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Analysis of Phenolic Compounds in Parkinson's Disease: A Bibliometric Assessment of the 100 Most Cited Papers

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Abstract

Objective: The aim of this study was to identify and characterize the 100 most cited articles on Parkinson's disease (PD) and phenolic compounds (PCs).

Methods: Articles were selected in the Web of Science Core Collection up to January 2022 based on predetermined inclusion criteria, and the following bibliometric parameters were extracted: the number of citations, title, keywords, authors, year, study design, tested PC and therapeutic target. MapChart was used to create worldwide networks, and VOSviewer software was used to create bibliometric networks. Descriptive statistical analysis was used to identify the most researched PCs and therapeutic targets in PD.

Results: The most cited article was also the oldest. The most recent article was published in 2020. Asia and China were the continent and the country with the most articles in the list (55% and 29%, respectively). In vitro studies were the most common experimental designs among the 100 most cited articles (46%). The most evaluated PC was epigallocatechin. Oxidative stress was the most studied therapeutic target.

Conclusion: Despite the demonstrations in laboratorial studies, the results obtained point to the need for clinical studies to better elucidate this association.

Keywords: Bibliometric**,** Parkinson's Disease, Phenolic compound

ABREVIATURES

Abbreviations: 5-HT = serotonin, 6-OHDA = 6-Hydroxydopamine, α-syn = α-synuclein, AChE = Acetylcholinesterase, Akb = Protein kinase B, ARE = Antioxidant response elemento, Bax = BCL2 Associated X, BBB = Blood–brain barrier, BCL2 = BCL2 Apoptosis Regulator, BDNF = Brain-derived neurotrophic fator, BTE = Black tea extract, CaMKII = Ca^{2+}/calmodulin-dependent protein kinase II, CAT = Catalase, C-Jun = Protein

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encoded by the JUN gene, COMT = Catechol O-methyltransferase, Cyt c = Cytochrome c, DA = Dopamine, DARPP-32 = Dopamine- and cAMP-regulated phosphoprotein-32, EGCG = Epigallocatechin gallate, ERK 1/2 = Extracellular signal-regulated kinases, GDNF = Glial cell-derived neurotrophic fator, GPx = Glutathione peroxidase, GSH = Glutathione, GSK-3β = Glycogen synthase kinase-3β, GTP = Green tea polyphenols, HMOX1 = Heme oxygenase-1, HVA = Homovanillic acid, IFN-γ = Interferon-gamma, IL = Interleukin, iNOS = Nitric oxide synthase, JNK 1/2 = c-Jun N-terminal cinase, Keap1 = Kelch-like ECH-associated protein 1, LDH = Lactate dehydrogenase, MAO-Bis = monoamine oxidase type B inhibitors, MDA = Malondialdehyde, MMP = Mitochondrial Membrane Potential, mRNA = Messenger ribonucleic acid, NDGA = Nordihydroguaiaretic acid, NF-κB = Nuclear factor-kappa B, NO = Nitric oxide, NQO1 = NAD(P)H:quinone oxidoreductase, Nrf-2 = Erythroid nuclear factor-2 related to factor 2, P38 = p38 mitogen-activated protein kinases, PCa = Carbonyl protein, PC = Phenolic compound, PD = Parkinson's disease, PIK-3 = Phosphoinositide 3-kinase, PKC = Protein kinase C, PLA2 = Phospholipase A2, ROS = Reactive oxygen species, SMAC = Second mitochondria-derived activator of caspase, SOD = Superoxide dismutase, TBARS = Thiobarbituric acid reactive substances, TCM = Traditional Chinese medicine, TH = Tyrosine hydroxylase, TH-ir = TH-immunoreactive, TNF-α = Tumor necrosis factor alpha, TRAP = Total reactive antioxidant potential, VOSviewer = Visualization of Similarities Viewer, WoS-CC = Web of Science Core Collectio

INTRODUCTION

Parkinson's disease (PD) is characterized by neurodegeneration and the presence of Lewy bodies, formed by α-synuclein (α-syn) fibrils, in the dopaminergic neurons (DNs) of the pars compacta of the substantia nigra of the brain [1].

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More than 10 million people worldwide are affected by PD. The prevalence of PD is approximately 0.3% in the general population, but this percentage increases to 1% and > 3% in adults over 60 years and 80 years, respectively [1]. The sum of the prevalences of PD in the 15 most popular nations in the world could reach 9 million people in 2030, approximately double the current prevalence, owing to population aging and advances in the treatment of PD [2].

The increase in prevalence influences the increase in the costs of the disease [2]. Direct and indirect costs of PD are derived from drug and nondrug treatment, the payment of social security, the loss of productivity and income, hospitalizations, and laboratory tests. In the USA, the cost of the PD reached approximately USD 52 billion per year [3] while in Europe, the cost reached EUR 13.9 billion in 2010 [4]. In Japan, the direct cost per patient was approximately USD 37,994, and the indirect cost was approximately USD 25,356 [5].

Current drug treatment for symptom reduction or control includes dopaminergic pharmacological targets such as L-dopa; catechol-O-methyltransferase inhibitors; monoamine oxidase type B inhibitors (MAO-BIs); dopamine (DA) agonists; and non-dopaminergic pharmacological targets such as istradefylline, safinamide, clozapine and amantadine [6].

Unfortunately, the treatment of PD has side effects, such as impulsive and compulsive behaviors, nausea and hallucinations, due to the hyperstimulation of dopaminergic receptors and the serotonergic and cholinergic systems, which results in disturbances in the limbic and frontal cortical structures. In addition to side effects, drug treatment does not prevent disease progression [7].

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This fact has motivated the search for new substances and the development of neuroprotective drugs that prevent the death of DNs and delay the progression of the disease while causing fewer side effects [8]. Furthermore, investing in treatments that delay disease progression by up to 20% could result in monetary benefits of USD 60,657 per patient [9].

In this context, MAO-BIs (rasagiline and selegiline) [10], coenzyme Q10 [11], creatine monohydrate [12], monoclonal antibodies directed against different parts of α-syn, [13], tocopherol, vitamin C [14], docosahexaenoic acid [15] and phenolic compounds (PCs) have been gaining attention through demonstrations of their neuroprotective properties.

PCs are secondary plant metabolites that have at least one hydroxyl linked to an aromatic ring in their chemical structure, and they are synthesized by two metabolic pathways: the shikimate and/or acetate pathways [16]. PCs can be classified according to their chemical structure mainly into flavonoids, phenolic acids, lignans and stilbenes [17].

PCs can act on cellular mechanisms that cause DN degeneration through the modulation of gene expression and the activation of antioxidant enzymes regulated by the nuclear factor erythroid 2-related factor 2 (NrF2) pathway, thus suggesting great neuroprotective potential for PD [18–20].

The number of citations is a bibliometric parameter that indirectly indicates quality, impact, productivity and prestige [21]. Bibliometric analysis makes it possible to identify the most cited articles and, based on that, characterize the scientific production in the area of interest [22]. Bibliometric analyses on PD have already been performed [23–26], but the role of PCs has not been addressed.

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The identification and characterization of scientific production through bibliometric parameters could contribute to the understanding of the development and direction of research on PD and PCs. Thus, this study aimed to identify and characterize the 100 most cited papers on PCs in PD.

MATERIALS AND METHODS

Search strategy and database

The paper search was carried out using the Web of Science Core Collection (WoS-CC). The search terms are detailed in Table 1.

Table 1Search strategy

Database	Section
Web of Science	Core Collection
	Search strategy
	TS = (“Phenolic compound” OR “phenolic acid” OR “benzoic acid” OR “hydroxycinnamic acid” OR flavonoid OR anthocyanin OR flavanol OR flavonol OR flavanone OR flavone OR isoflavone OR tannin OR coumarin OR lignan OR quinone OR stilben OR curcuminoid OR provinol OR phenol OR polyphenol OR “polyphenolic antioxidant compound”) AND TS = (“Lewy Body” OR Parkinson OR “Parkinson Disease” OR Parkinsonism OR “neurodegenerative disease” OR synuclein)

Papers published up to 20 January 2022 were searched with no restriction for language, publication year range, or methodology selection. Two researchers selected papers until the 100th most cited paper was found. Disagreements were resolved by the concordance method.

Data extraction

The articles were selected based on the following inclusion criteria: the words PD or PC or their synonyms (Table 1) were present in the title and/or abstract and/or

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keywords, tests were carried out only with PD models, tests were carried out with natural PCs, and pure PCs or the major PC (in the case of extracts) were identified and quantified. Conference papers and editorial papers were excluded.

The 100 most cited papers list was compiled in descending order based on the number of citations in the WoS-CC. In the event of a tie, the ranking was based on the highest citation density (the number of citations per year).

The article citation count, article title, publication year, study design, names of authors, the continent and country of origin, keywords, tested PC, tested therapeutic target and results of the top 100 most cited articles were recorded. The country of origin was determined by the published corresponding address.

Statistical analysis

Descriptive statistical analysis of the data extracted as described in the previous section was performed using the number of citations as the main variable. MapChart was used to represent the number of publications by country and continent. Articles were grouped according to the year of publication in 3-year periods.

Study designs were classified as follows: bibliographic studies, laboratory studies (in vitro, in vivo, in situ, ex vivo) and observational studies. Furthermore, compounds were classified according to the subclass determined in the Phenol Explorer database.

Quantitative and qualitative analysis

Visualization of Similarities Viewer (VOSviewer) software was used to generate coauthor ship and author keyword co-occurrence cluster maps [27].

The analysis units used were author name in the coauthor ship cluster maps and author keyword in the co-occurrence networks. Author names were linked to each other

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based on the number of joint authors, and author keywords were linked by occurrence. Units were included when they appeared in at least one of the 100 most cited articles in both networks.

The terms were organized into clusters, with each cluster represented by a color. More important terms had larger circles, and strongly related terms were positioned close to each other. Moreover, lines were drawn between items to indicate relations, with thicker lines indicating a stronger link between 2 items [27].

RESULTS

Through the search strategy used (Table 1), 2,273 articles were obtained. After listing the articles in descending order on the basis of the number of citations, 530 articles were screened by the eligibility criteria, of which 430 articles were excluded for not directly addressing PD and/or PCs (the titles of excluded articles can be found in the supplementary material), resulting in the 100 most cited articles on PD and PCs (Table 2). The position of articles in the list was based on the number of citations in the WoS-CC and the citation density.

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Table 2 The 100 most cited articles on Parkinson's disease and phenolic compounds

R[1]	Author (Reference)	Number of citations in the WoS-CC[2]	Study design	Pure compound(s) or major compound(s) in the extract (up to nine)	Therapeutic targets	Neuroprotective effects
1	Levites et al. [28]	434	Laboratorial (in vivo)	EGCG	Oxidative stress	Prevented DN loss, reduced TH levels, and increased SOD and CAT activity
2	Zhu et al. [29]	339	Laboratorial (in vitro)	Baicalein	α-Syn fibrils	Inhibited the formation and disaggregation of α-syn fibrils
3	Levites et al. [30]	317	Laboratorial (in vitro)	EGCG	Oxidative stress	Decreased cell death through PKC stimulation and gene modulation
4	Zbarsky et al. [31]	306	Laboratorial (in vivo)	Curcumin Naringenin Quercetin Fisetin	Oxidative stress	Curcumin and naringenin prevented the reduction in TH-positive cell levels and DA
5	Levites et al. [32]	245	Laboratorial (in vitro)	#	Oxidative stress	Inhibited both the nuclear translocation and the binding activity of NF-κB
6	Bureau et al. [33]	203	Laboratorial (in vitro)	Resveratrol Quercetin	Neuroinflammation	Both reduced inflammation-mediated apoptotic death
7	Caruana et al. [34]	178	Laboratorial (in vitro)	14 natural PCs and BTE	α-Syn fibrils	Baicalein, EGCG, myricetin, NDGA and BTE were classified as being the best combined inhibitors and disaggregators of α-syn fibrils
8	Mercer et al. [35]	178	Laboratorial (in vitro)	Catechin Quercetin Chrysin Puerarin	Oxidative stress	All attenuated the apoptotic lesions of mesencephalic DNs. Catechin also reduced the injury produced by hydrogen peroxide, 4-hydroxynonenal, rotenone and 6-OHDA

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9	Mythri et al. [36]	175	Bibliographic	Naringenin Genistein Curcumin	Oxidative stress neuroinflammation α-Syn fibrils	Acted on oxidative/nitrosative stress, mitochondrial dysfunction and protein aggregation
10	Khan et al. [37]	172	Laboratorial (in vivo)	Resveratrol	Oxidative stress	Increased antioxidant status; decreased DA loss; and attenuated the elevated level TBARS, PCa and PLA2 activity
11	Aquilano et al. [38]	170	Bibliographic	#	Oxidative stress neuroinflammation	Antioxidant and anti-inflammatory agents based on PCs were proposed for the treatment of PD
12	Uversky et al. [39]	164	Laboratorial (in vitro)	48 flavonoids belonging to several classes	α-Syn fibrils	Eriodictyol, gossypetin, baicalein and 5,6,7,4'-tetrahydroxyflavone bound and stabilized α-syn in its native unfolded conformation
13	Gao et al. [40]	160	Observational	#	Oxidative stress	Men with high consumption of foods rich in flavonoids, mainly anthocyanins, were less likely to develop PD during 20-22 years of follow-up
14	Guo et al. [41]	158	Laboratorial (in vitro)	#	Oxidative stress	Sequestered ROS, inhibited PKC/ERK1/2 and NF-κB, and modulated cell death and survival genes
15	Pandey et al. [42]	156	Laboratorial (in vitro)	Curcumin	α-Syn fibrils	Inhibited α-syn fibril aggregation, disaggregated preforms and increased the solubility of α-syn fibrils in cells
16	Okawara et al. [43]	151	Laboratorial (in vitro)	Resveratrol	Oxidative stress	Prevented ROS accumulation, depleted GSH, decreased DNs and increased the absorption of propidium iodide
17	Datla et al. [44]	145	Laboratorial (in vivo)	Tangeretin	Oxidative stress	Showed evidence of crossing the BBB and reduced the loss of both TH cells and the

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						striatal DN content
18	Li et al. [45]	144	Laboratorial (in vivo)	EGCG	Neuroinflammation	Inhibited the activation of microglial secretion of NO and TNF-α through the downregulation of NO synthase and TNF-α expression
19	Wruck et al. [46]	138	Laboratorial (in vitro)	Luteolin	Oxidative stress	Conferred neuroprotection against oxidative stress via Nrf-2
20	Hong et al. [47]	132	Laboratorial (in vitro)	Baicalein	α-Syn fibrils	Oligomers did not form fibrils even after a long time of incubation; they were globular species that were quite compact and extremely stable
21	Bournival et al. [48]	131	Laboratorial (in vitro)	Resveratrol Quercetin	Oxidative stress	Both decreased apoptotic neuronal activity by acting on the expression of the pro- and anti-apoptotic genes Bax and BCL2
22	Lou et al. [49]	130	Laboratorial (in vitro and in vivo)	Naringenin	Oxidative stress	Increased Nrf-2 protein levels and activated ARE pathway genes
23	Guo et al. [50]	130	Laboratorial (in vivo)	#	Oxidative stress	Prevented the increase in ROS and NO levels, lipid peroxidation, nitrite/nitrate content, inducible iNOS and protein-bound 3-nitro-tyrosine
24	Chao et al. [51]	125	Laboratorial (in vitro)	Oxyresveratrol	Oxidative stress	Reduced LDH release, caspase-3 activity and ROS generation
25	Zhang et al. [52]	122	Laboratorial (in vitro)	Baicalein	Oxidative stress	Increased transcriptional Nrf2/HMOX-1 expression and decreased Keap1, attenuating apoptosis
26	Mu et al. [53]	121	Laboratorial (in vitro and in vivo)	Baicalein	Oxidative stress	Prevented apoptosis and promoted neurite outgrowth, attenuated muscle tremor and increased the number of TH-positive neurons

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27	Karuppagounder et al. [54]	120	Laboratorial (in vivo)	Quercetin	Oxidative stress	Reduced unilateral rotations, attenuated the loss of striatal DNs and oxidized nigral DNs, reduced GSH activity, increased CAT and SOD activity, and regulated mitochondrial complex I activity
28	Lu et al. [55]	118	Laboratorial (in vivo)	Resveratrol	Oxidative stress	Protected against motor deficit, hydroxyl radical generation and neuronal loss
29	Lorenzen et al. [56]	117	Laboratorial (in vitro)	EGCG	α-Syn fibrils	Inhibited α-syn fibril toxicity, moderately reduced membrane binding and immobilized the C-terminal tail of the oligomer
30	Zhang et al. [57]	117	Laboratorial (in vitro)	Resveratrol	Neuroinflammation	Inhibited microglial activation and subsequently reduced pro-inflammatory factor release
31	Zhang et al. [58]	113	Laboratorial (in vitro and in vivo)	Quercetin	Neuroinflammation	Inhibited the overproduction of NO and the overexpression of iNOS and downregulated the overexpression of pro-inflammatory genes
32	Patil et al. [59]	111	Laboratorial (in vivo)	Apigenin Luteolin	Oxidative stress	Both protected DNs, probably by reducing oxidative damage, neuroinflammation and microglial activation and enhancing neurotrophic potential
33	An et al. [60]	111	Laboratorial (in vitro)	Protocatechuic acid	Oxidative stress	Increased cell viability and SOD and CAT activity and attenuated apoptosis
34	Nie et al. [61]	110	Laboratorial (in vitro)	Catechin EGCG Epicatechin EGC Epicatechin gallate	Oxidative stress	EGCG or epicatechin gallate led to apoptotic inhibition, while other catechins had little protective effect against cell death

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35	Jagatha et al. [62]	108	Laboratorial (in sílico and in vitro)	Curcumin	Oxidative stress	Restored the depletion of GSH levels, protected against protein oxidation and preserved mitochondrial complex I activity
36	Strathearn et al. [63]	105	Laboratorial (in vitro)	#	Oxidative stress	Extracts rich in anthocyanins and proanthocyanidins exhibited greater neuroprotective activity than extracts rich in other PCs
37	Kim et al. [64]	102	Laboratorial (in vitro and in vivo)	#	Oxidative stress	Regulated ROS, NO generation, Bcl-2 and Bax proteins, mitochondrial membrane depolarization, and caspase-3 activation and prevented bradykinesia and ND damage
38	Nie et al. [65]	100	Laboratorial (in vitro)	EGCG	Oxidative stress	Exerted significant protective effects against cell apoptosis. EGCG was more effective than the GTP mixture
39	Zhang et al.[66]	98	Laboratorial (in vitro and in vivo)	Protocatechuic acid Chrysin	Oxidative stress	When used in combination increased neuroprotective effects through a combination of cellular mechanisms of antioxidant and anti-inflammatory cytoprotection
40	Vauzour et al. [67]	98	Laboratorial (in vitro)	Caffeic acid Tyrosol *p*-Coumaric acid	Oxidative stress	All induced more powerful neuroprotective effects than those observed for flavonoids
41	Pan et al. [68]	94	Bibliographic	EGCG	Oxidative stress	Studies to understand biological activities and health benefits are still very limited. Further studies are needed to assess safety and efficacy in humans and determine neuroprotective mechanisms
42	Meng et al. [69]	93	Laboratorial (in vitro)	48 flavonoids belonging to	α-Syn fibrils	Baicalein, eriodictoil, and 6-hesperidin were classified as strong inhibitors of α-syn

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				several classes		fibrils
43	Tamilselvam et al. [70]	90	Laboratorial (in vitro)	Hesperidin	Oxidative stress	Attenuated the loss of mitochondrial membrane potential; ROS generation; the depletion of GSH; enhanced activities of CAT, SOD, and GPx; the upregulation of Bax, cyt C, and caspases 3 and 9; and the downregulation of Bcl-2
44	Jimenez-Del-Rio et al. [71]	90	Laboratorial (in vivo)	Gallic acid Ferulic acid Caffeic acid Coumaric acid Propyl gallate Epicatechin EGC EGCG	Oxidative stress	Locomotive activity was significantly recovered, although the times of effectiveness differed among compounds
45	Cheng et al. [72]	90	Laboratorial (in vivo)	Baicalein	Oxidative stress	Increased DA, HVA and 5-HT levels; increased TH-ir neurons; and inhibited oxidative stress and astroglial reaction
46	Long et al. [73]	89	Laboratorial (in vivo)	Resveratrol	Oxidative stress	Improved climbing ability and extended the average lifespan
47	Chen et al. [74]	85	Laboratorial (in vitro)	Luteolin	Neuroinflammation	Attenuated the decrease in DA uptake and the loss of TH-ir neurons and inhibited microglial activation and excessive production of TNF-α, NO and SOD
48	Liu et al. [75]	84	Laboratorial (in vivo)	Genistein	Oxidative stress	Prevented DN loss through enhancing BCL-2 gene expression.
49	Molina-Jiménez et al. [76]	79	Laboratorial (in vitro)	Fraxetin Myricetin	Oxidative stress	Both restored the GSH redox ratio and decreased the levels of lipid peroxidation
50	Magalingam,	75	Laboratorial	#	α-Syn fibrils	Gaps were identified in understanding the

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	Radhakrishnan, Haleagrahara [77]		(in vivo and in vitro)		Oxidative stress Neuroinflammation Mitochondrial dysfunction	mechanism why flavonoids protect neuronal cells; few clinical studies showing evidence of the neuroprotection of PCs in patients with PD
51	Ye et al. [78]	75	Laboratorial (in vitro)	EGCG	Oxidative stress	Increased cell viability and SOD1 and GPX1 mRNA expression, decreased ROS production and upregulated PGC-1α mRNA expression
52	Anusha, Sumathi, Joseph [79]	73	Laboratorial (in vivo)	Apigenin	Neuroinflammation	Attenuated the upregulation of NF-κB gene expression; inhibited the release of TNF-α, IL-6 and iNOS-1; prevented the reduction in BDNF and GDNF mRNA expression; downregulated α-syn aggregation; and upregulated the TH protein expression
53	Cui, Li, Zhu [80]	72	Laboratorial (in vivo)	Curcumin	Oxidative stress	Alleviated motor dysfunction, increased TH activity and GSH levels, reduced ROS and MDA content, and restored the expression levels of HMOX-1 and NQO1
54	Ardah et al. [81]	72	Laboratorial (in vitro)	Gallic acid	α-Syn fibrils	Binds to soluble oligomers with no β-sheet content and stabilized their structure
55	Bournival et al. [82]	72	Laboratorial (in vitro)	Quercetin Sesamin	Neuroinflammation	Both defended against increases in IL-6, IL-1β and TNF-α mRNA and reduced the expression of iNOS and mitochondrial superoxide radicals
56	Yu et al. [83]	72	Laboratorial (in vivo and in vitro)	Curcumin	Oxidative stress	Improved behavioral deficits, enhanced the survival of TH^+ neurons, inhibited the phosphorylation of JNK1/2 and C-Jun and cleaved caspase-3
57	Vauzour et al. [84]	71	Laboratorial (in vitro)	Pelargonidin Quercetin	Oxidative stress	No neuroprotective effects were observed with O-methylated flavan-3-ols

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				Hesperetin Caffeic acid 4'-O-Me derivatives of Catechin Epicatechin		Concentrations above 0.3 µM of quercetin were toxic
58	Chaturvedi et al. [85]	71	Laboratorial (in vivo)	#	Oxidative stress	Increased the number of TH-ir neurons, the level of TH protein and the expression of TH mRNA in the substantia nigra. Improved motor and neurochemical deficits when BTE was given before 6-OHDA
59	Zhang et al. [86]	70	Laboratorial (in vivo and in vitro)	Morin	Oxidative stress	Attenuated apoptosis, ROS formation, behavioral deficits and DN death
60	Sriraksa et al. [87]	68	Laboratorial (in vivo)	Quercetin	Oxidative stress	Improved motor deficits; increased DN density; increased SOD, CAT and GPx activity; and decreased AChE activity and MDA levels
61	Wang et al. [88]	68	Laboratorial (in vitro)	Genistein	Neuroinflammation	Attenuated the decrease in DA and TH-neurons; inhibited microglial activation and the production of TNF-α, NO and superoxide
62	Kim et al. [89]	67	Laboratorial (in vitro)	Naringin	Mitochondrial dysfunction	Blocked the phosphorylation of JNK and P38, prevented changes in BCL2 and BAX expression, and reduced the activity of caspase 3 and the cleavage of caspase 9
63	Chen et al. [90]	66	Laboratorial (in vivo)	Piceid	Oxidative stress	Attenuated motor deficits; prevented the changes induced in the levels of GSH, thioredoxin, ATP, MDA and SOD in the

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						striatum; and rescued DN degeneration
64	Liu et al. [91]	66	Laboratorial (in vitro)	Gallic acid	α-Syn fibrils	Stabilized the extended native structure and interacted with α-syn transiently, inhibiting fibril formation
65	Zhang et al. [92]	66	Laboratorial (in vivo and in vitro)	Chrysin	Neuroinflammation Oxidative stress	Decreased IL-1β and TNF-α gene expression and inhibited NO production and iNOS expression
66	Haleagrahara et al. [93]	66	Laboratorial (in vivo)	Quercetin	Oxidative stress	Increased DN and GSH levels and decreased carbonyl protein content
67	Tapias, Cannon, Greenamyre [94]	64	Laboratorial (in vivo)	#	Mitochondrial dysfunction, Oxidative stress Neuroinflammation	Increased terminal nigrostriatal depression, the loss of DNs, the inflammatory response and caspase activation
68	Lee et al. [95]	64	Laboratorial (in vivo)	Baicalein	Neuroinflammation	Improved motor ability and prevented dopaminergic neuron loss; reduced microglial, astrocyte, JNK and ERK activations; and suppressed the nuclear translocation of NF-κB
69	Kim et al. [96]	64	Laboratorial (in vitro)	Licochalcone E	Oxidative stress Neuroinflammation	Regulated the Nrf2-ARE system and upregulated downstream NQO1 and HMOX-1
70	Anandhan et al. [97]	63	Laboratorial (in vivo)	Theaflavin	Mitochondrial dysfunction	Increased the expression of TH and DA transporter and reduced caspase-3, 8, and 9
71	Chung, Miranda, Maier [98]	62	Laboratorial (in vitro)	EGCG	Oxidative stress	Potentiated the cytotoxicity of rotenone
72	Antunes et al. [99]	60	Laboratorial (in vivo)	Hesperidin	Oxidative stress	Improved motor and behavioral deficits; attenuated the reduction in GPx and CAT activity and TRAP and DA levels; and mitigated ROS levels and GSH activity
73	Ay et al. [100]	59	Laboratorial	Quercetin	Mitochondrial	Induced the activation of PKD1 and Akt,

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			(in vivo and in vitro)		dysfunction	increased mitochondrial biogenesis, improved behavioral deficits, and increased levels of TH-positive cells and DA
74	Kavitha et al. [101]	58	Laboratorial (in vivo)	Mangiferin	Oxidative stress	Prevented behavioral deficits, oxidative stress, apoptosis, dopaminergic neuronal degeneration and DA depletion.
75	Haleagrahara, Ponnusamy [102]	58	Laboratorial (in vivo)	#	Oxidative stress	Reduced lipid hydroperoxides and the protein carbonyl content and increased the levels of SOD, CAT and GPx
76	Xu et al. [103]	57	Laboratorial (in vivo)	EGCG	Oxidative stress	Rescued neurotoxicity by increasing the rotational latency; improved DA levels and substantia nigra ferroportin expression
77	Yabuki et al. [104]	57	Laboratorial (in vivo)	Nobiletin	Oxidative stress	Rescued motor and cognitive dysfunction in part by enhancing DA release
78	Roghani et al. [105]	57	Laboratorial (in vivo)	Pelargonidin	Oxidative stress	Attenuated the rotational behavior, protected the neurons and decreased the formation of TBARS
79	Hou et al. [106]	57	Laboratorial (in vitro)	EGCG	Mitochondrial dysfunction	Attenuated apoptosis, maintaining mitochondrial membrane potential, inhibiting caspase-3 activity and downregulating the expression of SMAC
80	Ren et al. [107]	56	Laboratorial (in vivo)	Dihydromyricetin	Oxidative stress	Attenuated behavioral impairments and DN loss, cell injury and ROS production; increased GSK-3 β phosphorylation
81	Zhu et al. [108]	56	Laboratorial (in vitro)	Quercetin Oxyquercetin	α-Syn fibrils	Oxidized quercetin species were stronger inhibitors than quercetin
82	Molina-Jiménez, Sanchez-Reus, Benedi [109]	56	Laboratorial (in vitro)	Fraxetin Myricetin	Oxidative stress	Signficantly decreased the cytotoxicity of rotenone, as well as the release of LDH, through the effect of fraxetin
83	Goes et al. [110]	55	Laboratorial	Chrysin	Neuroinflammation	Prevented behavioral changes; increased

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			(in vivo)			levels of TNF-α, IFN-γ, IL-1β, IL-2, IL-6 and NF-κB; and decreased levels of IL-10, DA, DOPAC, HVA and TH and TRAP
84	Cao et al. [111]	54	Laboratorial (in vivo and in vitro)	Amentoflavone	Neuroinflammation	Rescued DN loss; increased the activation of PI3K and Akt and the Bcl-2/Bax ratio; and alleviated gliosis and IL-1β and iNOS gene expression levels
85	Khan et al. [112]	54	Laboratorial (in vivo)	Pycnogenol	Oxidative stress Neuroinflammation	Decreased lipid peroxidation; restored GSH levels and the activities of GPx, GSH and SOD; increased striatal DA levels; normalized the expression of TH; and inhibited the expression of NF-κB and the release of COX-2, iNOS, TNF-α and IL-1β
86	Brunetti et al. [113]	53	Laboratorial (in vivo)	Hydroxytirosol Oleuropein aglycone	Oxidative stress	Increased the survival after heat stress, but only hydroxytirosol could prolong the lifespan in unstressed conditions
87	Wu et al. [114]	53	Laboratorial (in vitro)	Biochanin A	Neuroinflammation	Decreased the mRNA expression of TNF-α and IL-1β; inhibited iNOS mRNA and protein expression and the phosphorylation of JNK, ERK and P38
88	Pan et al. [115]	53	Laboratorial (in vivo and in vitro)	#	Mitochondrial dysfunction	Significantly attenuated the loss of TH-positive cells
89	Leem et al. [116]	52	Laboratorial (in vivo)	Naringin	Neuroinflammation	Increased GDNF levels in DA neurons, activated the mammalian target of rapamycin complex 1, and attenuated the level of TNF-α in microglia
90	Du et al. [117]	52	Laboratorial (in vivo)	Curcumin	Oxidative stress	Prevented the decrease in the levels of DA and DOPAC and inhibited the decrease in TH^+ neurons and the numbers of iron $^+$

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						cells
91	Xu et al. [118]	51	Laboratorial (in vitro)	EGCG	α-Syn fibrils	Inhibited α-syn fibril aggregation through unstable hydrophobic bonds
92	Subramaniam, Ellis [119]	51	Laboratorial (in vivo)	Umbelliferone Esculetin	Oxidative stress	Both significantly attenuated neurotoxicity in the substantia nigra pars compacta but not the striatum, prevented the increase in nitrosative stress and prevented caspase 3 activation but inhibited MAO activity
93	Khang et al. [120]	51	Laboratorial (in vivo and in vitro)	EGCG	Oxidative stress	Inhibited the O-methylation of L-dopa and moderately reduced the accumulation of 3-O-methyldopa in plasma and striatum
94	Guan et al. [121]	51	Laboratorial (in vitro)	Protocatechuic acid	Mitochondrial dysfunction	Prevented the formation of ROS, GSH depletion and the activation of caspase-3 and upregulated Bcl-2
95	Jiang et al. [122]	50	Laboratorial (in vitro)	Baicalein	α-Syn fibrils	Attenuated mitochondrial depolarization and proteasome inhibition and protected cells from toxicity as well as reduced fibrillation
96	Kujawska et al. [123]	49	Bibliographic	#	Oxidative stress	Analyzed studies encouraged the search for phytochemicals exerting neuroprotective effects on DA neurons, and delaying their degeneration was found to be highly desirable
97	Macedo et al. [124]	49	Laboratorial (in vitro)	Myricetin	α-Syn fibrils	Inhibited α-syn toxicity and aggregation in cells
98	Li et al. [125]	49	Laboratorial (in vitro)	Baicalein	Oxidative stress	Suppressed apoptosis, inhibited the accumulation of ROS, alleviated ATP deficiency, and acted in mitochondrial membrane potential dissipation and

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						caspase-3/7 activation
99	Park et al. [126]	49	Laboratorial (in vitro)	Carnosic acid	Oxidative stress	Prevented caspase-3 activation, JNK phosphorylation, and caspase-12 activation
100	Datla et al. [127]	49	Laboratorial (in vivo)	Tangeritin Nobiletin Catechin Epicatechin Epicatechin gallate Formononetin Genistein	Oxidative stress	Pretreatment with plant extracts rich in catechins did not protect nigrostriatal DNs

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The article “Green tea polyphenol (-)-epigallocatechin-3-gallate prevents N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced DN. Journal of Neurochemistry. 2001 Sep; 78 (5): 1073-1082” was the most cited (434 citations) and among the oldest in the top 100 list in the WoS-CC. Older articles tend to accumulate citations over time and then become reference.

Additionally, according to the same criteria, the most recent article in the list was “Healthspan Maintenance and Prevention of Parkinson's-like Phenotypes with Hydroxytyrosol and Oleuropein Aglycone in *C. elegans*. International Journal of Molecular Sciences, 2020, 21 ”, with 53 citations.

More recent articles, despite having lower numbers of citations, present new research possibilities within the area of interest [128]. The most recent article in the list [129] demonstrates that the mechanism involved in neuroprotection against PD may also occur due to the anti-inflammatory potential of PCs through the regulation of cytokines and neurotrophic factors.

The top 100 most cited articles were contributed by 497 authors. The author Fink, A. L. contributed the highest number of papers (n = 5), followed by authors Lee, S.M.Y., Zhang, Z.J. and Zhao, B.L. (n = 4); and Datla, K.P., Dexter, D.T., Du, G.H., Haleagrahara, N., He, G.R., Le, W.D., Levites, Y., Li, G.H., Li, X.X, Mandel, S., Manivasagam, T., Martinoli, M.G., Mu, X., Uversky, V.N., Xu, B. and Youdim, M.B.H. (n = 3). The other authors contributed ≤ 2 papers. The authors with the highest number of citations in the WoS-CC were Levites, Y, Mandel, S and Youdim, M.B.H. (a total of 996 citations).

VOSviewer map (Figure 1) was used to illustrate detailed clusters of the coauthor ship relationships in the top 100 list. In the main cluster, the collaborations carried out in 2012 produced more articles, as seen by the thickness of the lines between the authors

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present in that period (Figure 2-A). Furthermore, according to the citation density, the prominent authors in this cluster were Lee, S.M.Y., Zhang, Z.J., and Li, G.H. together with 17 other authors (Figure 2-B).

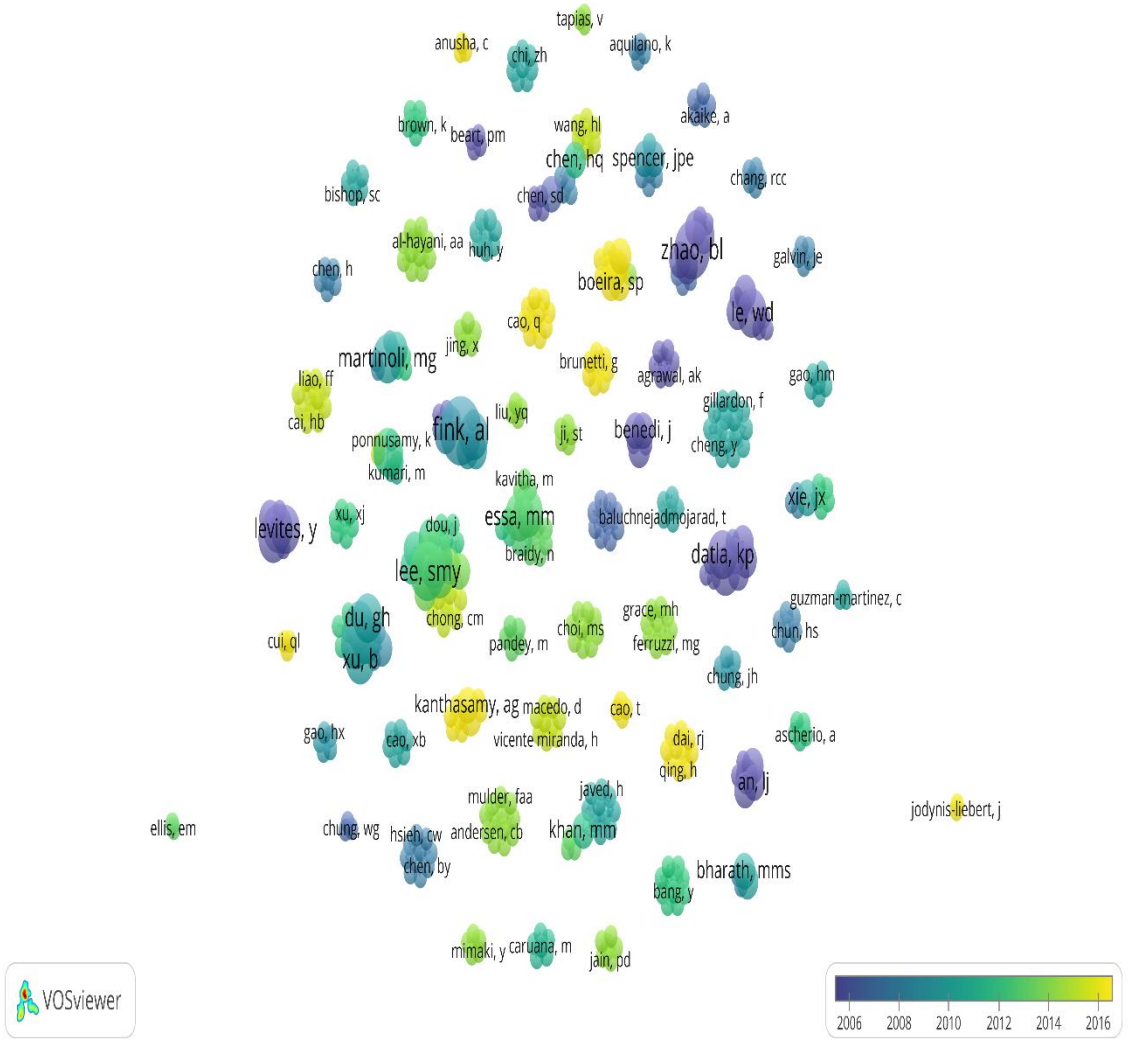

Figure 1 Coauthor contribution, overlay visualization map for all 497 authors in the top-cited papers. These authors formed 66 clusters. The size of the node represents the number of documents by the author, with larger nodes indicating higher numbers of publication

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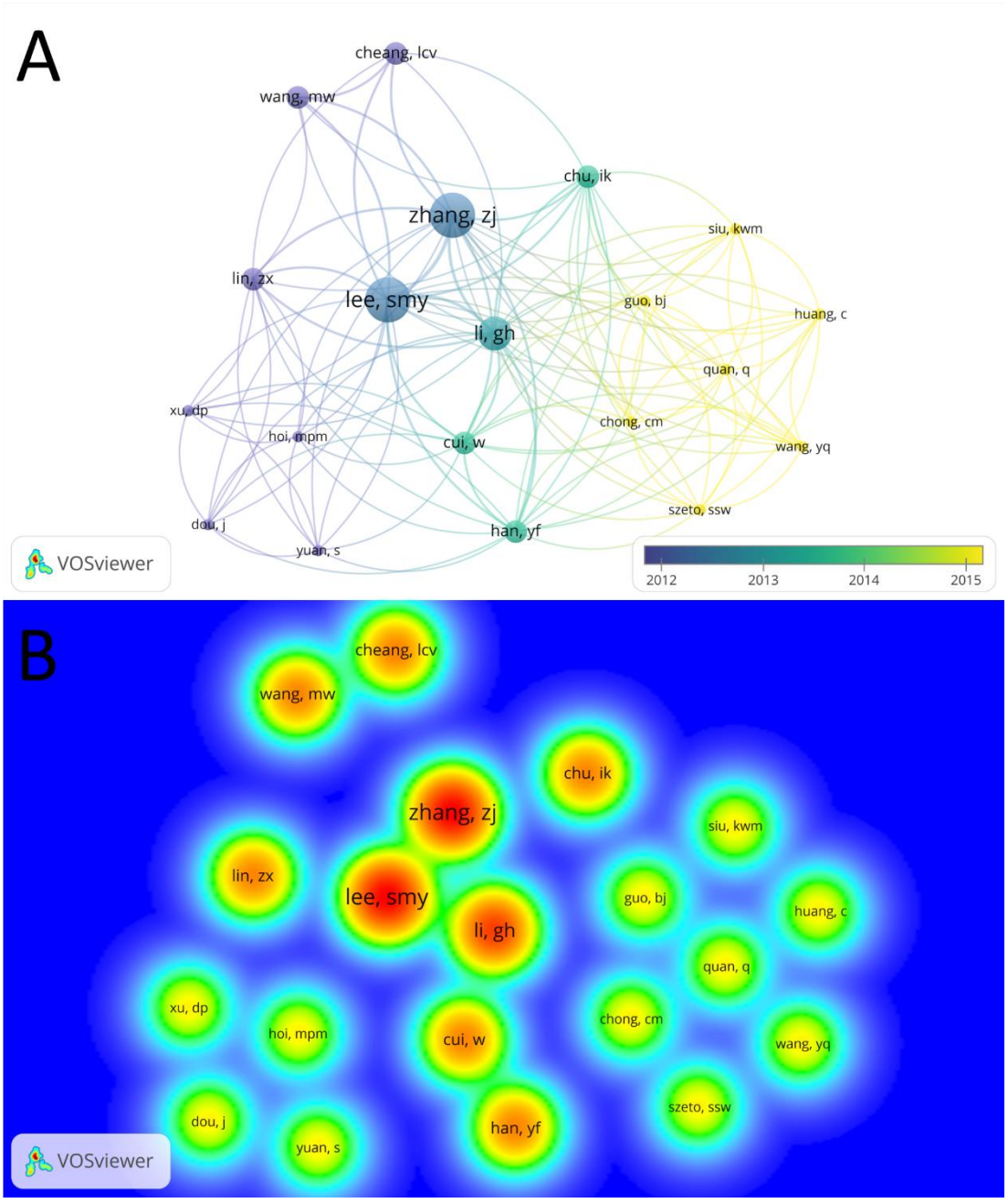

Figure 2 The largest set of connected items of coauthor contributions. A- The network consists of 20 authors and forms 3 clusters. B Coauthor ship map demonstrating author density and the existence of clusters among authors

Author Lee, S.M.Y. had the cluster with the highest number of articles (n = 20) in addition to having the greatest link strength (total link strength = 30), although he was not the author with the highest number of citations (n citation = 399). He is a professor and deputy director of the Institute of Chinese Medical Sciences at the University of Macau. He is interested in natural products that can be used as therapeutic agents in brain

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disorders. He is dedicated to education and research in the fields of molecular biochemistry biology, pharmacology pharmacy and neuroscience neurology.

The list of the 100 most cited articles in the WoS-CC had more articles from the continents of Asia (55%) and North America (23%) than from other continents. PD is the second most common neurodegenerative disease, and PD is the neurodegenerative disease with the highest incidence in the world. Its prevalence is higher in Anglo-Saxon America and Europe than in Asia, Latin America and Africa [130]. Despite the fact that Asia has a low prevalence of PD, it was the continent that published the most articles on PD and PCs.

Research on PD has increased 33-fold in the last 35 years in Asia. This increase may be related to population aging and the new phase of economic development based on the production, communication and consumption of knowledge [131]. The continent of Asia had more countries with articles in the list than other continents. Africa and Central America were the only continents that did not have countries with articles in the list.

China was the country with the most articles and the most citations in the list (Figure 3). In addition to China, countries such as the USA, India and South Korea also had high numbers of articles in the list. The high scientific production on PD and PCs may be related to traditional Chinese medicine (TCM), which has lower costs than Western medicine and more than 170 ingredients for the treatment of the disease, including PCs. The benefits and molecular mechanisms of TCM have been evaluated in preclinical studies, which may lead to the discovery of new therapeutic candidates for the treatment of PD [132].

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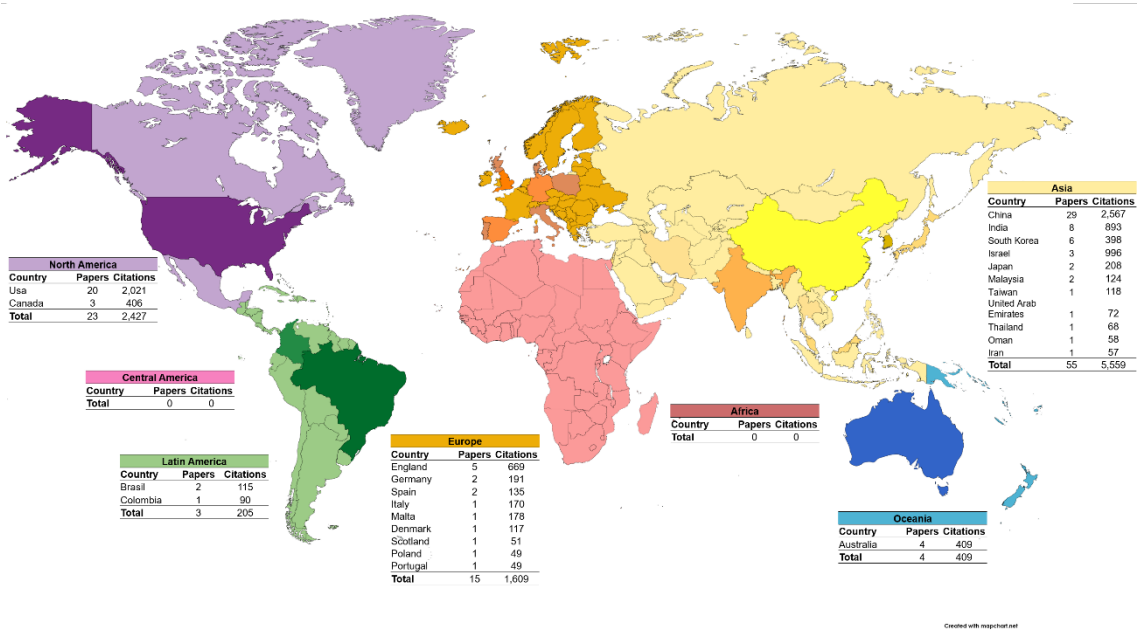

Figure 3 Worldwide distribution of the top 100 most cited papers on PD and PCs

In addition, China already stood out in scientific production on PD between 2013 and 2017, publishing 3,986 articles, behind only the USA. The high number of publications in this period was related to the standardization through guidelines [133] on the management of the disease in the country, efforts to reduce the economic burden related to the treatment of the disease and government incentives for publication in English newspapers [25].

The number of citations an article receives also contributes to the impact factor that determines the academic prestige of scientific journals. Thus, journals that have articles with a high number of citations do not necessarily have a high impact factor, as is the case of the three journals with the highest number of articles in the list. Brain Research Journal had the highest number of articles in the list (n = 5). The journals Free Radical Biology and Medicine and Journal of Neuroscience Research presented 4 articles. The other journals that were in the list had ≤ 3 articles (Table 3).

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The most prolific periods in terms of publications in the list of the 100 most cited articles in the WoS-CC were 2012-2010 (n = 26), 2009-2007 (n = 23) and 2015-2013 (n = 22) (Table 3). On the other hand, the period with the most cited articles from the date of publication to the date of data extraction (December 20, 2021) was 2015-2013 (3,681 citations), followed by 2009-2007 (2,479) and 2012-2010 (2,249).

The most commonly used PD study designs were in vitro (46 papers), in vivo (33 papers) and in vitro + in vivo (14 papers), with the highest number of citations (5,124, 3,120 and 1,134, respectively) (Table 3). Other study designs, such as bibliographic studies that did not specify the type of review (5 papers), observational (cross-sectional) (01 paper) studies and in vitro + in silico (01 paper) studies, had a low occurrence in the top 100 list in the WoS-CC (Table 3).

Table 3 Characteristics of the 100 most cited papers on PD and PCs

Characteristics	n papers	n citations
Journal (at least 4 papers)		
Brain Research Journal	5	481
Free Radical Biology and Medicine	4	489
Journal of Neuroscience Research	4	462
Period of publications		
2021-2019	1	53
2018-2016	9	526
2015-2013	22	3,681
2012-2010	26	2,249
2009-2007	23	2,479
2006-2004	10	1,505
2003-2001	9	1,554
Study design		
Bibliographic studies	5	563
Observational studies	1	160
Laboratorial studies		
in vitro + in vivo	14	1,134
in vitro + in silico	1	2,008
in vivo	33	3,120
in vitro	46	5,124

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The level of evidence of research is related to the experimental design. According to evidence-based practice, systematic reviews and clinical studies are considered the most important. As seen in the 100 articles, laboratory studies were the most common experimental design, and there was only 1 clinical study and no systematic review or meta-analysis. The development of preliminary studies through laboratory studies is necessary to perform an initial screening for the effective concentration for bioactivity and toxicity [134]. However, laboratory studies are not representative of the concentrations and chemical structure of PCs reaching the target organ in humans.

After consumption, PCs can be hydrolyzed by intestinal enzymes, but most reach the colon, where they undergo hydrolysis and biotransformation reactions by microbiota enzymes and are then absorbed. Metabolites undergo conjugation reactions in the liver before entering the brain. The penetration of metabolites into the brain depends on the ability to bind to brain efflux transporters present in the blood–brain barrier and on lipophilicity. Metabolites reach the brain at concentrations less than 1 nmol/g of brain tissue [135].

More than 10,000 phenolic compounds have been identified, of which approximately 500 are dietary compounds [17]. The number of compounds that occurred among the 100 most cited articles (n = 51) is not representative of the amount of dietary phenolic compounds, however the compounds EGCG, quercetin and baicalein were the most evaluated among the papers (15, 12 and 11 papers, respectively), with the highest number of citations (1,937, 1,443 and 1,402, respectively).

EGCG, the most evaluated compound in the list, can be found abundantly in green tea leaves, oolong tea, and black tea leaves [136]. The estimated daily intake of EGCG through green tea consumption can reach approximately 560 mg/day for individuals

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consuming an average of 750 mL/day of green tea [137]. Green tea is among the foods that are prescribed for the prevention of PD in TCM [132].

Quercetin and baicalein compounds were widely evaluated among the papers as well. Quercetin is mostly conjugated to sugar moieties such as glucose or rutinose and can be found in high concentrations in Ginkgo Biloba, a traditional Chinese medicine herb, onion, lettuce, chili pepper, cranberry, tomato, broccoli and apple, which contribute to an estimated dietary intake of 6–18 mg/day in the United States, China and the Netherlands [138,139].

Baicalein can be found in the root of *Scutellaria baicalensis*, an east Asian plant widely used in TCM to treat diseases [140]. Baicalein has low water solubility for this reason, and it is poorly bioavailable, which makes its application in neuroprotective therapies difficult [141]

PCs, despite having common structural elements, have structural characteristics such as their degree of oxidation and substituents (position, number and nature of groups attached to rings A and B and the presence of glycosidic bonds) that affect their bioactive potential [142]. The subclasses flavanol, flavones and flavonol were the most discussed (28, 25 and 20 papers, respectively) in the top 100 list in the WoS-CC, with the highest number of citations (3,087, 2,781 and 2,401, respectively) (Table 4).

Table 4 Number of articles published according to phenolic compounds, subclasses and therapeutic targets

Compound (≥ 4 papers)	**n papers**	**n citations[a]**
EGCG	15	1,937
Quercetin	12	1,443
Baicalein	11	1,402
Curcumin	7	941
Resveratrol	7	981
Naringenin	5	733
Myricetin	4	362
Chrysin	4	397

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Genistein	4	379
Epicatechin	4	320
Subclasses (≥ 5 papers)	**n papers**	**n citations[a]**
Flavanols	28	3,087
Flavones	25	2,781
Flavonols	20	2,401
Flavanones	11	1,304
Stilbenes	9	1,172
Curcuminoids	7	941
Isoflavonoids	7	659
Hydroxybenzoic acids	7	578
Therapeutic Targets	**n papers**	**n citations[a]**
Oxidative stress	68	7,183
Neuroinflammation	20	1,821
Fibrils of α-syn	15	1,773
Mitochondrial dysfunction	8	489

Flavanols, the most evaluated subclass among the 100 articles, present the ortho-dihydroxy (catecholic) group in the B ring, providing the delocalization of electrons, which contributes to a high antioxidant activity, which may be related to the number of studies that evaluated PCs and their effects on oxidative stress as a therapeutic target [143].

The most discussed targeted PD therapy in the WoS-CC top 100 list was oxidative stress (68 articles). The interest in the mechanism used by PCs to reduce intracellular levels of ROS is recent, although the demonstration of the antioxidant potential of PCs in neurons is not [144]. The search for answers makes this therapeutic target the most studied through laboratory models that are important tools, as they provide insights into behavioral improvements in parallel with the improvement in the oxidative state after exposure to PCs, for example, modulating the Nrf-2 signaling pathway and inducing increased expression of antioxidant enzymes such as SOD, CAT and GSH (Table 2).

Other therapeutic targets for PCs in PD demonstrated in the 100 most cited articles were neuroinflammation (20 articles), α-syn fibrils (15 articles) and mitochondrial

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dysfunction (8 articles) (Table 4). The neuroprotective effects of PCs include reduced expression of cytokines such as IL-6, TNF-α, IL-1b and COX-2; the breakdown and inhibition of the formation of α-syn fibrils; and the upregulation of complex I activity in the mitochondria (Table 2).

Out of the top 100 most cited publications, only 82 articles contained author keywords. The keywords that occurred in at least 2 articles are presented in Figure 4. The most frequently used keyword was PD (n = 54), followed by oxidative stress (n = 23), neuroprotection (n = 20), apoptosis (n = 11), rotenone (n = 11), 6-hydroxydopamine (n = 9), α-syn (n = 8), and polyphenols (n = 8). A total of 214 author keywords were identified. These words can help in the search for articles related to the topic in addition to indicating an overview of the research because they are words that represent the therapeutic targets, mechanisms of the neuroprotective effect and neurotoxins used in the papers.

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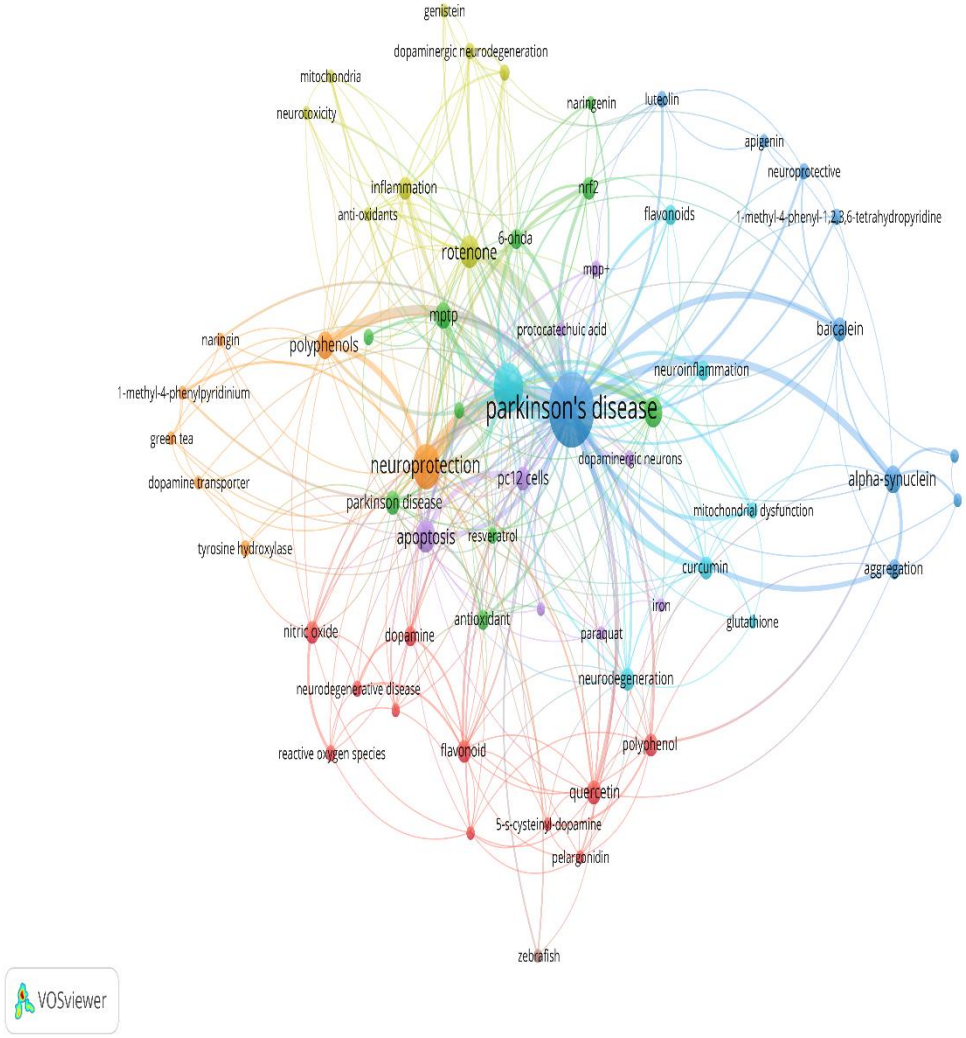

Figure 4Network analysis of author keywords with 2 or more occurrences. The size of the node represents the frequency of the keyword, with larger nodes indicating higher frequency

Keywords are essential for discovering scientific articles. They are used as codes to access literature in a particular area. When using keywords in the search, more relevant results are accessed than when using a phrase. Despite their importance, there were articles that did not include keywords, making retrieval difficult during the search [145].

CONCLUSIONS

The present study identified the 100 most cited articles on PD and PCs. The increased incidence of aging-related diseases due to the increase in the number of elderly

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people in the world has motivated countries such as China and the USA to seek other strategies for the treatment of PD to reduce the side effects and costs of available treatments. Plant-based foods and beverages have been used for a long time in traditional Chinese medicine to treat neurodegenerative diseases, encouraging the search for the mechanisms behind the neuroprotective effect. Research mainly in laboratory models on the use of PCs against PD has grown since 2007 and has highlighted bioactive potentials that include antioxidant and anti-inflammatory activity. Despite the promising results obtained, clinical studies are needed to obtain more conclusive answers about the neuroprotective effects of PCs in humans, as the bioactive potential is influenced by bioavailability.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

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