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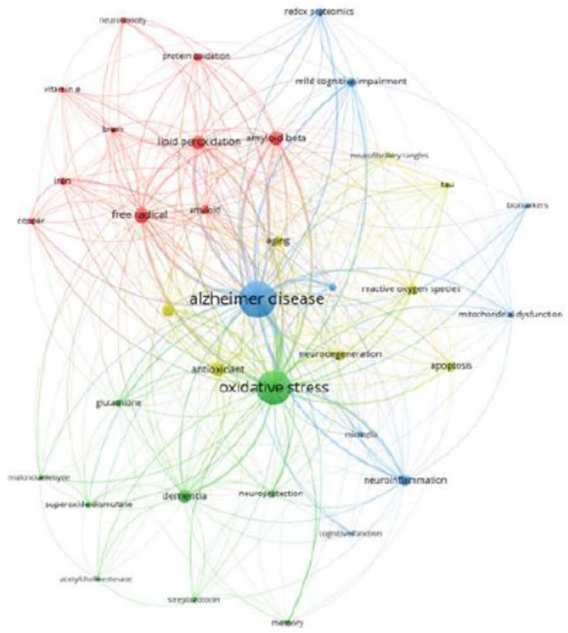

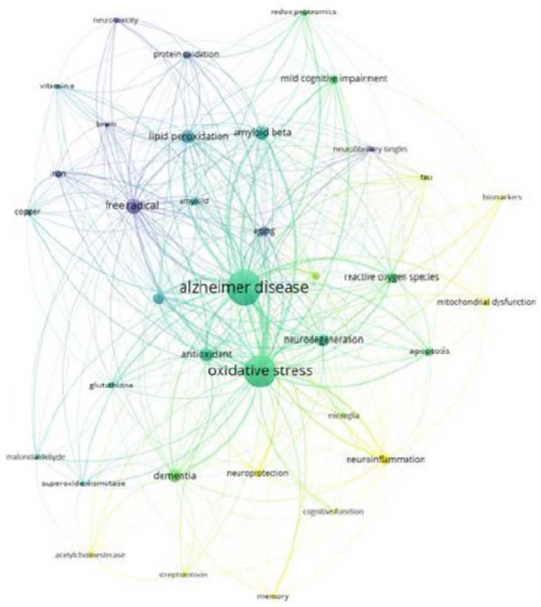

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AIM AND SCOPES
Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

Areas of particular interest are four topics. They are;

A- Ion Channels (Na^+- K^+ Channels, Cl^- channels, Ca^{2+} channels, ADP-Ribose and metabolism of NAD^+, Patch-Clamp applications)

B- Oxidative Stress (Antioxidant vitamins, antioxidant enzymes, metabolism of nitric oxide, oxidative stress, biophysics, biochemistry and physiology of free oxygen radicals)

C- Interaction Between Oxidative Stress and Ion Channels in Neuroscience
(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD^+ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

D- Gene and Oxidative Stress
(Gene abnormalities. Interaction between gene and free radicals. Gene anomalies and iron. Role of radiation and cancer on gene polymorphism)

READERSHIP

Biophysics	Biochemistry
Biology	Biomedical Engineering
Pharmacology	PhysiologyGenetics
Cardiology	Neurology
Oncology	Psychiatry
Neuroscience	Neuropharmacology

Keywords
Ion channels, cell biochemistry, biophysics, calcium signaling, cellular function, cellular physiology, metabolism, apoptosis, lipid peroxidation, nitric oxide, ageing, antioxidants, neuropathy, traumatic brain injury, pain, spinal cord injury, Alzheimer's Disease, Parkinson's Disease.

RESEARCH ARTICLE

J Cell Neurosci Oxid Stress 2021;13(1): 971-984.

Quantitative description of publications (1986-2020) related to Alzheimer disease and oxidative stress: A bibliometric study

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List of Abbreviations;

***AD**, Alzheimer's Disease; **TP**, Total number of publications; **TC**, Total citations; **SJR**, SCImago Journal Rank; **SNIP**, Source Normalized Impact per Paper; **NCP**, Number of cited publications; **C/P**, Average citations per publication; **C/CP**, Average citations per cited publication; **h**, h-index; **g**, g-index; **ROS**, Reactive oxygen species; **RNS**, Reactive nitrogen species; **AChE**, Acetylcholinesterase.*

Abstract

While the pathological mechanism of Alzheimer's Disease (AD) is unclear, oxidative stress has been proposed to be one of its related theories, which can help to uncover the disease's pathological factors. This review aims to provide a quantitative description and data visualisation of AD and oxidative stress research from the literature obtained from the Scopus database. Based on the keywords used, which are related to AD and oxidative stress in the article title, 996 documents were retrieved for further analysis. Microsoft Excel, VOSviewer and Harzing's Publish or Perish were used to conduct the frequency analysis, data visualisation, and citation analysis. There is a continuous growth in the number of publications on research in AD and oxidative stress, starting from 1986 and spanning 35 years. The most cited article was "Oxidative stress hypothesis in Alzheimer's disease". The Journal of Alzheimer Disease published the most number of publications related to AD and oxidative stress, while the United States and its institutions were the main contributors. Our findings suggest that research on

aetiopathology, biomarkers and neuroprotective agents for AD dominated this research field.

Our bibliometric analysis provides distinct trends in AD and oxidative stress research in the last 35 years. Our findings highlight current hot topics related to biomarkers for screening and diagnosis of AD as well as neuroprotective agents used as disease-modifying therapies of AD.

Keywords: Alzheimer's disease; oxidative stress; bibliometric; VOSviewer; Harzing's Publish or Perish.

Introduction

Alzheimer's disease (AD) is a steadily progressing and chronic neurodegenerative disease of the brain that was first identified by Alois Alzheimer, a German psychiatrist in 1906 (Ahmed and Gilani 2014). Clinical manifestations of AD include poor cognition, nervousness, depression, hallucination, delusion, insomnia, and wandering (Burns et al. 1990; Lahiri et al. 2002; Burns and Iliffe 2009). The disease progresses within 8 years of the onset from memory loss to dementia and death (Avramopoulos 2009). AD contributes 60-80% of all dementia cases and is the major cause of dementia (Alzheimer's disease Facts and Figures 2021).

It is worth noting that several current AD-related theories such as the amyloid-β cascade hypothesis, tau protein hypothesis, cholinergic hypothesis, and oxidative hypothesis, can help uncover the disease's pathological factors (Teixeira et al. 2019). The hallmarks of oxidative stress can be seen early in the progression of AD (Matsuoka et al. 2001; Mariani et al. 2005; Butterfield et al. 2006; Mangialasche et al. 2009; Moreira et al. 2010; Mecocci and Polidori 2012). Mitochondrial dysfunction is observed in several neurodegenerative diseases including AD whereby it causes excessive production of reactive oxygen species (ROS) in addition to reducing ATP production (Cioffi et al. 2019). Oxidative stress is a condition in which cellular ROS levels are elevated and/or decreased capacity of antioxidant defense system to mitigate the potentially harmful effects of ROS (Ramassamy et al. 1999; Mattson 2004; Persson et al. 2014; Akbar et al. 2016). The electron transport chain in mitochondria is halted by an increase in ROS, resulting in oxidative imbalance and elevated by-products of DNA, RNA, protein and lipids oxidation (Jiang et al. 2016). The oxidative imbalance that contributes to neuronal damage has been shown to play a key role in AD (Singh et al. 2019).

There are several bibliometric studies related to AD that have been conducted in the past (Sorensen 2009; Sorensen et al. 2010; Chen et al. 2014; Song et al. 2015; Serrano-Pozo et al. 2017; Dong et al. 2019; Schilder et al. 2020). Sorensen (2009) used PubMed and Social Science Index to find the top 100 AD researchers and AD-specific h-index to measure the productivity and impact of AD research. In 2010, Sorensen et al. (2010) conducted author co-citation network analysis using bibliometric data from 269 Alzheimer investigators and 167,142 researchers to identify major researchers in AD. Chen et al. (2014) conducted a bibliometric study of cholinesterase inhibitors aimed to find the trend of AD research and the order of medications that were well tolerated or more successful in the treatment of AD. In the latter study, a total of 4,982 articles and reviews published between 1993 and 2012 from the Science Citation Index Expanded database were analysed. The investigators found that the publication of cholinesterase inhibitor research increased over time and the order of medications was donepezil, galantamine, rivastigmine, tacrine, memantine and huperzine A. They also discovered that the pathogenesis of the oxidative stress hypothesis in AD garnered a lot of coverage.

Later, Song et al. (2015) conducted a bibliometric analysis involving 96,081 articles retrieved from PubMed. They analysed 16 main topics of the AD literature from pre-1950 to 2014 (primarily 2000–2013) and found a noticeably increasing trend in the topic of transgenic mouse. In 2017, Serrano-Pozo and colleagues conducted a bibliometric study to find the trend in research output, funding, publication subtypes, research themes, diagnosis, pathophysiology, and prevention, as well as the impact of AD research using PubMed, Scopus, Web of Science, and Alzheimer's Funding Analyzer databases from 1975 to 2014 (Serrano-Pozo et al. 2017). More recently, Dong et al. (2019) conducted a 30-year bibliometric analysis to look at the publication trends for AD worldwide and in China. The investigators found that Chinese researchers contributed significantly to global AD research, accounting for 30.93% of the publications, and proposed that the researchers strengthen their international collaboration.

The most recent bibliometric study was related to drug development for AD (Schilder et al. 2020). The

study aimed to gain insights into the current lack of an effective treatment for AD by tracing the progression of research paths in the scientific fields of basic, preclinical and clinical research from the disease's discovery in 1906 to 2016. Despite the numerous bibliometric analysis done throughout the years, a quantitative description of publications specifically related to AD and oxidative stress is still lacking. Thus, this study aims to fill this gap by providing a quantitative description, and data visualisation of AD and oxidative stress research obtained from the Scopus database.

Material and methods

Searches were conducted on 12 April 2021, using the Scopus database. The search term "reactive oxygen*" OR superoxide OR "hydrogen peroxide" OR "hydroxyl radical" OR "oxidative stress" OR "free radical" OR "lipid peroxidation" OR ROS OR "nitrosative stress" OR "redox*" OR "nitro*oxidative" AND Alzheimer* OR dementia in the title of the article were used to search relevant articles related to research on AD and oxidative stress. We refined the search to publishing year up to 2020 and omit "erratum" from document type. We included published documents in all languages and all types of documents and sources. **Figure 1** summarizes the search strategy used in this study.

Results

Descriptive statistics

We found 996 documents that were published between 1986 to 2020 with a total citation of 73785. The sample presents an average citation rate of 2108.14 cites/year and 74.08 cites/paper (**Table 1**). However, 57 or 5.72% of the documents have never been cited, and 219 or 21.98% have been cited between one and ten times.

Distribution of publications

Figure 2 shows the chronological distribution of publications on AD and oxidative stress. The first traceable document was published in 1986, and from then on, the number of publications steadily increased, though with some fluctuations. The highest number of publications was in 2020 which indicates that the topic of AD has caught some attention among scholars recently.

Most cited publications

Table 2 lists the publications that have been cited over 500 times. The topmost cited article "Oxidative stress hypothesis in Alzheimer's disease" (Markesbery 1997), accounted for 1843 citations. The article was published in Free Radical Biology and Medicine in 1997. The second most cited article, "A model for β-amyloid aggregation and neurotoxicity based on free radical generation by the peptide: relevance to Alzheimer disease" (Hensley et al. 1994) was published earlier in Proceedings of the National Academy of Sciences of the United States of America. It received a total of 1039 citations. "Iron accumulation in Alzheimer disease is a source of redox-generated free radicals" (Smith et al. 1997) was the third most cited article accounting for 1033 citations. This article was also published in Proceedings of the National Academy of Sciences of the United States of America.

Most productive journals

Table 3 lists the top ten journals based on the number of publications in AD and oxidative stress research. Journal of Alzheimer's disease ranked first with 68 or 6.8% documents, followed by Free Radical Biology and Medicine with 49 (4.9%), Neurobiology of Aging with 28 (2.8%) documents, Oxidative Medicine and Cellular Longevity with 25 (2.5%), Antioxidants and Redox Signaling with 16 (1.6%), Current Alzheimer Research with 16 (1.6%), Annals of the New York Academy of Sciences with 15 (1.5%), Neuroscience Letters with 14 (1.4%), Neurobiology of Disease with 13 (1.3%) and Neurochemical Research with 12 (1.2%) documents.

Most important authors

Table 4 shows the top ten authors based on their number of citations per publication related to AD and oxidative stress research. According to the result, Markesbery WR becomes the most important author with 281.64 citations per publication. The subsequent authors are Smith MA, Perry G, Butterfield DA and Pierce WM. Nevertheless, the top five authors who have a higher number of publications are Butterfield DA, Perry G, Smith MA, Zhu X and Sultana R. Articles written by some of these authors were also listed in top-cited. For instance, Butterfield DA (5 articles), Perry G (4 articles), Smith MA (3 articles), Markesbery WR (2 articles) and Zhu X (1 article) (**Table 2**).

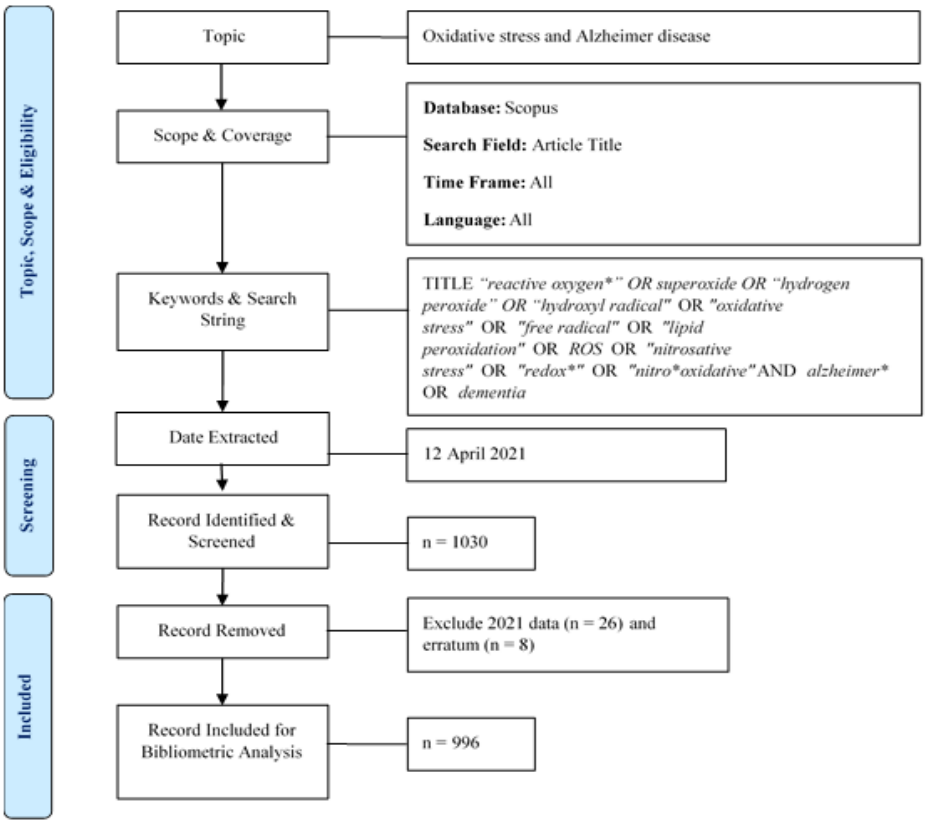

Figure 1. Flow diagram of the search. strategy.

Table 1: *Citation Metric*

Publication years	1986-2020
Total publications	996
Citations	73785
Cites/year	2108.14
Cites/paper	74.08
Authors/paper	5.28
h-index	139
g-index	229

Table 2: *Top articles based on number of citations (only articles with more than 500 citations were included).*

Rank	Title	Source	Year	Cites
1	Oxidative stress hypothesis in Alzheimer's disease (Markesbery, 1997)	Free Radical Biology and Medicine	1997	1843
2	A model for β-amyloid aggregation and neuro-toxicity based on free radical generation by the peptide: relevance to Alzheimer disease (Hensley et al., 1994)	Proceedings of the National Academy of Sciences of the United States of America	1994	1039
3	Iron accumulation in Alzheimer disease is a source of redox-generated free radicals (Smith et al., 1997)	Proceedings of the National Academy of Sciences of the United States of America	1997	1033
4	4-Hydroxynonenal-derived advanced lipid peroxidation end products are increased in Alzheimer's disease (Sayre et al., 1997)	Journal of Neurochemistry	1997	883
5	Oxidative stress and Alzheimer disease (Christen, 2000)	American Journal of Clinical Nutrition	2000	856
6	Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: Implications for free radical generation and oxidative damage in disease progression (Manczak et	Human Molecular Genetics	2006	786

	al., 2006)			
7	Lipid peroxidation and protein oxidation in Alzheimer's disease brain: Potential causes and consequences involving amyloid beta-peptide-associated free radical oxidative stress (Butterfield & Lauderback, 2002)	Free Radical Biology and Medicine	2002	778
8	Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease (Cutler et al., 2004)	Proceedings of the National Academy of Sciences of the United States of America	2004	734
9	Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine (De Felice et al., 2007)	Journal of Biological Chemistry	2007	663
10	Amyloid beta-peptide (1-42)-induced oxidative stress and neurotoxicity: Implications for neurodegeneration in Alzheimer's disease brain. A review (Butterfield, 2002)	Free Radical Research	2002	636
11	Increased lipid peroxidation precedes amyloid plaque formation in an animal model of Alzheimer amyloidosis (Praticò et al., 2001)	Journal of Neuroscience	2001	623
12	Oxidative stress in Alzheimer's disease (Smith et al., 2000)	Biochimica et Biophysica Acta - Molecular Basis of Disease	2000	621
13	Review: Alzheimer's amyloid Î²-peptide-associated free radical oxidative stress and neurotoxicity (Varadarajan et al., 2000)	Journal of Structural Biology	2000	599
14	Oxidative stress and mitochondrial dysfunction in Alzheimer's disease (Wang et al., 2014)	Biochimica et Biophysica Acta - Molecular Basis of Disease	2014	553
15	Oxidative stress and the amyloid-beta peptide in Alzheimer's disease (Cheignon et al., 2018)	Redox Biology	2018	544
16	Evidence that amyloid beta-peptide-induced lipid peroxidation and its sequelae in Alzheimer's disease brain contribute to neuronal death (Butterfield et al., 2002)	Neurobiology of Aging	2002	543
17	Four-hydroxynonenal, a product of lipid peroxidation, is increased in the brain in Alzheimer's disease (Markesbery & Lovell, 1998)	Neurobiology of Aging	1998	542

Table 3. *Top ten journals based on number of publications.*

Source Title	TP	TC	Publisher	Cite Score	SJR 2019	SNIP 2019
Journal of Alzheimer's Disease	68	4481	IOS Press	6.0	1.586	1.070
Free Radical Biology and Medicine	49	7077	Elsevier	9.7	1.841	1.566
Neurobiology of Aging	28	3614	Elsevier	7.7	2.021	1.151
Oxidative Medicine and Cellular	25	1242	Hindawi	7.3	1.394	1.500

Longevity						
Antioxidants and Redox Signaling	16	1461	Mary Ann Liebert	10.7	2.163	1.560
Current Alzheimer Research	16	793	Bentham	6.3	1.079	0.873
Annals of the New York Academy of Sciences	15	1839	Wiley-Blackwell	8.2	1.726	1.416
Neuroscience Letters	14	1241	Elsevier	**4.1**	0.854	0.719
Neurobiology of Disease	13	1286	Elsevier	8.8	2.285	1.231
Neurochemical Research	12	1094	Springer Nature	5.5	0.910	0.805

Notes: TP=total number of publications; TC=total citations; Cite Score=Cite Score measures average citations received per document published in the serial; SJR 2019=SCImago Journal Rank measures weighted citations received by the serial. Citation weighting depends on the subject field and prestige (SJR) of the citing serial; SNIP 2019=Source Normalized Impact per Paper measures actual citations received relative to citations expected for the serial's subject field.

Table 4. *Top ten important authors based on number of citations per publication.*

Author's Name	Affiliation	Country	TP	NCP	TC	C/P	C/CP	*h*	*g*
Markesbery, W.R.	University of Kentucky	United States	22	22	6196	281.64	281.64	22	22
Smith, M.A.	VistaGen Therapeutics, Inc.	United States	68	67	10159	149.40	151.63	48	68
Perry, G.	University of Texas at San Antonio	United States	78	75	11422	146.44	152.29	54	78
Butterfield, D.A.	University of Kentucky HealthCare	United States	100	100	14535	145.35	145.35	68	100
Pierce WM	James Graham Brown Cancer Center	United States	14	14	1975	141.07	141.07	14	14
Zhu, X.	Case Western Reserve University	United States	42	42	5663	134.83	134.83	34	42
Perluigi, M.	Sapienza Università di Roma	Italy	15	15	1815	121.00	121.00	15	15
Sultana, R.	University of Kentucky	United States	42	42	5007	119.21	119.10	35	42
Nunomura, A.	Jikei University School of Medicine	Japan	36	33	4291	119.19	130.03	26	36
Moreira, P.I.	Universidade de Coimbra, Centro De Neurociências e Biologia Celular	Portugal	28	27	2530	90.36	93.70	19	28

Notes: TP = total number of publications; NCP = number of cited publications; TC = total citations; C/P = average citations per publication; C/CP = average citations per cited publication; h = h-index; and g = g-index.

A total number of 3676 researchers participated in publishing retrieved documents giving a mean of 5.28 authors per document. **Figure 3** shows the co-authorship visualisation analysis of authors using the VOSviewer technique with minimum productivity of 8 documents and a minimum total citation of 500. The map included 29 circles, each representing one author. The top five authors who have a higher number of publications possess bigger circles compared to the rest. Closed circles indicate authors with close research collaboration. For instance, the strong-link researchers, Perry G, Smith MA, Zhu X and Nunomura A are grouped in a cluster (green). While, Markebery WR, Butterfield DA, Perluggi M and Sultana R are grouped in another cluster (red) and closely linked in cooperation with AD and oxidative stress research.

Most influential institutions

Table 5 lists the top institutions' published literature on AD and oxidative stress. Both the University of Kentucky and the University of Kentucky HealthCare in the United States have the highest number of publications (n=125) and total citations (20577 citations). The second top institution is Case Western Reserve University also in the United States with 82 total publications and 12009 citations. Other top institutions are mostly in the United States, while Portugal, Japan, Italy and Australia have one institution each.

Most outstanding countries

The United States published the largest number of articles on AD and oxidative stress (412), followed by China with 131 articles, Italy with 99 articles, Japan with 60 articles, Spain with 56 articles, India with 54 articles, the United Kingdom with 43 articles, Germany with 40 articles, Canada with 37 articles and France with 33 articles (**Table 6**). The United States had the highest total citations (50354), C/P, C/CP, h-index and g-index. Italy ranked second in terms of TC, h-index and g-index, but Japan ranked second in terms of C/P and C/CP. The high C/P and C/CP may be contributed by highly cited papers originating from the country.

Clustering analysis and the evolution of collaboration among countries on AD and oxidative stress research

A total number of 70 countries participated in publishing the retrieved documents. **Figure 4** shows the co-authorship visualisation analysis of countries using the VOSviewer technique with minimum productivity of 5 documents and a minimum number of citations of 1 of a country. The map included 33 circles, each representing one country. The top five productive countries i.e. United States, China, Italy, Japan and Spain possessed bigger circles, which represent a higher number of documents compared to the rest. Seven different clusters shown in Figure 4 represent different camps on AD and oxidative stress research. Closed circles indicate countries with close research collaboration. For instance, the United States (n = 410), Japan and Portugal were grouped in a cluster (cyan), while China (n= 132), United Kingdom and Malaysia were grouped in another cluster (purple). The subsequent camps were Italy (n = 98) and Chile (orange); Spain (n = 57), France, Germany, Netherlands, Romania, Sweden and Switzerland (green); India (n = 54), Australia, Brazil, Czech Republic, Egypt, Oman, Russian Federation, Saudi Arabia and Slovakia (red); Canada (n = 37), Iran, South Korea, Taiwan and Turkey (blue); and Poland (n = 20), Mexico Colombia and Belgium (yellow).

The average publication year was 2003 for Germany, 2004 for Switzerland, 2006 for Japan, and 2007 for both the United States and the United Kingdom. These countries were among the pioneer in AD and oxidative stress research. Emerging countries in this research field with average publication years between 2015-2019 were India, Saudi Arabia, Romania, Egypt, Oman and Malaysia.

Clustering analysis and the evolution of topic within authors' keywords in publications on AD and oxidative stress research

Figure 5 shows 36 out of 1672 authors' keywords that occured at least 10 times in the publications related to AD and oxidative stress. The keywords were grouped into 4 clusters. Apart from oxidative stress and Alzheimer's disease, other keywords like free radicals, lipid peroxidation, mitochondria, antioxidants, neurodegeneration, dementia, reactive oxygen species, mild cognitive impairment, apoptosis, aging, inflammation and amyloid were commonly used. While, the newer keywords (2014 onwards) were neuroinflammation, neuroprotection, acetylcholinesterase, biomarkers, mitochondrial dysfunction, memory, and streptozotocin.

Table 5. *Top ten institutions based on number of publications.*

Rank	Institution	Country	TP	TC	C/P
1	University of Kentucky	United States	125	20577	164.62
2	Case Western Reserve University,	United States	82	12009	146.45
3	University of Texas at San Antonio	United States	32	3678	114.94
4	Universidade de Coimbra	Portugal	30	3077	102.57
5	Asahikawa Medical University	Japan	26	3616	139.08
6	Sapienza Università di Roma	Italy	24	2428	101.17
7	University of Louisville	United States	17	2365	139.12
8	Massachusetts General Hospital	United States	17	1729	101.71
9	Harvard Medical School	United States	12	1155	96.25
10	University of Melbourne	Australia	12	1665	138.75

Notes: TP = total number of publications; TC = total citations; C/P = average citations per publication.

Table 6. *Top ten countries based on number of publications.*

Country	TP	NCP	TC	C/P	C/CP	*h*	*g*
United States	412	402	50354	122.22	125.26	121	211
China	131	117	3702	28.26	31.64	30	58
Italy	99	97	7328	74.02	75.55	51	85
Japan	60	57	5765	96.08	101.14	34	60
Spain	56	53	2221	39.66	41.91	28	46
India	54	51	1867	34.57	36.61	24	43
United Kingdom	43	42	2040	47.44	48.57	24	43
Germany	40	40	3546	88.65	88.65	31	40
Canada	37	37	1903	51.43	51.43	24	37
France	33	31	2805	85.00	90.48	19	33

Notes: TP = total number of publications; NCP = number of cited publications; TC = total citations; C/P = average citations per publication; C/CP = average citations per cited publication; h = h-index; and g = g-index..

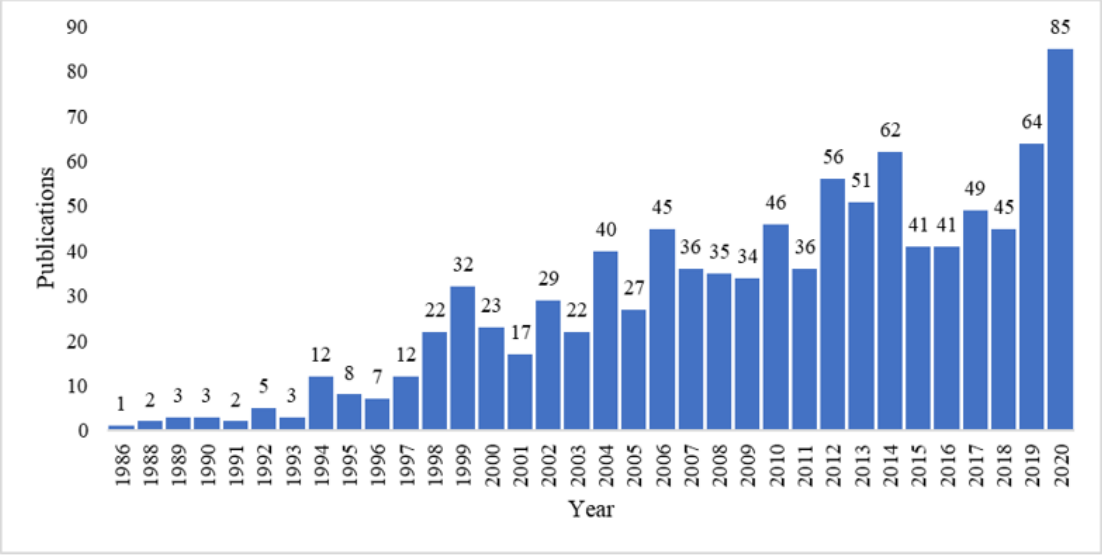

Figure 2. Number of publications on AD and oxidative stress.

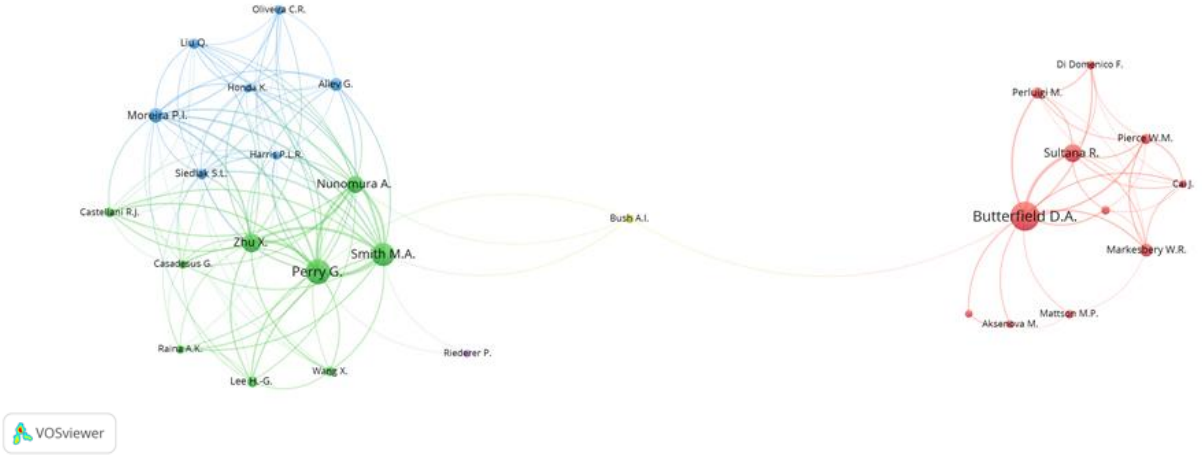

Figure 3. Co-authorship authors with 8 minimum number of documents to an author and 500 minimum number of citations to an author. Thirty-one authors reach the threshold (29 appears in the figure).

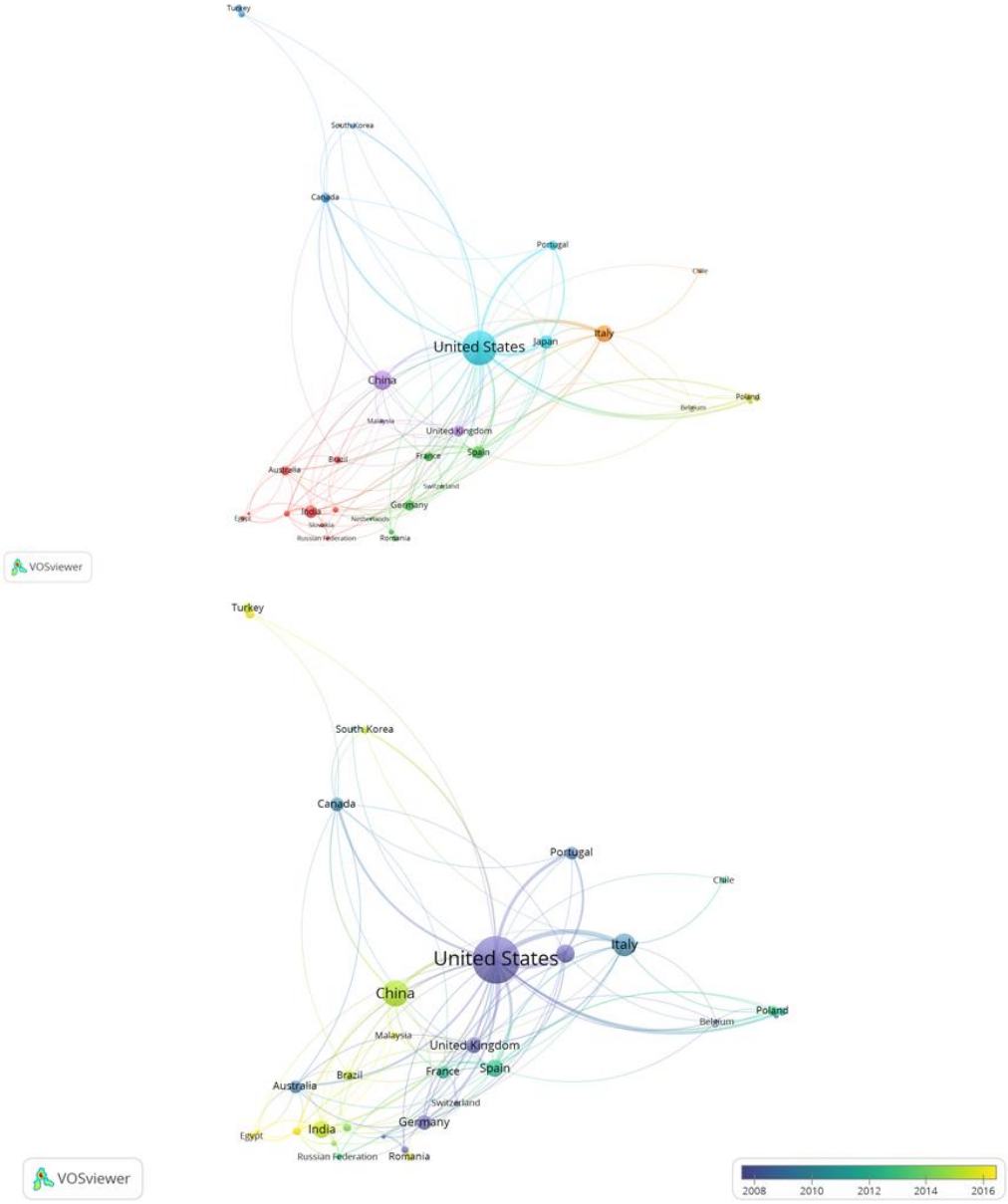

Figure 4. Co-authorship visualisation analysis of countries. Network visualisation (top) and overlay visualisation (bottom). A minimum number of documents of a country: 5 and a minimum number of citations of a country: 1. Thirty-three countries meet the threshold.

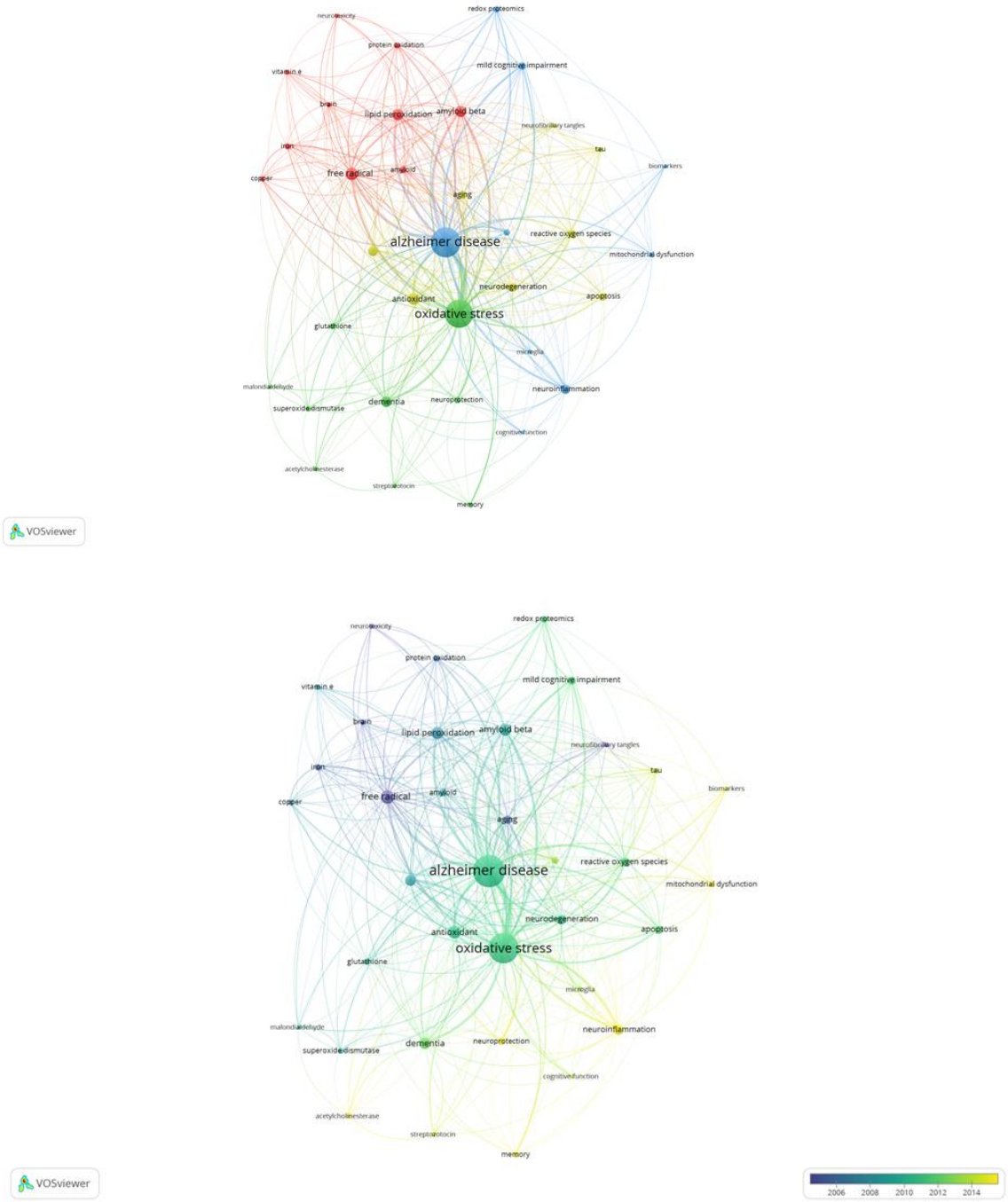

Figure 5. Keywords map showing the network visualisation (top) and overlay visualisation (bottom) of 36 terms that occurred at least 10 times in publications on AD and oxidative stress.

Discussion

Our bibliometric study of AD and oxidative stress research shows some important patterns of publications between 1986 and 2020. There was a limited number of publications between 1986 and 1993 (less than 10 documents), whereas from 1993 onwards the number of publications started to increase with some fluctuations and was the highest in 2020. This finding was consistent with other bibliometric studies related to AD (Song et al. 2015; Dong et al. 2019).

"Oxidative stress hypothesis in Alzheimer's disease" (Markesbery 1997), published in Free Radical Biology and Medicine in 1997, was the topmost cited article. This review paper suggested that free radicals are possibly involved either primarily or secondarily in the pathogenesis of neuronal death in AD. The free radical generation is part of a cascade of events that leads to neuronal death. They proposed that in AD, therapeutic efforts aimed at removing ROS or preventing their development may be helpful. The second most cited article "A model for β-amyloid aggregation and neurotoxicity based on free radical generation by the peptide: relevance to Alzheimer disease" (Hensley et al. 1994) was published in Proceedings of the National Academy of Sciences of the United States of America in 1994. This original article developed a free radical-induced beta-amyloid model, which is relevant to AD. The third most cited article, "Iron accumulation in Alzheimer disease is a source of redox-generated free radicals" (Smith et al. 1997), was also published in Proceedings of the National Academy of Sciences of the United States of America. This original article indicated that iron accumulation could be an important contributor to the oxidative damage in AD.

The Journal of Alzheimer's Disease produced the most publication (6.8%) on AD and oxidative stress. It is a multidisciplinary international journal dedicated to advancing knowledge of AD's aetiology, pathogenesis, epidemiology, genetics, behaviour, treatment and psychology. This journal has been ranked first (Song et al. 2015) and second (Dong et al. 2019) most productive journal related to AD research. The journal Free Radical Biology and Medicine ranked second as the top journal. Although it was not listed as the top journal in the earlier bibliometric studies related to AD, this journal received the highest total citations surpassing the Journal of Alzheimer's Disease. This could be explained by the focus of this journal as the premier venue for cutting-edge studies in the redox biology of both health and disease. Neurobiology of Aging ranked third and published findings from research with a focus on mechanisms of nervous system changes with age or age-related diseases. This journal was ranked first (Dong et al. 2019) and second (Song et al. 2015) in the earlier bibliometric studies on AD.

Markesbery WR ranked first as the most important author with 281.64 cites/paper. Although he has a total of 22 publications, he authored the article ranked first and seventeenth in the top-cited article. This could be the reason for his high C/P and C/CP. Butterfield DA, however, was the most prolific author with a total of 100 publications followed by Perry G, Smith MA, Zhu X and Sultana R. Smith MA and Perry G had been listed as the most productive authors in the earlier bibliometric study on AD (Song et al. 2015). Most of the top authors either contributed to the top-cited articles as main or co-author or originated from the most influential institutions. Among the top institutions were the University of Kentucky, Case Western Reserve University and the University of Texas in the United States, Sapienza Università di Roma in Italy and Universidade de Coimbra in Portugal.

Similar to the earlier bibliometric study on AD, the topmost outstanding country that published literature related to AD and oxidative stress was the United States (Dong et al. 2019). This could be explained by the fact that the majority (7 out of 10) of the top institutions are located in the United States. As seen in the co-authorship visualisation analysis of countries, United States, China, Italy, Japan and Spain were the most productive countries. Countries like China and India are the new emerging countries in research related to AD and oxidative stress.

The keywords map illustrates the co-occurrence network of the authors' keywords in AD and oxidative stress research. The top authors' keywords were oxidative stress, AD, free radicals, lipid peroxidation, mitochondria, antioxidants, neurodegeneration, dementia, ROS, mild cognitive impairment, apoptosis, aging, inflammation and amyloid. Also, a new series of keywords such as neuroinflammation, neuroprotection, acetylcholinesterase, biomarkers, mitochondrial dysfunction, memory, and streptozotocin have been gradually introduced to evaluate the role of oxidative stress in AD.

The appearance of neuroinflammation, acetylcholinesterase and mitochondrial dysfunction hints at the possible mechanisms behind AD (Melo et al. 2003; Tobore 2019; Simpson and Oliver 2020). Mitochondria are one of the main sources of ROS and reactive nitrogen species (RNS), and mitochondria dysfunction has been implicated in the pathogenesis and pathophysiology of AD (Tobore 2019). Elevated ROS may act as second messengers activating pro-inflammatory pathways in microglia (Simpson and Oliver 2020). The loss of acetylcholinesterase (AChE) function, the enzyme responsible for acetylcholine hydrolysis, from both cholinergic and non-cholinergic neurons in the brain is one of the hallmark changes of AD (Atack et al. 1987). The involvement of oxidative stress in the enhancement of acetylcholinesterase activity has also been reported (Melo et al. 2003).

Besides the keywords associated with the mechanisms or aetiopathogenesis of AD, keywords like neuroprotection, memory, biomarkers and streptozotocin also appeared. Streptozotocin administered via intracerebroventricular or intraperitoneal injection induces AD characterised by poor memory and accumulation of beta-amyloid and tau protein in the animal's brain (Kamat 2015). Besides streptozotocin, other animal models for AD such as lipopolysaccharide (Zakaria et al. 2017), polyinosinic:polycytidylic acid (Weintraub et al. 2013), okadaic acid (Kamat et al. 2013) and colchicine (Kumar et al. 2007) do not, however, show up in the keyword map. In addition, this analysis shows that searching for suitable biomarkers for screening and diagnosis of AD (Blennow and Zetterberg 2018); and neuroprotective agents as disease-modifying therapies for AD (Cummings et al. 2016) are among the current research work related to AD and oxidative stress.

In conclusion, the current bibliometric analysis highlights studies conducted around the world on oxidative stress as one of the underlying mechanisms of AD. Current research focuses on finding suitable biomarkers for screening and diagnosis of AD as well as the neuroprotective agents as disease-modifying therapies for it.

Authors' contributions

ZO planned and designed the research. AA and RZ provided methodological support/advice; EYAQ, KFA and IL extract data. AHA performed the statistical analysis. RZ wrote the manuscript. AA, KNSS and AHA revised the manuscript. All authors approved the final version of the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflict of interest with respect to the research, authorship and/or publication of this article.

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