al.*, 2020). There is a need for more comprehensive research in this field. Furthermore, the implementation of standardized protocols that broaden the spectrum of analysis is essential. These protocols could include high-throughput strategies to address the chemical complexity of phenols, as allowed by *in silico* analyses (Carecho *et al.*, 2023).

In silico studies

In the last four decades, with the increase of computational resources and advancement in microprocessing technologies, *in silico* studies have occupied a central role in drug discovery workflows. Moreover, *in silico* analysis of phenolic compounds has been applied to find alternative strategies for AD. A systematic increase in the number of publications regarding Alzheimer's with chemical-computational tools is the principal metric that reveals the interest of the scientific community. For the last decade (2013- 2023), a 2.5-fold increase regarding in silico research is evident, as shown in Figure 1A. In 2001, only 32 studies were carried out in this field, but in 2023, this number increased to 1,638 investigations and continues to grow. It is worth noting that a maximum was recorded in 2008, with a total of 4,597 published papers. Overall, to date, a total of 17,312 research studies have been published in this field (Dimensions, 10/10/23).

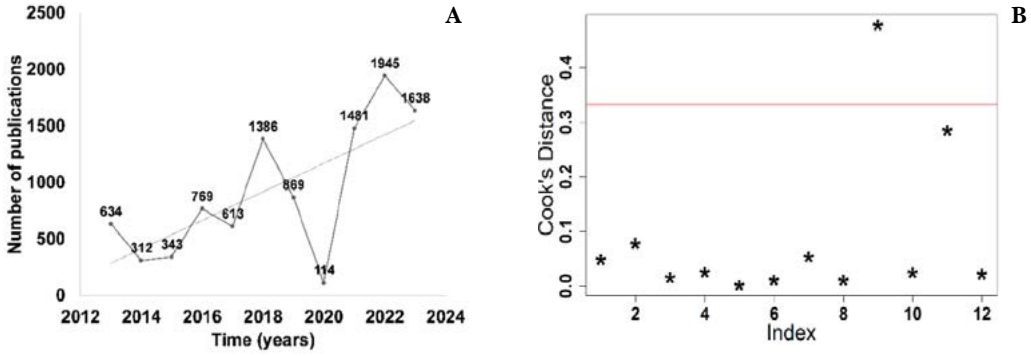

Figure 1. A) Scatter plot: sustained growth in academic contributions on Alzheimer's disease with chemical-computational tools in the last ten years (2013-2023). B) Cook's distance for annual publications from 2012 to 2023.

The sustained growth in academic contributions on Alzheimer's disease with chemical-computational tools in the last ten years (2013-2023) is summarized in Figure 1. Each point represents the influence of a specific year in the regression model. The red line denotes the overall threshold (4/n), where points above are considered potentially influential. Notably, the year 2020 (index 9) exceeds this threshold, indicating a significant influence on the model. The increase in the number of investigations is reflected in a positive upward trend, with a value of $R^2=0.48$ and $\alpha<0.05$. It is important to note that although the correlation value is not statistically significant, this is due to the leverage effect caused by the low scientific production in 2020.

Two methods were employed to determine the influence of the year 2020 on the observed correlation. First, a residual analysis to assess the discrepancies between the observed values and those predicted by the model annually, was performed. Subsequently, the specific impact of 2020 on the regression model was quantified using Cook's distance. This analysis yielded a value of 0.4782631, significantly exceeding the typically established threshold, illustrated by a red line (Figure 1B). Generally, those points in which Cook's distance exceeds 4/n are considered as influent or outliers. In this case, with n corresponding to the total number of observations (12 years), the threshold is 0.3333; since 0.4782631 exceeds this threshold, it is evident that the data corresponding to the year 2020 exerts a significant influence on the model, substantially affecting the estimates of its coefficients. The results mentioned above are supported by bibliometric network analysis of co-occurring terms.

Three clusters were identified in the first decade (2001-2011) (Figure 2A). Cluster I covered topics related to drugs and studies of a genetic nature, in addition to research exploring the action of peptide aggregates such as beta-amyloid and tau. Cluster II highlighted research aimed at therapeutic targets of protein origin with *in vitro* evaluations. Cluster III focused on work of genetic interest that explores the biological origin of Alzheimer's disease. During 2012-2023, four clusters were identified (Figure 2B): Cluster I group articles highlighting the biological properties of naturally occurring phenolic compounds. Cluster II complements the findings of Cluster I by highlighting the bioactivity of biomolecules in pathological events associated with Alzheimer's disease. As for Clusters III and IV, the outstanding inhibitory activity of phenols on various enzymes, including AChE, is highlighted. AChE

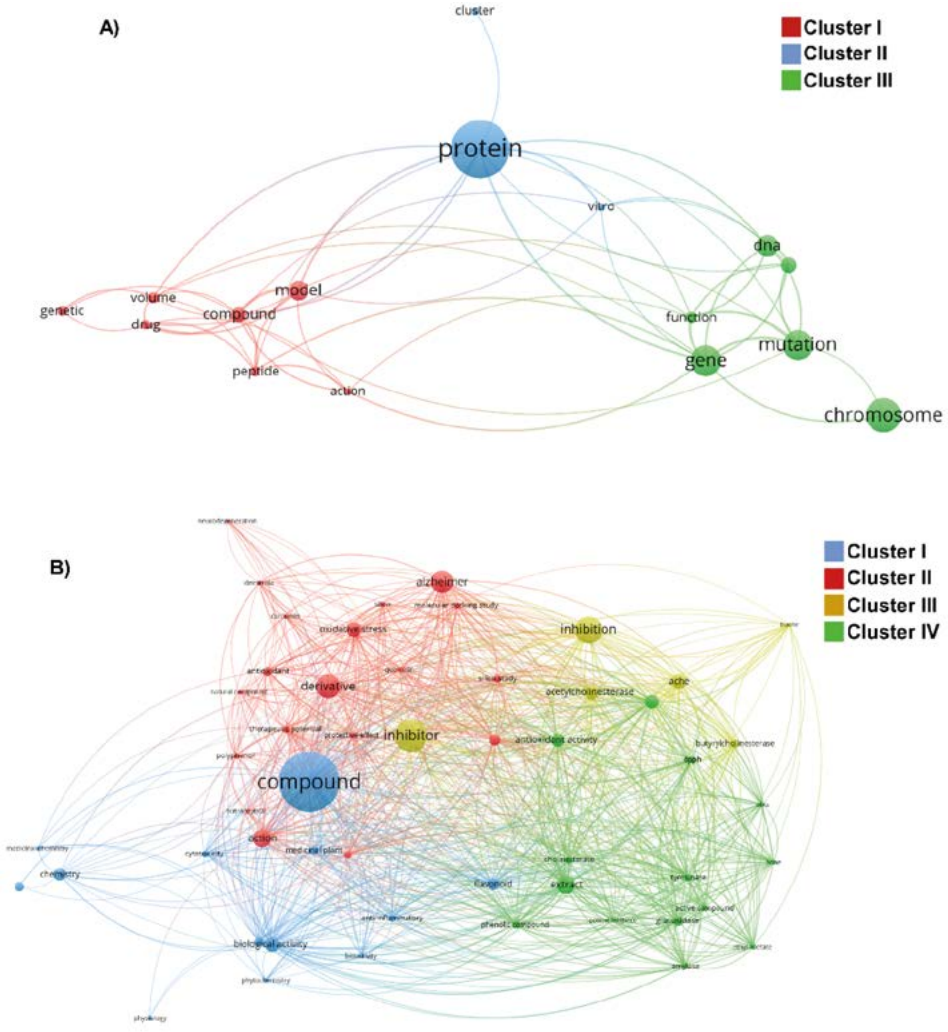

Figure 2. Bibliometric network analysis of co-occurring terms. A) most representative items used in Alzheimer's research from 2001-2011. B) most representative items of the last decade (2012-2023).

is essential in the degradation of the neurotransmitter acetylcholine and has been a critical therapeutic target since the early stages of Alzheimer's research. The *in silico* node shows a significant connection to this network's four previously mentioned clusters; the results are presented in Figure 2, where the contribution of computational-theoretical research to Alzheimer's disease is evident. This result differs from the network corresponding to 2001-2011, where the clusters focus on experimental (*in vitro*) approaches and place the items "cluster," which refers to *in silico* studies, in a distant position with low interconnection.

According to our results, the networks have allowed the definition of two key lines of research in recent years (Figure 3). The first of these lines focuses on predicting the bioactivity of phenolic compounds, with particular emphasis on the antioxidant and anti-inflammatory activity of flavonoids (Cluster I). In comparison, the second cluster focuses on the deciphering of the mechanisms of action of phenols in AD pathological events, such as oxidative stress, inflammation, and protein aggregation. Both clusters are

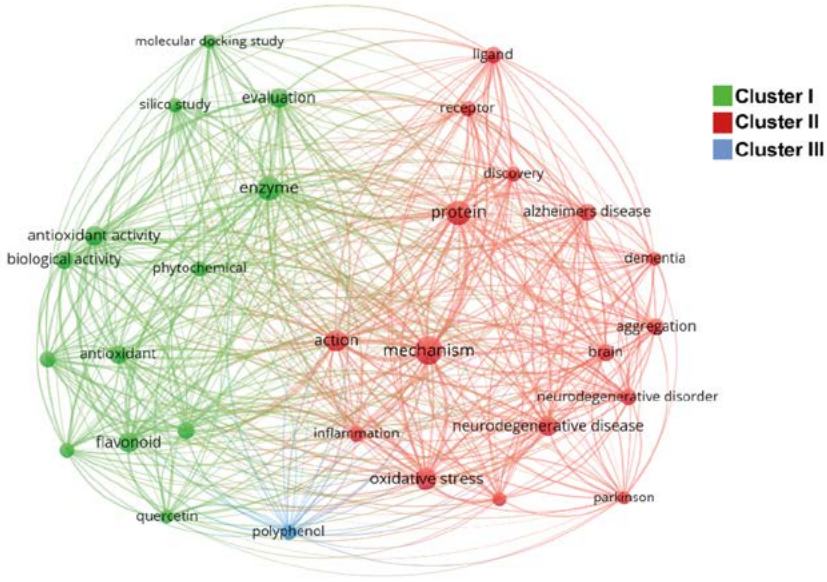

Figure 3. Generalized bibliometric network based on the most representative items of the last two decades (2001-2023). In the network, two apparent aspects can be identified that start from a common origin (polyphenols), which correspond to studies carried out on phenolic compounds, and the second to mechanisms of action on pathogenic events in Alzheimer's disease (green and red), respectively.

interconnected through the "polyphenol" node (Cluster II), representing a pivot in the chemical computational studies of the last two decades. This third network encompasses the studies analyzed in this research (2001-2023). It underlines the importance of evaluating these phytochemicals in therapeutic targets of AD with the assistance of computational theoretical analyses.

The above is reflected in several reports, such as Benchikha and collaborators (2022), which describe an experimental model to evaluate different biological activities, *i.e.* antioxidant, hypoglycemic, and cholinesterase inhibition, enriched with chemical-computational analyses implementing molecular docking techniques. Moreover, these in silico analyses can approximate the binding affinity of the phenols present in the extract of zamarilla (*Teucrium polium* L) against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes, which are first-order therapeutic targets in the progression of AD. Another in silico report sought to evaluate 3150 phytochemicals of diverse origins, including phenolic compounds, to identify secondary metabolites with inhibitory potential against the BACE-1 (β-secretase) enzyme. The pipeline included a first screening phase based on pharmacokinetic profiles to select metabolites that met the predefined ranges in ADME processes (absorption, distribution, metabolism, and excretion). Molecular docking analysis was performed to select metabolites by comparing their binding energies with reference drugs. Subsequently, electronic effects and reactivity at the active site of the BACE-1 enzyme were evaluated using hybrid density functional theory (DFT). Taken together, *in silico* / computational tools allowed the identification of seven compounds (shinflavanone, glabrolide, glabrol, prenillicoflavone A, macleanine,

3a-dihydro-cadambine, and volvalerelactone B) that exhibited inhibitory potential against BACE-1.

However, *in silico* results should be subjected to experimental validation (*in vitro* and *in vivo*), as suggested by Arif *et al.*, 2020. Barai *et al.*, 2018 showed that docking and molecular dynamics analyses are tools that can be employed as tools to predict, compare, and target inhibitory bioactivities of phenol bergenin towards specific therapeutic targets related to Alzheimer's disease, such as acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), Tau protein kinase 1 and β-secretase (BACE-1). The ability of bergenin to exhibit dose-dependent inhibitory bioactivity, specifically about AChE and BuChE enzymes, was addressed in this report. Interestingly, the results from animal models (*in vivo*), showed a significant reduction in neuro-inflammation, suggesting a remarkable improvement in cognitive function in bergenin-treated rats. Consequently, it is pertinent to suggest that *in silico* analyses facilitate the prediction of the bioactivity of phenolic molecules on specific molecular targets, such as enzymes related to dementia. Through both in vitro and *in vivo* assays, these compounds have demonstrated their capacity as bioactive molecules with promising pharmacological applications. Likewise, it is worth noting that *in silico* analyses enabled massive screening of secondary metabolites, resulting in the identification of specific phenols with activity on crucial Alzheimer's disease (AD) related targets. Furthermore, these computational approaches provided accurate predictions of anti-Alzheimer's bioactive activities and contributed to a deeper understanding of the mechanisms of action of phenols in this disease (Monteiro *et al.*, 2018; Cruz-Vicente *et al.*, 2021).

The impact of chemical-computational tools on drug Discovery

Drug development has undergone remarkable advances over the years. The traditional approach consists of evaluating the efficacy of secondary metabolites through a process that involves three fundamental stages, as shown in Figure 4. The first of these stages is discovery, in which the identification of candidate molecules and their subsequent synthesis is carried out. This process begins with a broad chemical space to illustrate the magnitude of the challenge to be considered, and according to other models, the starting point is 9,000 molecules, which will eventually require four to nine years of experimental research (De la Calle, 2009). The second stage is known as the preclinical stage and involves profiling a more manageable and economically viable set of molecules. In this phase, the number of molecules is significantly reduced to around 100 (less than 1%). These molecules are subjected to *in vitro* assays, which allows for the identification and discarding of those chemical units that lack biological activity. In this phase, screening is performed on *in vitro* models in line with their biochemical characterization, which allows for refining the selection of candidates with therapeutic potential in a time interval of three to four years of analysis (Hernández Cabanillas, 2020). In the clinical phase, ca. five molecules undergo rigorous evaluations in patients, and only one of them manages to meet the necessary regulatory requirements to be introduced into the market (Saldívar-González *et al.*, 2017). This final stage can extend over a period that can be around ten years of clinical explorations in animal models and, finally, be transferred to human candidates (Carranza-Aranda *et al.*, 2019).

This lengthy drug development process can take up to 15 to 18 years before a drug is approved (De la Fuente, 2009; Hernández Cabanillas, 2020). This extended duration poses significant challenges that include delayed response to public health emergencies, high costs that often fall on the consumer, limited access to treatments, disincentives for innovation, and the risk of treatments becoming obsolete, as has occurred in the case of Alzheimer's disease (Goldman *et al.*, 2018). Consequently, optimizing drug development processes and reducing costs without compromising drug quality have become imperative. In this area, pharmaceutical research, through computational chemistry, plays an essential role during drug development (Saldívar-González *et al.*, 2017) with computer-aided design (CADD). The CADD has become a relevant approach that streamlines this process and allows the execution of predictive and comprehensive analyses of secondary metabolites, significantly reducing periods that can hover between three and twelve years of research (Figure 4). Furthermore, as a result, these challenges lead to the efficient selection, design,

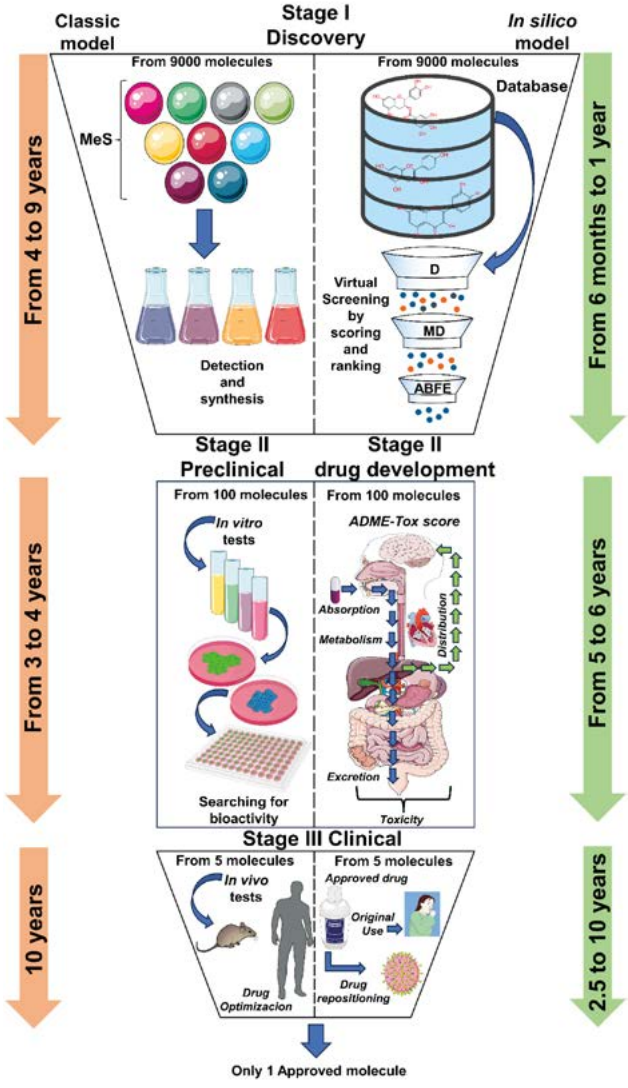

Figure 4. Comparative model of the classical (experimental) drug design versus the in silico model.

optimization, and repositioning of the most promising phytochemical candidates and their orientation toward fundamental molecular targets in Alzheimer's disease progression (Lin, 2022; Ece, 2023).

In summary, *in silico* assays have improved the efficiency and cost-effectiveness of drug design, minimizing investment in laboratory experimental resources, and optimizing the management of new drug alternatives (Shaker *et al.*, 2021). Using theoretical-computational approaches such as molecular docking and molecular dynamics has revolutionized the discovery of natural molecules by predicting how they bind and react in biological systems and improves efficiency in the identification of pharmacological compounds, accelerating the availability and reducing costs of effective treatments, offering an alternative to the classical method.

On the other hand, in stage I, or the discovery phase of the *in silico* approach, candidate molecules are obtained from open-access databases, mostly containing naturally occurring compounds (Önder *et al.*, 2023). Then, through computational execution, structural similarity studies are carried out, and affinities are calculated using techniques such as docking (D), molecular dynamics (MD), and absolute binding free energy (ABFE). These techniques allow the identification of potential ligands with the ability to interact and bind to therapeutic targets, as depicted in Figure 4. In stage II, corresponding to drug development (Geerts & Vander Heyden, 2011), theoretical-computational predictions are carried out to estimate and optimize ADME-Tox pharmacokinetic properties (Absorption, Distribution, Metabolism, Excretion, and Toxicity). These processes are fundamental in drug research and development (Cerny *et al.*, 2023), as they predict possible drug interactions with the organism through the calculation of ADME-Tox properties, thus providing a detailed profile of their efficacy and safety. Computational calculations play a crucial role by ruling out inefficient, nonspecific, toxic or unstable molecules (Bruno *et al.*, 2019; Więckowska *et al.*, 2020). With this, the allocation of resources and time to discover new natural molecules with pharmacological potential in neurodegenerative diseases can be optimized (Loele *et al.*, 2022). In Phase III, chemical-computational analyses have enabled the repositioning and optimization of drugs, with successful examples such as the case of lopinavir, a drug initially designed to treat HIV-1 infection. This drug was redirected to emergency health care to treat severe acute respiratory syndrome (SARS) caused by COVID-19 (Mohamed *et al.*, 2021; Ramirez Salinas *et al.*, 2023).

In this review, we have evaluated the scientific evidence related to the effects of phenols, a group of secondary metabolites of plant origin, in preventing and treating Alzheimer's disease, the most common form of dementia worldwide. The results of this analysis indicate that phenols present therapeutic potential in addressing Alzheimer's disease, given their remarkable antioxidant, anti-inflammatory, and neuroprotective properties and ability to modulate cell signaling. Despite these promising findings, it is worth noting that some reviewed studies have presented shortcomings and contradictions. Therefore, further research in this field is mandatory for a more complete understanding of the benefits and limitations of phenols in Alzheimer's disease.

Epidemiological studies reviewed have revealed an inversely proportional relationship between the consumption of phenol-rich foods, such as tea, coffee, wine, chocolate, and

fruits, and the risk of developing Alzheimer's disease (Pintać *et al.*, 2022; Rivero-Pino *et al.*, 2023). These results support the hypothesis that phenols may prevent or delay the onset of this disease by protecting neurons from oxidative stress and inflammation, two critical pathogenic factors in Alzheimer's disease (Cherbuin *et al.*, 2022; Juiz & Lenarz, 2023). However, it is fundamental to recognize that these studies have certain limitations. These include indirect measures to assess phenol consumption, variability in diagnostic criteria, and the difficulty in establishing a robust causal relationship between exposure and effect. Therefore, there is a clear need for more rigorous and specific epidemiological studies. These studies should assess the consumption of individual phenols or groups of phenols, employ biomarkers for both exposure and effect, standardize models for the administration of phenols (Ohishi *et al.*, 2021), and conduct long-term follow-up of participants to confirm detected changes in the incidence and progression of Alzheimer's disease.

The *in vitro* and *in vivo* studies reviewed provide evidence of the molecular and cellular mechanisms through which phenols may exert a beneficial effect on Alzheimer's disease (Phan *et al.*, 2019). These investigations demonstrate that phenols can reduce the formation and aggregation of amyloid and tau proteins, which are responsible for the growth of senile plaques and neurofibrillary tangles, respectively. Such aggregates are distinctive histological features in AD brains (Barai *et al.*, 2018). In addition, phenols can improve mitochondrial function (Mthembu *et al.*, 2021; Flannery & Trushina, 2019), restore calcium homeostasis (Palmerini *et al.*, 2005;) and induce autophagy (Michałowicz *et al.*, 2018; Hung & Livesey, 2021). Moreover, phenols have demonstrated the ability to promote neurogenesis (Corona & Vauzour, 2017) and to modulate the activity of various cell signaling pathways, acting on transcription factors (CREB), insulin receptor substrate (IRS), signal transducers, and activator of transcription (STAT3), among others. These pathways play a significant role in the progression of Alzheimer's dementia and other neurodegenerative diseases. (Kooshki *et al.*, 2023). However, it is worth noting that these *in vitro* and *in vivo* studies have notable drawbacks, such as lack of specificity and selectivity of phenols, assessment of synergistic activity in crude extracts, variability in experimental models, lack of randomized controlled trials, and lack of translation of results to the clinical level (Karim *et al.*, 2020). Therefore, further experimental support in representative models under standardized conditions is always required. It also includes considering the activity of phenols in assays that reproduce the pathological conditions of Alzheimer's disease.

A clear trend shown in the scatter plot (Figure 1A) presents a steady increase in papers incorporating computational theoretical studies over time. In addition, through the generation of co-occurrence networks, the leading research approaches during the last two decades have been identified. From 2001 to 2011, the focus was on questions related to genetic diagnostics and causation (Cluster III) and exploring various protein hypotheses (Cluster II). Collectively, these investigations have moved to the development of an integrative model of Alzheimer's disease on set and progression (Cluster I). In the second period, which covered from 2012 to 2023, the co-occurrence network revealed an exponential increase, with the implementation of chemical-computational tools and the study of phenols as inflection points, leading to a radical change in the focus of research, which emphasizes the identification of protein targets of Alzheimer's disease (Cluster III),

where *in silico* analyses allowed to model phenolic compounds' affinity and intermolecular interactions, *i.e.*, inhibition mechanisms of AChE and other enzymes (Cluster II and IV). The previous proposes a multidisciplinary approach that addresses different pathogenic events in Alzheimer's disease (Cluster I) by studying bioactive molecules such as phenols. The *in silico* publications reviewed highlight the applicability of theoretical, computational calculations as complementary tools for the design and optimization of new phenol-based drugs to treat Alzheimer's disease, with computational techniques such as virtual screening, molecular docking, molecular dynamics, and pharmacological modeling the selection of ligands that interact with enzymes involved in AD is possible (Barai *et al.*, 2018; Arif *et al.*, 2020), as well as, prediction and optimization of pharmacokinetic and pharmacodynamic properties of the potential phenolic drug (Kumar & Ayyannan, 2022; Sahadevan *et al.*, 2022). Integrating computational chemistry into the classical drug design model represents an opportunity to foster innovation and develop more effective and accessible treatments for patients suffering from multifactorial neurodegenerative diseases, such as Alzheimer's.

CONCLUSION

This review highlights the role of phenols as promising candidates in developing new drugs for Alzheimer's dementia due to their multiple beneficial effects on general health, particularly those reported in mitigating pathogenic progression. However, it is also clear that research in this field still needs improving since systematization and deepening must come from multidisciplinary and integrative studies (epidemiological data, molecular investigations, and computational studies). Epidemiological studies may lack precision and traceability in some cases. In contrast, *in vitro* and *in vivo* studies, although promising, need to address specificity issues and validate their findings in controlled clinical trials. On the other hand, in silico studies have demonstrated efficiency and cost-effectiveness but require experimental substantiation and validation. Consequently, collaborative epidemiological, *in vitro*, *in vivo*, and *in silico* studies should be conducted as an integral part of the research and development process for new drugs. This interdisciplinary collaboration will broaden the understanding of the effects of phenols in Alzheimer's disease and promote significant advances in the search for effective and accessible treatments for patients facing this multifactorial neurodegenerative disease.

REFERENCES

Akula, R., & Ravishankar, G. A. (2011). Influence of abiotic stress signals on secondary metabolites in plants. *Plant signaling & behavior, 6*(11), 1720-1731. https://doi.org/10.4161/psb.6.11.17613

Alhazmi, H. A., & Albratty, M. (2022). An update on the novel and approved drugs for Alzheimer disease. *Saudi Pharmaceutical Journal*. https://doi.org/10.1016/j.jsps.2022.10.004

Ammar, S., Abidi, J., Luca, S., Boumendjel, M., SkalickaβWoźniak, K., & Bouaziz, M. (2020). Untargeted metabolite profiling and phytochemical analysis based on RP-HPLC-DAD-QTOF-MS and MS/MS for discovering new bioactive compounds in *Rumex algeriensis* flowers and stems.*Phytochemical analysis*: PCA. https://doi.org/10.1002/pca.2928.

Angeloni, C., Malaguti, M., Barbalace, M. C., & Hrelia, S. (2017). Bioactivity of olive oil phenols in neuroprotection. *International Journal of Molecular Sciences, 18*(11), 2230. https://doi.org/10.3390/ijms18112230

Arif, N., Subhani, A., Hussain, W., & Rasool, N. (2020). *In silico* inhibition of BACE-1 by selective phytochemicals as novel potential inhibitors: molecular docking and DFT studies. *Current Drug Discovery Technologies, 17*(3), 397-411. DOI: https://doi.org/10.2174/1570163816666190214161825

Arrieta-Cruz, I., & Gutiérrez-Robledo, L. M. (2015). Demencias en México: la necesidad de un Plan de Acción. *Gaceta Médica de México, 151*(5), 667-673 https://www.medigraphic.com/cgibin/new/resumen.cgi?IDARTICULO=61983

Arruda, H., Silva, E. R., Lessa, M., Proença Jr, D., & Bartholo, R. (2022). VOSviewer and bibliometrix. *Journal of the Medical Library Association: JMLA, 110*(3), 392. doi: 10.5195/jmla.2022.1434

Asgar, M. D. (2013). Anti-diabetic potential of phenolic compounds: A review. *International Journal of Food Properties, 16*(1), 91-103.https://doi.org/10.1080/10942912.2011.595864

Azar, J., Salama, M., Chidambaram, S. B., Al Balushi, B., Essa, M. M., & Qoronfleh, M. W. (2021). Precision health in Alzheimer disease: Risk assessment based strategies. *Precision Medical Sciences, 10*(2), 54-70. https://doi.org/10.1002/prm2.12036

Bach, J., & Weber, T. (1989). Enzymic synthesis of mevalonic acid in plants. In Biological Role of Plant Lipids (pp. 279-282). Boston, MA: Springer US. https://doi.org/10.1007/978-1-4684-1303-8_66

Barai, P., Raval, N., Acharya, S., Borisa, A., Bhatt, H., & Acharya, N. (2019). Neuroprotective effects of bergenin in Alzheimer's disease: Investigation through molecular docking, *in vitro* and *in vivo* studies. *Behavioural Brain Research*, 356, 18-40. https://doi.org/10.1016/j.bbr.2018.08.010

Behl, T., Bungau, S., Kumar, K., Zengin, G., Khan, F., Kumar, A., & Mosteanu, D. E. (2020). Pleotropic effects of polyphenols in cardiovascular system. *Biomedicine & Pharmacotherapy*, 130, 110714. https://doi.org/10.1016/j.biopha.2020.110714

Beigoli, S., Behrouz, S., Memarzia, A., Ghasemi, S. Z., Boskabady, M., Marefati, N., & Boskabady, M. H. (2021). Effects of Allium cepa and its constituents on respiratory and allergic disorders: A comprehensive review of experimental and clinical evidence. Evidence-based complementary ad alternative medicine: eCAM, 2021.https://doi.org/10.1155/2021/5554259

Benchikha, N., Messaoudi, M., Larkem, I., Ouakouak, H., Rebiai, A., Boubekeur, S., & Youssef, F. S. (2022). Evaluation of possible antioxidant, anti-hyperglycaemic, anti-alzheimer and anti-inflammatory effects of *Teucrium polium* aerial parts (Lamiaceae). *Life, 12*(10), 1579. https://doi.org/10.3390/life12101579

Bermejo-Pareja, F., Llamas-Velasco, S., & Villarejo-Galende, A. (2016). Alzheimer's disease prevention: A way forward. *Revista Clínica Española (English Edition), 216*(9), 495-503. https://doi.org/10.1016/j.rceng.2016.06.006

Bhuyan, D. J., & Basu, A. (2017). Phenolic compounds potential health benefits and toxicity. Utilisation of bioactive compounds from agricultural and food production waste, 27-59.

Bondam, A. F., da Silveira, D. D., dos Santos, J. P., & Hoffmann, J. F. (2022). Phenolic compounds from coffee by-products: Extraction and application in the food and pharmaceutical industries. *Trends in Food Science & Technology*, 123, 172-186 https://doi.org/10.1016/j.tifs.2022.03.013

Böttger, A., Vothknecht, U., Bolle, C., Wolf, A., Böttger, A., Vothknecht, U., & Wolf, A. (2018). Secondary metabolites in plants: general introduction. Lessons on Caffeine, Cannabis & Co: Plant-derived Drugs and their Interaction with Human Receptors, 143-152. https://doi.org/10.1007/978-3-319-99546-5_9

Bruno, A., Costantino, G., Sartori, L., & Radi, M. (2019). The *in silico* drug discovery toolbox: applications in lead discovery and optimization. *Current Medicinal Chemistry, 26*(21), 3838-3873. DOI: https://doi.org/10.2174/0929867324666171107101035

Cammisuli, D. M., Cipriani, G., Giusti, E. M., & Castelnuovo, G. (2022). Effects of reminiscence therapy on cognition, depression and quality of life in elderly people with Alzheimer's disease: A systematic review of randomized controlled trials. *Journal of Clinical Medicine, 11*(19), 5752.https://doi.org/10.1038/s41398-020-01168-8

Carecho, R., Carregosa, D., Ratilal, B. O., Figueira, I., Ávila-Gálvez, M. A., Dos Santos, C. N., & Loncarevic-Vasiljkovic, N. (2023). Dietary (Poly) phenols in Traumatic Brain Injury. *International Journal of Molecular Sciences, 24*(10), 8908. https://doi.org/10.3390/ijms24108908

Caretto, S., Linsalata, V., Colella, G., Mita, G., Lattanzio, V. (2015). Carbon fluxes between primary metabolism and phenolic pathway in plant tissues under stress. *International Journal of Molecular Sciences, 16*(11), 26378-26394. https://doi.org/10.3390/ijms161125967

Carranza-Aranda, A. S., Segura-Cabrera, A., Cárdenas-Vargas, A., & Herrera-Rodríguez, S. E. (2020). Reposicionamiento de fármacos identificados por métodos computacionales (SVBS), para su uso como terapias contra el cáncer. *Salud Jalisco, 7*(1), 48-57. https://www.medigraphic.com/cgi-bin/new/resumenI.cgi?IDARTICULO=93753

Carregosa, D., Pinto, C., Ávila Gálvez, M. Á., Bastos, P., Berry, D., & Santos, C. N. (2022). A look beyond dietary (poly) phenols: The low molecular weight phenolic metabolites and their concentrations in

human circulation. *Comprehensive Reviews in Food Science and Food Safety, 21*(5), 3931-3962. https://doi.org/10.1111/1541-4337.13006

Cerny, M. A., Spracklin, D. K., & Obach, R. S. (2023). Human Absorption, Distribution, Metabolism, and Excretion Studies: Origins, Innovations, and Importance. *Drug Metabolism and Disposition, 51*(6), 647-656. DOI: https://doi.org/10.1124/dmd.122.001006

Cherbuin, N., Walsh, E. I., Leach, L., Brüstle, A., Burns, R., Anstey, K. J., & Baune, B. T. (2022). Systemic inflammation predicts Alzheimer pathology in community samples without dementia. *Biomedicines, 10*(6), 1240. https://doi.org/10.3390/biomedicines10061240

Chomel, M., GuittonnyβLarchevêque, M., Fernandez, C., Gallet, C., DesRochers, A., Paré, D, and Baldy, V. (2016). Plant secondary metabolites: a key driver of litter decomposition and soil nutrient cycling. *Journal of Ecology, 104*(6), 1527-1541. https://doi.org/10.1111/1365-2745.12644

Chu, J., Zhang, W., Liu, Y., Gong, B., Ji, W., Yin, T., & Yin, Y. (2023). Biomaterials-based anti-inflammatory treatment strategies for Alzheimer's disease. *Neural Regeneration Research, 19*(1), 100-115. DOI: 10.4103/1673-5374.374137

ICD-11 (2023). Clasificación internacional de enfermedades, 11.ª edición. 1 para estadísticas de mortalidad y morbilidad (Versión: 01/2023) http://id.who.int/icd/entity/795022044

Corona, G., & Vauzour, D. (2017). Neuroprotective Effects of Polyphenols in Aging and AgeβRelated Neurological Disorders. Neuroprotective Effects of Phytochemicals in Neurological Disorders, 65-78. https://doi.org/10.1002/9781119155195.ch3

Cruz-Vicente, P., Passarinha, L. A., Silvestre, S., & Gallardo, E. (2021). Recent developments in new therapeutic agents against Alzheimer and Parkinson diseases: in-silico approaches. *Molecules, 26*(8), 2193. https://doi.org/10.3390/molecules26082193

De la Calle, F. (2009). Fármacos de origen marino. *Treballs de la Societat Catalana de Biologia*, 58, 141-155. DOI: 10.2436/20.1501.02.50

de Paulo Farias, D., de Araujo, F. F., Neri-Numa, I. A., & Pastore, G. M. (2021). Antidiabetic potential of dietary polyphenols: A mechanistic review. *Food Research International*, 145, 110383. https://doi.org/10.1016/j.foodres.2021.110383

Devi, S. A., & Chamoli, A. (2020). Polyphenols as an effective therapeutic intervention against cognitive decline during normal and pathological brain aging. *Reviews on New Drug Targets in Age-Related Disorders*, 159-174. https://doi.org/10.1007/978-3-030-42667-5_7

Dhingra, A. K., & Chopra, B. (2023). Neuroprotection of Multitargeted Phytochemicals against Alzheimer: A Desperate Need from Nature. *The Natural Products Journal, 13*(5), 2-22. https://doi.org/10.2174/2210315512666220627153553

Digital Science. (2018-) Dimensions [Software] available from https://app.dimensions.ai. Accessed on (10/10/2023), under licence agreement.

Ece, A. Computer-aided drug design. BMC Chemistry 17, 26 (2023). https://doi.org/10.1186/s13065-023-00939-w https://doi.org/10.1186/s13065-023-00939-w

Elansary, O., Szopa, A.H., Klimek-Szczykutowicz, M., Jafernik, K., Ekiert, H., Mahmoud, E. A., & O. El-Ansary, D. (2019). Mammillaria species—Polyphenols studies and anti-cancer, anti-oxidant, and anti-bacterial activities. *Molecules, 25*(1), 131. https://doi.org/10.3390/molecules25010131

Essa, M. M., Akbar, M., & Guillemin, G. (Eds.). (2016). The Benefits of Natural Products for Neurodegenerative Diseases (Vol. 232). Cham, Switzerland: Springer. https://doi.org/10.1007/978-3-319-28383-8

Fernández, S. S. M., & Ribeiro, S. M. L. (2018). Nutrition and Alzheimer disease. *Clinics in geriatric medicine, 34*(4), 677-697. Doi:https://doi.org/10.1016/j.cger.2018.06.012

Flannery, P. J., & Trushina, E. (2019). Mitochondrial dysfunction in Alzheimer's disease and progress in mitochondria-targeted therapeutics. *Current Behavioral Neuroscience Reports*, 6, 88-102. https://doi.org/10.1007/s40473-019-00179-0

Foscolou, A., Chrysohoou, C., Dimitriadis, K., Masoura, K., Vogiatzi, G., Gkotzamanis, V., & Stefanadis, C. (2021). The association of healthy aging with multimorbidity: IKARIA study. *Nutrients, 13*(4), 1386. https://doi.org/10.3390/nu13041386

Gao, S., Burney, H. N., Callahan, C. M., Purnell, C. E., & Hendrie, H. C. (2019). Incidence of dementia and Alzheimer disease over time: A metaβanalysis. *Journal of the American Geriatrics Society, 67*(7), 1361-1369. https://doi.org/10.1111/jgs.16027

Garcia-Mier, L., Jimenez-García, S. N., Salazar, C. S., Contreras-Medina, L. M., Escalante, K. E., Martinez, C. G., & Feregrino-Perez, A. A. (2019). Strategies that influence the production of secondary metabolites in plants. *Nutritional Quality Improvement in Plants*, 231-270. https://doi.org/10.1007/978-3-319-95354-0_9

Gauthier, S., Rosa-Neto, P., Morais, J. A., & Webster, C. (2021). World Alzheimer Report 2021: Journey through the diagnosis of dementia. *Alzheimer's Disease International*, 2022, 30. https://www.alzint.org/resource/world-alzheimer-report-2021/

Geerts, T., & Vander Heyden, Y. (2011). In silico predictions of ADME-Tox properties: drug absorption. *Combinatorial chemistry & high throughput screening, 14*(5), 339-361.

Gibney, E. R., Milenkovic, D., Combet, E., Ruskovska, T., Greyling, A., González-Sarrías, A., & Rodriguez-Mateos, A. (2019). Factors influencing the cardiometabolic response to (poly) phenols and phytosterols: A review of the COST Action POSITIVe activities. *European journal of nutrition, 58*(Suppl 2), 37-47. https://doi.org/10.1007/s00394-019-02066-6

Goldman, D. P., Fillit, H., & Neumann, P. (2018). Accelerating Alzheimer's disease drug innovations from the research pipeline to patients. *Alzheimer's & Dementia, 14*(6), 833-836. https://doi.org/10.1016/j.jalz.2018.02.007

González-Cabanelas, D., Hammerbacher, A., Raguschke, B., Gershenzon, J., & Wright, L. P. (2016). Quantifying the metabolites of the methylerythritol 4-phosphate (MEP) pathway in plants and bacteria by liquid chromatography–triple quadrupole mass spectrometry. In Methods in enzymology (Vol. 576, pp. 225-249). Academic Press. https://doi.org/10.1016/bs.mie.2016.02.025

Gustavsson, E., Raaschou, P., Lärfars, G., Sandman, L., & Juth, N. (2022). The ethics of disease-modifying drugs targeting Alzheimer disease: response to our commentators. *Journal of Medical Ethics, 48*(3), 193-193. http://dx.doi.org/10.1136/medethics-2022-108157

Hernández Cabanillas, A. (2020). Prospección de nuevos antiinfecciosos, desde la naturaleza a la síntesis química. Tesis Doctoral inédita leída en la Universidad Autónoma de Madrid. Facultad de Ciencias, Departamento de Química Orgánica. https://repositorio.uam.es/bitstream/handle/10486/692428/hernandez_cabanillas_alfredo.pdf?sequence=1&isAllowed=y

Hernández-Reyes, J., Galo-Hooker, E., Ruiz-Delgado, G. J., & Ruiz-Argüelles, G. J. (2012). Systemic immunoglobulin light-chain amyloidosis (AL) in Mexico: a single institution, 30-year experience. *Revista de investigacion clinica, 64*(6. II), 604-608 https://www.medigraphic.com/cgi-bin/new/resumenI.cgi?IDARTICULO=42763

Hithamani, G., Naveen, J., & Pushpalatha, H. G. (2023). Phenolic Compounds: Stress Markers of Plants and Their Protective Role. In Plant Metabolites under Environmental Stress (pp. 249-276). https://doi.org/10.1201/9781003304869

Holland, T. M., Agarwal, P., Wang, Y., Leurgans, S. E., Bennett, D. A., Booth, S. L., & Morris, M. C. (2020). Dietary flavonols and risk of Alzheimer dementia. *Neurology, 94*(16), e1749-e1756. DOI: https://doi.org/10.1212/WNL.0000000000008981

Huang, L. K., Chao, S. P., & Hu, C. J. (2020). Clinical trials of new drugs for Alzheimer disease. *Journal of biomedical science, 27*(1), 1-13. https://doi.org/10.1186/s12929-019-0609-7

Hung, C., & Livesey, F. J. (2021). Endolysosome and autophagy dysfunction in Alzheimer disease. *Autophagy, 17*(11), 3882-3883. https://doi.org/10.1080/15548627.2021.1963630

Jamwal, K., Bhattacharya, S., & Puri, S. (2018). Plant growth regulator mediated consequences of secondary metabolites in medicinal plants. *Journal of applied research on medicinal and aromatic plants*, 9, 26-38. https://doi.org/10.1016/j.jarmap.2017.12.003

Juiz, J., & Lenarz, T. (2023). Alzheimerβs disease amyloid pathology correlates with higher auditory thresholds and increased oxidative stress and cochlear inflammation in a mouse model combining presbycusis and Alzheimerβs disease. *Laryngo-Rhino-Otologie*, 102, S294-S294. DOI: 10.1055/s-0043-1767438

Karim, N., Khan, H., Khan, I., Guo, O., Sobarzo-Sánchez, E., Rastrelli, L., & Kamal, M. A. (2020). An increasing role of polyphenols as novel therapeutics for Alzheimer's: A review. *Medicinal chemistry, 16*(8), 1007-1021. https://doi.org/10.2174/1573406415666191105154407

Khan, H., Ullah, H., Aschner, M., Cheang, W. S., & Akkol, E. K. (2019). Neuroprotective effects of quercetin in Alzheimer's disease. *Biomolecules, 10*(1), 59. https://doi.org/10.3390/biom10010059

Khokar, R., Hachani, K., Hasan, M., Othmani, F., Essam, M., Al Mamari, A., & Khan, S. A. (2021). Anti-Alzheimer potential of a waste by-product (peel) of Omani pomegranate fruits: Quantification of phenolic compounds, *in-vitro* antioxidant, anti-cholinesterase and *in-silico* studies. *Biocatalysis and Agricultural Biotechnology,* 38, 102223. https://doi.org/10.1016/j.bcab.2021.102223

Kim, S., Lee, E. Y., Hillman, P. F., Ko, J., Yang, I., & Nam, S. J. (2021). Chemical structure and biological activities of secondary metabolites from *Salicornia europaea* L. *Molecules, 26*(8), 2252. https://doi.org/10.3390/molecules26082252

Kooshki, L., Zarneshan, S. N., Fakhri, S., Moradi, S. Z., & Echeverria, J. (2023). The pivotal role of JAK/STAT and IRS/PI3K signaling pathways in neurodegenerative diseases: Mechanistic approaches to polyphenols and alkaloids. *Phytomedicine*, 112, 154686. https://doi.org/10.1016/j.phymed.2023.154686

Kovacic, P. (2017). Phenolic Antioxidants as Drugs for Alzheimerâ€™s Disease: Oxidative Stress and Selectivity. *Novel Approaches in Drug Designing & Development, 2*(5), 95-97. DOI: 10.19080/NAPDD.2017.02.555598

Kumar, S., & Ayyannan, S. R. (2022). Identification of new small molecule monoamine oxidase-B inhibitors through pharmacophore-based virtual screening, molecular docking and molecular dynamics simulation studies. *Journal of Biomolecular Structure and Dynamics*, 1-22. https://doi.org/10.1080/07391102.2022.2112082

Lattanzio, V. (2013). Phenolic compounds: introduction 50. Nat. Prod, 1543-1580. https://www.researchgate.net/profile/Vincenzo-Lattanzio/publication/249970213_Phenolic_Compounds_Introduction/links/0deec51e7bb057837e000000/Phenolic-Compounds-Introduction.pdf

Lin, Y. (2022). Review of Modern Computer-aided Drug Design Methods. *International Journal of Biology and Life Sciences, 1*(1), 47-50. DOI: https://doi.org/10.54097/ijbls.v1i1.3230

Li, Y., Huang, Y., Li, Z., & Sun, J. (2023). Recent Advances in Regioselective C–H Bond Functionalization of Free Phenols. *Molecules, 28*(8), 3397. https://doi.org/10.3390/molecules28083397

Loele, G., Chieffallo, M., Occhiuzzi, M. A., De Luca, M., Garofalo, A., Ragno, G., & Grande, F. (2022). Anticancer drugs: recent strategies to improve stability profile, pharmacokinetic and pharmacodynamic properties. *Molecules, 27*(17), 5436. https://doi.org/10.3390/molecules27175436

Luna-Guevara, M. L., Luna-Guevara, J. J., Hernández-Carranza, P., Ruíz-Espinosa, H., & Ochoa-Velasco, C. E. (2018). Phenolic compounds: A good choice against chronic degenerative diseases. *Studies in natural products chemistry*, 59, 79-108. https://doi.org/10.1016/B978-0-444-64179-3.00003-7

Makrakis, D., Holt, S. K., Bernick, C., Grivas, P., Gore, J. L., & Wright, J. L. (2022). Intravesical BCG and Incidence of Alzheimer Disease in Patients With Bladder Cancer: Results From an Administrative Dataset. *Alzheimer Disease & Associated Disorders, 36*(4), 307-311. DOI: 10.1097/WAD.0000000000000530

Mejía Arango, S., Singelmann, J., & Sáenz, R. (2020). Cognitive Decline Among the Elderly: A Comparative Analysis of Mexicans in Mexico and in the United States. *Developments in Demography in the 21st Century*, 179-194. https://doi.org/10.1007/978-3-030-26492-5_12

Michałowicz, J., Włuka, A., Cyrkler, M., Maćczak, A., Sicińska, P., & Mokra, K. (2018). Phenol and chlorinated phenols exhibit different apoptotic potential in human red blood cells (*in vitro* study). *Environmental toxicology and pharmacology*, 61, 95-101. https://doi.org/10.1016/j.etap.2018.05.014

Mohamed, K., Yazdanpanah, N., Saghazadeh, A., & Rezaei, N. (2021). Computational drug discovery and repurposing for the treatment of COVID-19: a systematic review. *Bioorganic chemistry*, 106, 104490. https://doi.org/10.1016/j.bioorg.2020.104490

Monteiro, A. F. M., Viana, J. D. O., Nayarisseri, A., Zondegoumba, E. N., Mendonça Junior, F. J. B., Scotti, M. T., & Scotti, L. (2018). Computational studies applied to flavonoids against Alzheimer's and Parkinson's diseases. *Oxidative medicine and cellular longevity*, 2018. https://doi.org/10.1155/2018/7912765

Mthembu, S. X., Dludla, P. V., Ziqubu, K., Nyambuya, T. M., Kappo, A. P., Madoroba, E., & Mazibuko-Mbeje, S. E. (2021). The potential role of polyphenols in modulating mitochondrial bioenergetics within the skeletal muscle: a systematic review of preclinical models. *Molecules, 26*(9), 2791. https://doi.org/10.3390/molecules26092791

Niu, S., Xia, M., Chen, M., Liu, X., Li, Z., Xie, Y., & Zhang, G. (2019). Cytotoxic polyketides isolated from the deep-sea-derived fungus *Penicillium chrysogenum* MCCC 3A00292. *Marine Drugs, 17*(12), 686. https://doi.org/10.3390/md17120686

Ohishi, T., Fukutomi, R., Shoji, Y., Goto, S., & Isemura, M. (2021). The beneficial effects of principal polyphenols from green tea, coffee, wine, and curry on obesity. *Molecules, 26*(2), 453. https://doi.org/10.3390/molecules2602045.

Önder, f. c. 2023 Discovery of donepezil-like compounds as potential acetylcholinesterase inhibitors determined by pharmacophore mapping-based virtual screening and molecular docking. *sdü Tıp Fakültesi Dergisi, 30*(2), 143-153. https://doi.org/10.17343/sdutfd.1204410

Palmerini, C. A., Carlini, E., Saccardi, C., Servili, M., Montedoro, G., & Arienti, G. (2005). Activity of olive oil phenols on lymphomonocyte cytosolic calcium. The Journal of Nutritional Biochemistry, 16(2), 109-113. https://doi.org/10.1016/j.jnutbio.2004.10.00

Phan, H. T., Samarat, K., Takamura, Y., Azo-Oussou, A. F., Nakazono, Y., & Vestergaard, M. D. C. (2019). Polyphenols modulate alzheimer's amyloid beta aggregation in a structure-dependent manner. *Nutrients, 11*(4), 756. https://doi.org/10.3390/nu11040756 https://doi.org/10.3390/nu11040756

Pintać, D., Bekvalac, K., Mimica-Dukić, N., Rašeta, M., Anđelić, N., Lesjak, M., & Orčić, D. (2022). Comparison study between popular brands of coffee, tea and red wine regarding polyphenols content and antioxidant activity. *Food Chemistry Advances*, 1, 100030. https://doi.org/10.1016/j.focha.2022.100030

Quinn, J., Kaye, J., Montine, T., & Stackman, R. (2004). Phytochemicals in Alzheimer disease: the development of clinical trials. Pharmaceutical biology, 42(sup1), 64-73. Oxidative Stress and Selectivity. *Novel Approaches in Drug Designing & Development, 2*(5), 95-97. https://doi.org/10.3109/138802090893531

Ramírez-Salinas, G. L., López Rincón, A., García Machorro, J., Correa Basurto, J., & Martínez Archundia, M. (2023). In silico screening of drugs that target different forms of E protein for potential treatment of COVID-19. *Pharmaceuticals, 16*(2), 296. https://doi.org/10.3390/ph16020296

Rasmann, S., Hiltpold, I., & Ali, J. (2012). The Role of Root-Produced Volatile Secondary Metabolites in Mediating Soil Interactions, Advances in Selected Plant Physiology Aspects, Montanaro, G, editor. InTech Open Access Publisher; DOI: 10.5772/34304.

Rigacci, S., & Stefani, M. (2015). Nutraceuticals and amyloid neurodegenerative diseases: a focus on natural phenols. *Expert Review of Neurotherapeutics, 15*(1), 41-52. https://doi.org/10.1586/14737175.2015.986101

Rivero-Pino, F., Grao-Cruces, E., Lopez-Enriquez, S., Alba, G., Marquez-Paradas, E., Claro-Cala, C. M., & Montserrat-de la Paz, S. (2023). Modulation of beta-amyloid-activated primary human neutrophils by dietary phenols from virgin olive oil. *Nutrients, 15*(4), 941. https://doi.org/10.3390/nu15040941

Rodriguez-Concepcion, M. (2016). The methylerythritol 4-phosphate pathway as a metabolic crossroad for microbial and plant volatile organic compounds. *Plant, Cell & Environment, 39*(12), 2589-2591. https://doi.org/10.1111/pce.1283

Rodriguez-Mateos, A., Heiss, C., Borges, G., & Crozier, A. (2014). Berry (poly) phenols and cardiovascular health. *Journal of agricultural and food chemistry, 62*(18), 3842-3851. https://doi.org/10.1021/jf403757g

Rojas-García, A., Fernández-Ochoa, Á., Cádiz-Gurrea, M. D. L. L., Arráez-Román, D., & Segura-Carretero, A. (2023). Neuroprotective effects of agri-food by-products rich in phenolic compounds. *Nutrients, 15*(2), 449. https://doi.org/10.3390/nu15020449

Romero-Márquez, J. M., Navarro-Hortal, M. D., Orantes, F. J., Esteban-Muñoz, A., Pérez-Oleaga, C. M., Battino, M., & Forbes-Hernández, T. Y. (2023). *In Vivo* Anti-Alzheimer and Antioxidant Properties of Avocado (*Persea americana* Mill.) Honey from Southern Spain. *Antioxidants, 12*(2), 404. https://doi.org/10.3390/antiox12020404

Sá, R. R., Matos, R. A., Silva, V. C., da Cruz Caldas, J., da Silva Sauthier, M. C., dos Santos, W. N. L., & Júnior, A. D. F. S. (2017). Determination of bioactive phenolics in herbal medicines containing *Cynara scolymus*, *Maytenus ilicifolia* Mart ex Reiss and *Ptychopetalum uncinatum* by HPLC-DAD. *Microchemical Journal*, 135, 10-15. https://doi.org/10.1016/j.microc.2017.07.009

Sagar, N. A., Pareek, S., & Gonzalez-Aguilar, G. A. (2020). Quantification of flavonoids, total phenols and antioxidant properties of onion skin: A comparative study of fifteen Indian cultivars. *Journal of food science and technology*, 57, 2423-2432. https://doi.org/10.1007/s13197-020-04277-w Ali

Sahadevan, R., Singh, S., Binoy, A., & Sadhukhan, S. (2022). Chemico-biological aspects of (−)-epigallocatechin-3-gallate (EGCG) to improve its stability, bioavailability and membrane permeability: Current status and future prospects. *Critical Reviews in Food Science and Nutrition*, 1-30. https://doi.org/10.1080/10408398.2022.2068500

Saldívar-González, F., Prieto-Martínez, F. D., & Medina-Franco, J. L. (2017). Descubrimiento y desarrollo de fármacos: un enfoque computacional. *Educación química, 28*(1), 51-58. https://doi.org/10.1016/j.eq.2016.06.002

Santos-Sánchez, N. F., Salas-Coronado, R., Hernández-Carlos, B., & Villanueva-Cañongo, C. (2019). Shikimic acid pathway in biosynthesis of phenolic compounds. *Plant physiological aspects of phenolic compounds*, 1, 1-15. DOI: 10.5772/intechopen.83815

Shahidi, F., & Yeo, J. (2018). Bioactivities of phenolics by focusing on suppression of chronic diseases: A review. *International journal of molecular sciences, 19*(6), 1573. https://doi.org/10.3390/ijms19061573

Shaker, B., Ahmad, S., Lee, J., Jung, C., & Na, D. (2021). In silico methods and tools for drug discovery. *Computers in biology and medicine*, 137, 104851. https://doi.org/10.1016/j.compbiomed.2021.104851

Sharma, R., Kaur, G., Bansal, P., Chawla, V., & Gupta, V. (2023). Bioinformatics Paradigms in Drug Discovery and Drug Development. *Current Topics in Medicinal Chemistry, 23*(7), 579-588. DOI: 10.2174/1568026623666221229113456

Sherman, J. C., Henderson Jr, C. R., Flynn, S., Gair, J. W., & Lust, B. (2021). Language decline characterizes amnestic mild cognitive impairment independent of cognitive decline. *Journal of Speech, Language, and Hearing Research, 64*(11), 4287-4307. https://doi.org/10.1044/2021_JSLHR-20-00503

Shishtar, E., Rogers, G. T., Blumberg, J. B., Au, R., & Jacques, P. F. (2020). Long-term dietary flavonoid intake and risk of Alzheimer disease and related dementias in the Framingham Offspring Cohort. *The American journal of clinical nutrition, 112*(2), 343-353. DOI:https://doi.org/10.1093/ajcn/nqaa079

Silva, A. S., Reboredo-Rodríguez, P., Süntar, I., Sureda, A., Belwal, T., Loizzo, M.R., & Nabavi, S. M. (2020). Evaluation of the status quo of polyphenols analysis: Part I—phytochemistry, bioactivity, interactions, and industrial uses. *Comprehensive Reviews in Food Science and Food Safety, 19*(6), 3191-3218. https://doi.org/10.1111/1541-4337.12629

Thompson, C. E., Freitas, L. B., & Salzano, F. M. (2018). Molecular evolution and functional divergence of alcohol dehydrogenases in animals, fungi and plants. *Genetics and molecular biology, 41*, 341-354. https://doi.org/10.1590/1678-4685-GMB-2017-0047

Tobias, M. C., Morrison, J. G., Tobias, M. C., & Morrison, J. G. (2014). Food that Might Protect Your Brain and Save Your Life: A Discussion About the Ecology of Alzheimer's with Dr. Neal Barnard. Why Life Matters: Fifty Ecosystems of the Heart and Mind, 81-87. https://doi.org/10.1007/978-3-319-07860-1_13

Van Eck, N., & Waltman, L. (2010). Software survey: VOSviewer, a computer program for bibliometric mapping. scientometrics, 84(2), 523-538. https://www.vosviewer.com/

Vargas-Restrepo, F., Sabogal-Guáqueta, A. M., & Cardona-Gómez, G. P. (2018). *Quercetin ameliorates* inflammation in CA1 hippocampal region in aged triple transgenic Alzheimer's disease mice model. *Biomédica*, 38, 62-69. https://doi.org/10.7705/biomedica.v38i0.3761

Vetrani, C., Costabile, G., Vitale, M., & Giacco, R. (2020). (Poly) phenols and cardiovascular diseases: Looking in to move forward. *Journal of Functional Foods*, 71, 104013 https://doi.org/10.1016/j.jff.2020.104013

Więckowska, A., Szałaj, N., Góral, I., Bucki, A., Latacz, G., Kiec-Kononowicz, K., & Marco-Contelles, J. (2020). *In vitro* and *in silico* ADME-tox profiling and safety significance of multifunctional monoamine oxidase inhibitors targeting neurodegenerative diseases. *ACS chemical neuroscience, 11*(22), 3793-3801. https://doi.org/10.1021/acschemneuro.0c00489

Xu, H., Wang, G., Zhang, J., Zhang, M., Fu, M., Xiang, K., & Chen, X. (2022). Identification of phenolic compounds and active antifungal ingredients of walnut in response to anthracnose (*Colletotrichum gloeosporioides*). *Postharvest Biology and Technology*, 192, 112019.

Yamada, M., Ono, K., Hamaguchi, T., & Noguchi-Shinohara, M. (2015). Natural phenolic compounds as therapeutic and preventive agents for cerebral amyloidosis. Natural compounds as therapeutic agents for amyloidogenic diseases, 79-94. https://doi.org/10.1007/978-3-319-18365-7_4

Zhang, J., Miao, D., Zhu, W. F., Xu, J., Liu, W. Y., Kitdamrongtham, W., & Feng, F. (2017). Biological activities of phenolics from the fruits of *Phyllanthus emblica* L. (Euphorbiaceae). *Chemistry & Biodiversity, 14*(12), e1700404. https://doi.org/10.1002/cbdv.201700404

Zhang, Z., Zhang, W., Tu, J., Li, Y., Xu, G., & Zhang, Y. (2018). Simultaneous Detection of Protocatechuic Acid, Chlorogenic Acid and Caffeic Acid in Honey by HPLC with Ultraviolet and Electrochemical Detectors. *Int. J. Electrochem. Sci*, 13, 6655-6665. Doi: 10.20964/2018.07.44