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MORE THAN FIVE DECADES OF RESEARCH ON UREASE INHIBITORS: A BIBLIOMETRIC STUDY

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Abstract: This study focuses on works related to urease inhibitors published from 1970 to 2021, gathered from the Web of Science database. This paper aims to examine the trends of research involving urease inhibitors, as there have been no centralised study that utilises bibliometric methods on the related research fields, methods used, as well as collaborations. The total number of publications examined in this paper after filtering is 574 and the number of review articles on urease inhibitors is on the low side considering other research topics published within the 51-year period. Experimental works are still the core method of gathering information on the usefulness of urease inhibitors in all fields within the investigated time span. From the mid-2000s, theoretical investigations emerged as a complement to experimental research, mostly in the form of molecular docking studies. As in the other fields of study, theoretical works have been accepted as part of research methods to examine the molecular interactions between compounds and urease. The main partners to consider for cooperation in this field of study are those in Pakistan, China, the United States, New Zealand and Spain as their institutions house researchers that are outstanding in the field and they produce articles that are highly cited.

Keywords: Urease inhibitor, bibliometric study.

Introduction

Urease is an enzyme that can be sourced from plants and bacteria. It fast tracks the hydrolysis of urea into carbamate and ammonia. However, as the adsorption rate of plants are unable to match the excessive release rate of the nutrient, fertilisers are usually applied to crops to compensate the wasted supply, resulting in the surplus of nutrients into the environment. The excessive nitrogen effluent from fertilisers leads to disastrous long-term environmental issues (Amtul *et al.,* 2002; Khan *et al.,* 2018; Modolo *et al.,* 2018; Sigurdarson *et al.,* 2018) as well as damage to germinating seedlings and young plants (Engelstad & Hauck, 1974), apart from economic losses. In the pharmaceutical field, urease is responsible for causing mouth and gastrointestinal ulcers, which can lead to cancer.

To overcome the aforementioned problems, the use of the urease inhibitors (Modolo *et al.,* 2015; Kafarski & Talma, 2018; Modolo *et al.,* 2018; Rego *et al.,* 2018) is suggested. In this approach, urease is combined with the inhibitors to hinder the interaction between urease with urea (Benini *et al.,* 2004; Watson *et al.,* 2008; Barakat *et al.,* 2015; Noreen *et al.,* 2015). Urease inhibitors will form a bond with urease to block its active sites of the urease, which have the potential to hydrolyse urea. The urease active sites contain two nickel atoms, with the distances between them depending on the sources, for example, *Bacillus pasteurii* 3.7 Å (Benini *et al.*, 1999), *Klebsiella aerogenes* 3.6 Å (Pearson *et al.*, 1997), Jack bean 3.6 Å, *Helicobacter pylori* 3.5 Å (Cunha *et al.*, 2021). The inhibition mechanism may involve intermediate steps, as discussed in the works of Ciurli's and Cantarella's groups (Zambelli *et al.*, 2011; Cantarella *et al.*, 2018; Mazzei *et al.*, 2020).

In this paper, we examined the published works related to urease inhibitors in the agriculture and pharmaceutical fields. Many compounds have been suggested and used as urease inhibitors. Recent candidates include tryptamine derivatives (Kanwal *et al.,* 2019), atenolol derivatives (Wahid *et al.,* 2020),

thiobarbiturate derivatives (Abdulwahab *et al.,* 2020), flavonoid analogues (Liu *et al.,* 2020) and 5,6-dichloro-2-methyl-1H-benzimidazole derivatives (Menteşe *et al.*, 2019), just to name a few. With advances in research technology, computational studies are being increasingly used to search for new urease inhibitors, especially through molecular docking to study the binding interactions and mechanisms (Abid *et al.,* 2021; Ali *et al.,* 2021; Babaee *et al.,* 2021; Taha *et al.,* 2021). While experiments are still the major approach in validating the role of inhibitors, the information provided by molecular docking studies complement experimental results.

This paper employs the bibliometric method which is a quantitative method to gauge the impacts of research and publications. As studies involving urease inhibitors cover a wide range of topics, the bibliometric method would be a suitable method for this paper and this method is different from meta-analysis and systematic literature review (Donthu *et al.,* 2021). The main objective is to use bibliometrics analysis to provide a broad overview of existing research publications on urease inhibitors in the pharmaceutical, agricultural and chemical fields. The findings of this bibliometric analysis can provide an understanding of the landscape of urease inhibitor research and identify well-developed research areas and emerging and under-studied research themes that require more attention. Furthermore, interested researchers and policymakers can use the findings as a point of reference when navigating the field.

Materials and Methods

This descriptive study involved three steps: Creating a review database, performing a trend analysis using Microsoft Excel and mapping using VOSviewer. As stated earlier, the main goal of this study is to deliver a bibliometric analysis of existing literature on urease inhibitor, which include top cited articles and journals as previously reported by Chan *et al.* (2020) and Wan *et al.* (2021). The bibliometric analysis was focused on the data retrieved from the Web of Science (WoS) database, from 1970 to April 2021. As there was debate on the selection of database, WoS was chosen purely due to convenience, as we followed the views of Archambault and Campbell, who said the choice of database was immaterial as the difference was negligible (Archambault *et al.,* 2009). All the databases within WoS were included in the search. The keyword used was "urease inhibitor" (without quotes), under field tag "Title". All results were collected in a CSV-formatted Excel workbook.

Manual filtering was performed on the collected data to separate whether the published works are in the fields of agricultural, pharmaceutical or chemistry. In categorising these fields, agricultural refers to works purely on crops and fertilisers, while pharmaceutical is for works involving medicine, microbiology or pharmacy. The works categorised under chemistry are those involving interactions between inhibitors and proteins, and have no mentions of either agricultural or pharmaceutical (e.g., engineering) practices. To reduce sample bias, the screening of the records was also performed by reading the title and abstracts by the authors of this study (Serra *et al.,* 2018). The subfields from WoS, faculties of authors, journal names and keywords were referred to in the manual identification. Another manually performed filtering involves the type of work, whether it is experimental, theoretical or a mix of the two. With the available computing software that can be used to study molecular interactions to complement experimental results or to provide new insights into the behaviour of the inhibitors, it is of interest to find the numbers of theoretical investigations involving urease inhibitors. As for meeting abstracts, since part of the analysis involve determining the type of work based on the details of the abstracts, only those with available abstracts were retained. We note here that the selective exclusion (after exhaustive online search for the abstract) might be a limitation of this study (Scherer & Saldanha, 2019). The steps involved in the retrieving and screening stages of this study are shown in Figure 1.

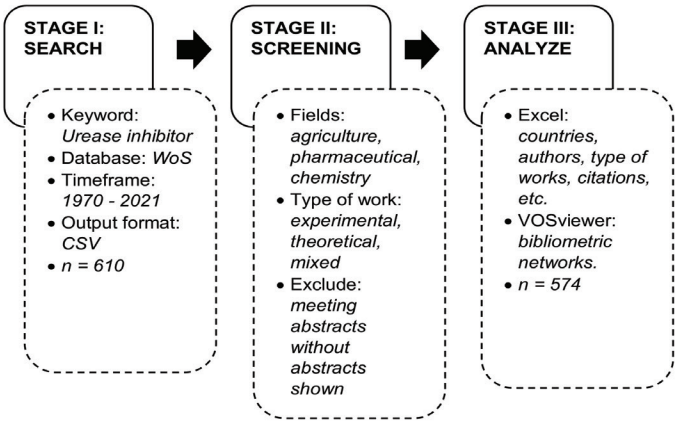


Figure 1: Flowchart of the steps in retrieving and -processing data in this study

The software Microsoft Excel and VOSviewer are used in the analysing stage. Microsoft Excel was used to organise and produce graphical representation of the data obtained from WoS. VOSviewer is a tool for constructing bibliometric networks of various items such as authors, organisations, citations and keywords (van Eck & Waltman, 2010). Different network analysis such as citation, co-citation, bibliographical coupling, co-author and keyword were performed using VOSviewer to identify major thematic clusters, most influential journals, publications and authors.

Results and Discussion

Table 1 shows the output of the urease inhibitors search. Over the span of 51 years (1970 to 2021), 610 publications were shown to have "urease inhibitor" in the title. Following manual inspection, the number was reduced to 574, which are due to the truncation of the "meeting abstract" as discussed in the previous section of this paper. The analysis of items in Table 2 and their derivatives are grouped using Microsoft Excel and VOSviewer.

A. Microsoft Excel Analysis

Trend of Publications with Year

There are 46 different research areas related to urease inhibitors listed in 574 published articles. Only 12 areas had been mentioned more than 10 times out of a total of 889. Out of this number, only three areas are researched more than 100 times: Agriculture, chemistry and pharmacology pharmacy with 225, 178 and 107 frequencies, respectively. The distribution of the publication frequency is as shown in Table 2.

Table 1: Main information from the search of "urease inhibitor" in WoS

Item	Output
Total documents	610
Document types	10
Language	6
Research areas	46
Countries	6
Authors	1,867
WoS categories	71
Funding agencies	318
Total citations	**13,000**

Table 2: Research areas involving urease inhibitors with a frequency of more than 10

Research Areas	Frequency	% (*N* = 574)
Agriculture	225	38.927
Chemistry	178	30.796
Pharmacology pharmacy	107	18.512
Biochemistry molecular biology	99	17.218
Environmental sciences ecology	56	9.689
Plant sciences	39	6.747
Food science technology	19	3.287
Science technology other topics	18	3.114
Microbiology	15	2.595
Engineering	13	2.249
Biotechnology applied microbiology	12	2.076
Biophysics	11	1.903

Collectively, the trend of publications according to the year can be seen as increasing as shown in Figure 2. As mentioned in the Methodology section, the research areas are grouped under the umbrella of agriculture (A), pharmaceutical (P) and chemistry (C). Separately, the number of publications in the agricultural field is higher than the pharmaceutical field (orange versus grey curves in Figure 2). However, the trend is reversed from mid-2010s to 2020, in which the pharmaceutical field has the higher number of publications per year. Of the total 574 publications analysed, more than half (299 or 52.1%) were from the agricultural field. As can be seen in Figure 2, starting from the 1970s, the focus on urease enzyme in the agricultural field has not waned and the same can be said for the pharmaceutical fields. As for the chemistry field, the number of publications started to increase continuously from the mid-2000s. Generally, all three fields have increases in publications but the quantum of increase for the agricultural and pharmaceutical fields are larger than that of the chemistry field. That means that the agricultural and pharmaceutical fields still attract talent and churn out more publications.

Trend of Publications with Language

Figure 3 clearly shows that English is the dominant language used in the publications (552 of 574). This is not surprising as English, in most part of the world is the lingua franca in communication, science and scientific communications (Van Weijen, 2012). German, Portuguese, Czech, Polish and Chinese are the other languages found in the records. Publishing in English language allows the articles to reach a wider audience and for non-English speaking authors, there might be other barriers impeding the process. Interested readers can refer to the article by Márquez and Porras (2020) and references therein for a discussion on the topic. The last publication in German was in 1986. Even though the publications are labelled as published in Portuguese, Czech, Polish and Chinese, they have abstracts in English, as is the usual practice for journals published in native languages.

Types of WoS Categories

Based on the categories defined in WoS, agriculture-related categories can be seen as popular categories. A graphical representation of the categories is shown in Figure 4. “Soil Science” has the highest number of publications

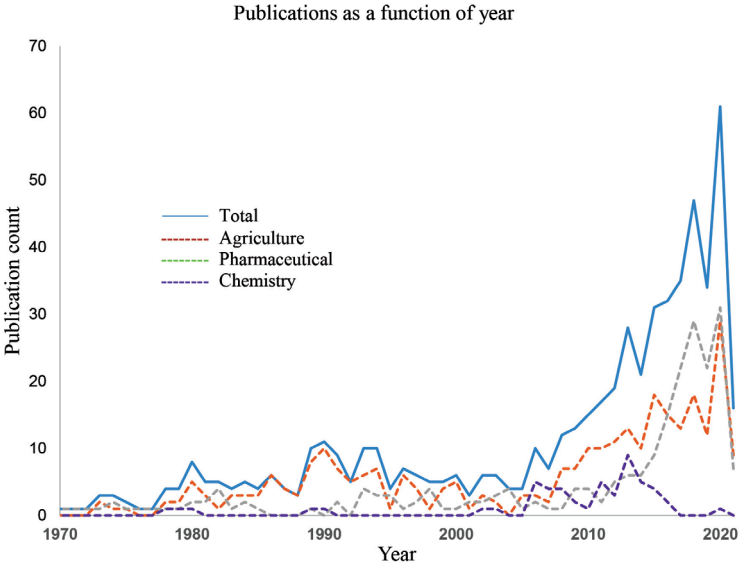


Figure 2: Number of publications in the range of years considered

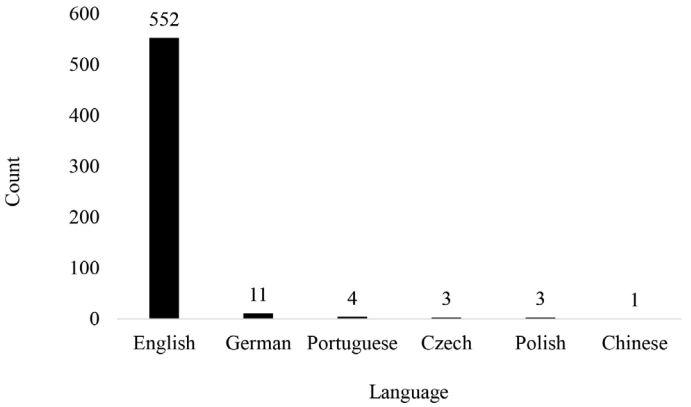


Figure 3: The variation of languages found in the retrieved data

(113 from the data retrieved), followed by "Chemistry Medicinal" (92), "Agronomy" (66) and the others. The results indicate that even though the agriculture-related categories received more attention in terms of research publications, pharmaceutical studies are still actively carried out. Overall, this figure can be interpreted as showing the same trend as observed in Figure 2, where the agricultural saw more publications than the pharmaceutical field.

Types of Research Works: Experimental, Theoretical, Mixed or Review?

Figure 5 shows the yearly progression of the published works (in the agricultural, pharmaceutical and chemistry fields), separated into experimental, theoretical, mixed and review studies. It can be seen that experimental work dominates the number of publications. Mixed work, where experimental work is combined with prediction or complemented with computational simulations, sees an increase around the year 2010 onwards. Theoretical research can be

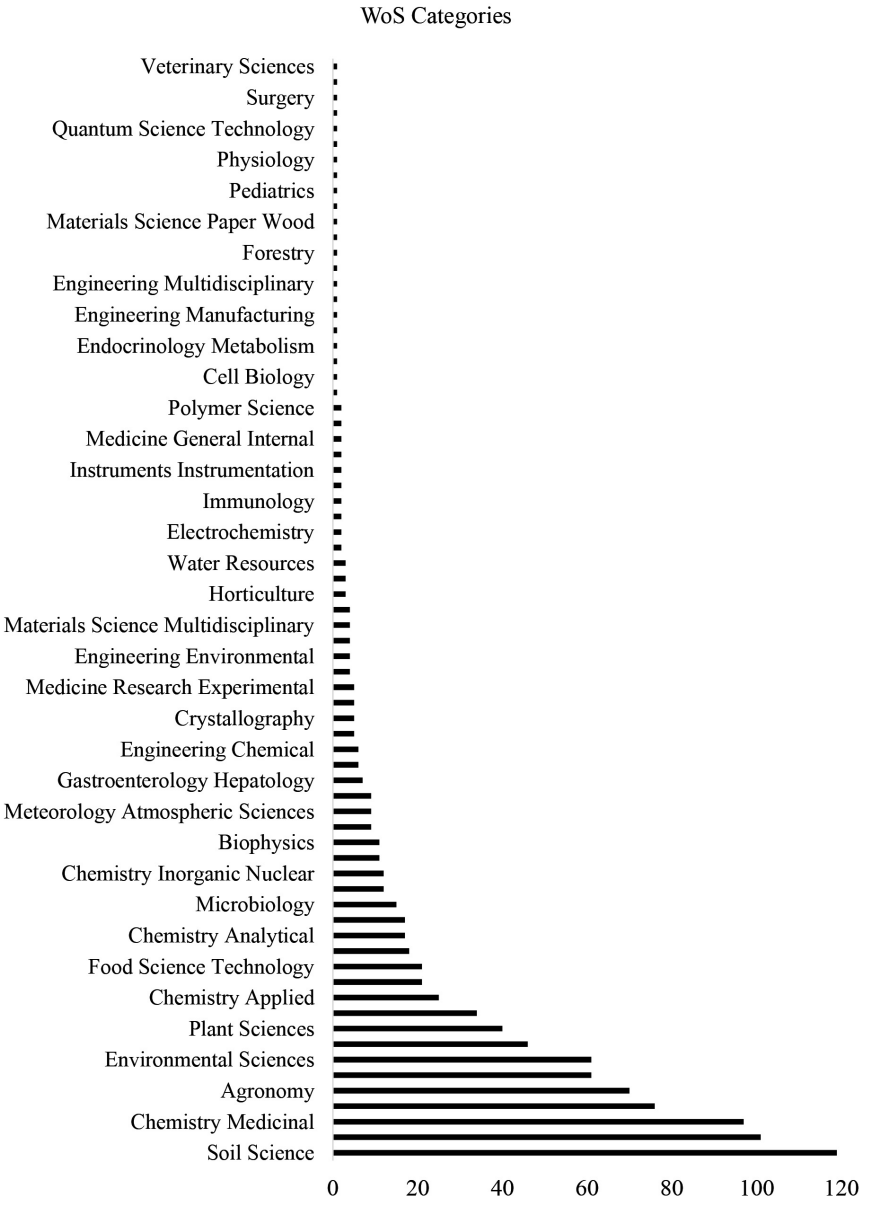


Figure 4: Number of publications according to the WoS categories

described as a rare occurrence: One in 1990 and another one in 2002, before the number increases from 2006 to 2020. Review articles did not exist in the 1970s, according to WoS and there are three in the early part of 1980s. However, in the whole 1990s, only one review article in the field of agriculture was published. The 2000s saw no review article publication. However, starting from 2011, review articles were published yearly.

Funding Agencies

The funding agencies involved in supporting research involving urease inhibitors are shown in Figure 6. To simplify the graphical representation, only those who have funded

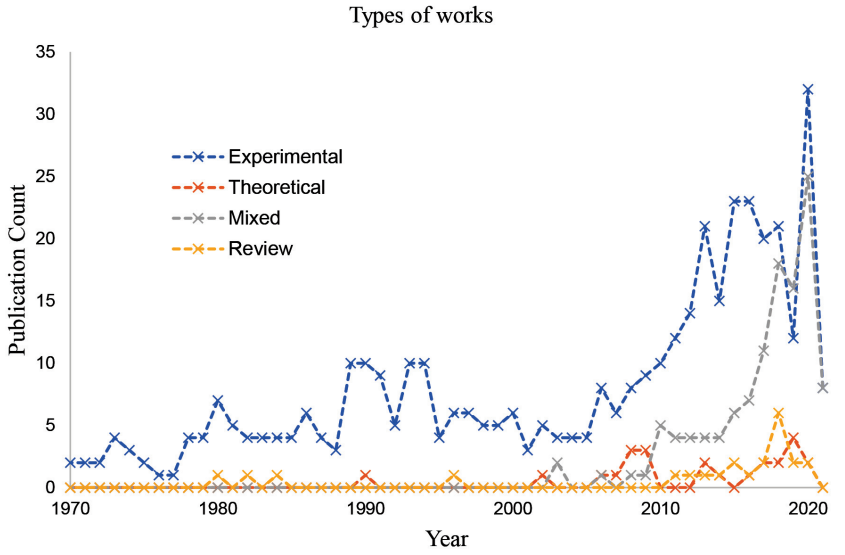


Figure 5: The yearly progression of experimental, theoretical, mixed and review types of research works

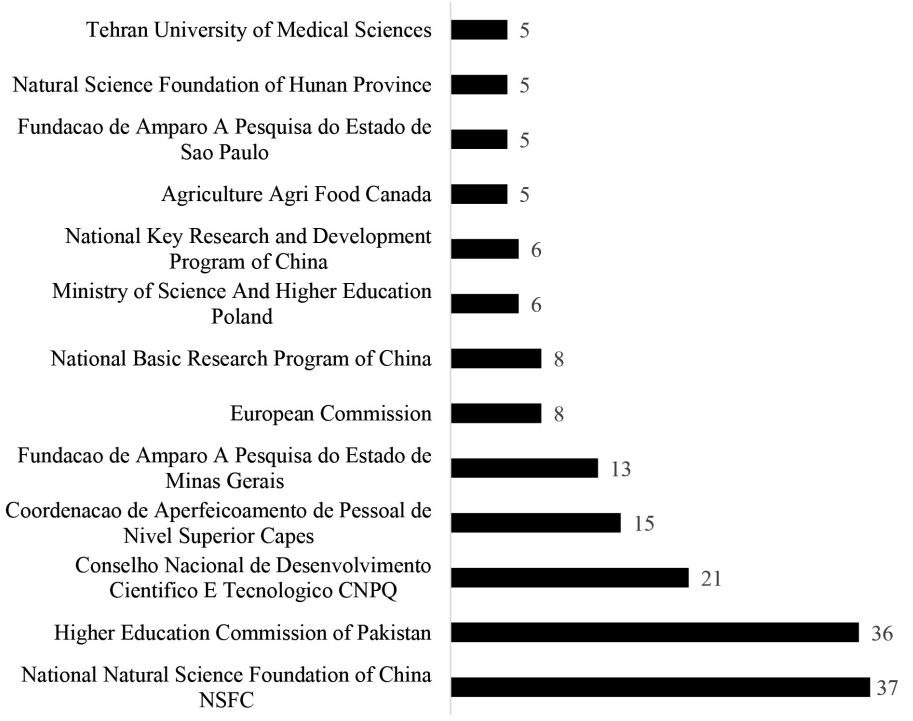


Figure 6: Funding agencies for works involving urease inhibitors. Only those funded five times and above are included in the figure

five or more studies were included. The funding frequencies shown here are not counting publications with the sole support of the funding agencies. Publications involving collaborations between authors from different agencies with different funding agencies are counted, as long as it is indicated in the published research.

Of the 13 top agencies funding research in urease inhibitors, six are from Asia. This shows the intensity of the research in this region.

Trend of Publications with Countries

As can be seen in Figure 7, Asia has the highest number of publications (46%), followed by Europe and North America, South America, Oceania and Africa. Figure 8 which shows the top 20 countries that have the highest number of publications, provides some view on the breakdown of the countries in the continents shown in Figure 7. The country with the highest number of publications on urease inhibitors is Pakistan, followed by the United States, China, Germany and Brazil. Of the countries shown in Figures 8 and 10 are in Asia. The reason Pakistan dominates the number of publications in this topic may be due to the fact that agriculture is the driver of Pakistan's economy. Agriculture accounts for about 20.9% of Pakistan's GDP and employs about 43.5% of the labour force (Chandio *et al.,* 2016). The supportive government policy may also contribute to this observation. The agricultural sector has shown improved performance and recorded the highest gain in the last 13 years; hence, it should be of no surprise if high numbers of urease inhibitors and agriculture research work are being carried out.

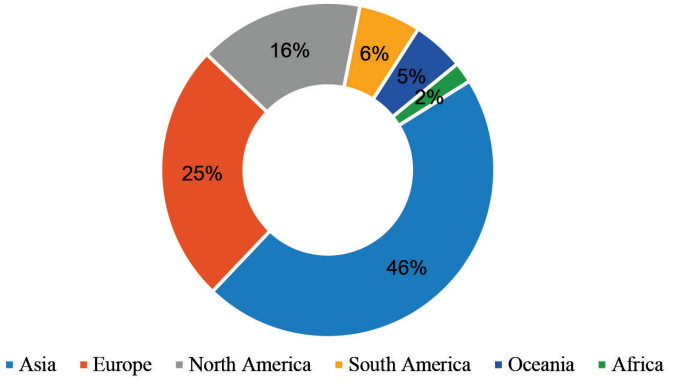


Figure 7: Publications by continents

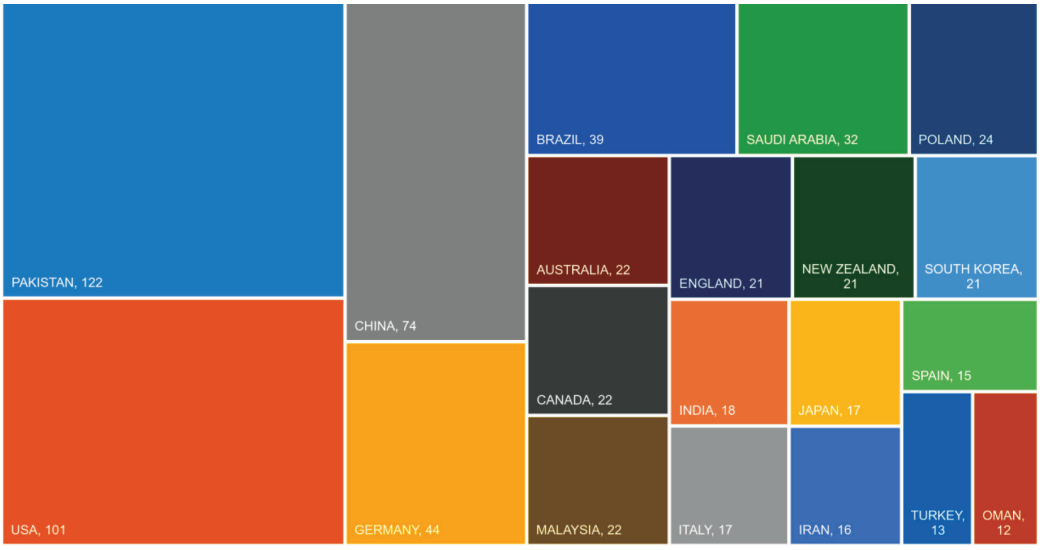


Figure 8: Publications from countries in the world. Only the top 20 are shown

The trends according to the countries were supported by the analysis of authors, in which authors with the topmost numbers of publications were listed. From the dataset, a total of 1,867 authors were found to be involved in works related to urease inhibitors. Of the number, 1,403 authors (75.1%) published one study, 260 (13.9%) published two studies and 205 authors (11.0%) published three or more studies related to urease inhibitors. Figure 9 shows the name of the 18 authors who have double-digit publications. Of the total, 17 were from Asia and only one is from Europe. One of the key findings of this task was that Choudhary MI was the most productive author, who have 37 (1.98%) records of publications contained in the dataset, followed by Khan KM with 29 (1.55%) records of publications. Upon closer inspection, these top two scientists are in the field of organic chemistry and their publications are pharmaceutical-related studies.

Citations

The average citation for the 574 articles is 22.65. Based on this value, we set out to analyse articles that has a higher-than-average number of citations. Out of the 574 records, 177 articles fulfilled the criterion of being cited 23 times. Publications with higher number of citations are generally more impactful. The ten top-cited articles based on their citation count and top ten publisher based on their recorded publications involving urease inhibitors are listed in Table 3 and Table 4. However, it has to be approached with caution as an article may be cited due to different reasons. Interested readers are encouraged to read the articles by Aksnes *et al.* (2019) and references therein. As shown in Figure 10, in the range between years 2005 and 2019, there is a significant increase and decrease in the highest citation numbers.

Contribution by Organization

Table 5 shows the top ten organisations involved in research related to urease inhibitors from 1970 to 2021 around the world.

As seen in Table 5, there are 12 organisations currently publishing articles in urease inhibitor research. Out of this number, it was found that some of the organisations are from the same country. Pakistan and China have the highest

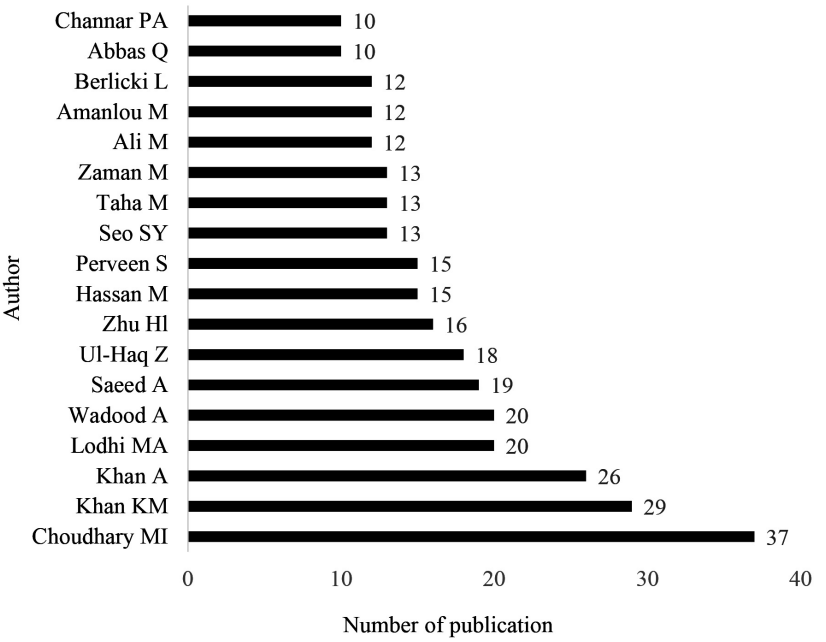


Figure 9: Analysis of authors and their number of publications

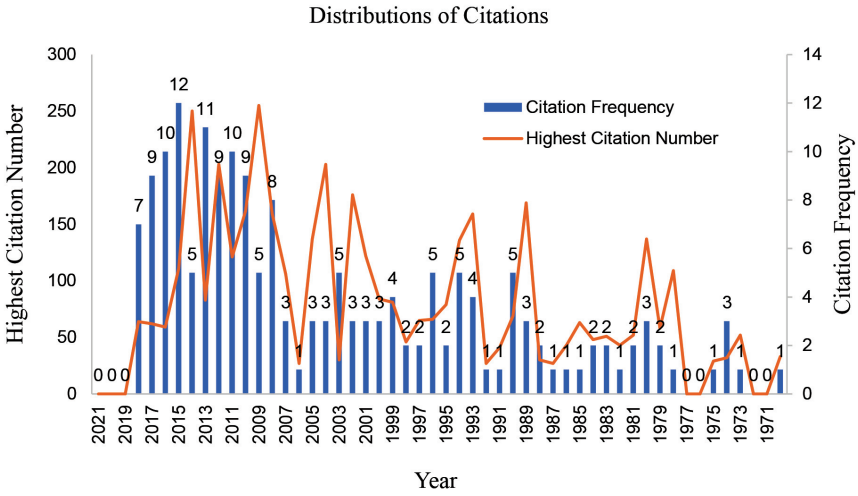


Figure 10: Distribution of citations in the years investigated

Table 3: The list of ten top-cited articles involving urease inhibitors arranged according to their total citations count

No.	Article's Title	Source	Year Published	Citations	
				Total Times Cited	Average Per Year
1	Effect of urease and nitrification inhibitors on N transformation, gaseous emissions of ammonia and nitrous oxide, pasture yield and N uptake in grazed pasture system	Soil Biology & Biochemistry	2009	254	21.2
2	Meta-analysis of the effect of urease and nitrification inhibitors on crop productivity and nitrogen use efficiency	Agriculture Ecosystems & Environment	2014	248	35.4
3	Ammonia volatilization losses from surface-applied urea with urease and nitrification inhibitors	Soil Biology & Biochemistry	2012	202	20.2
4	Effects of the different rates of urease and nitrification inhibitors on gaseous emissions of ammonia and nitrous oxide, nitrate leaching and pasture production from urine patches in an intensive grazed pasture system	Agriculture Ecosystems & Environment	2010	162	13.5
5	Reducing NH_3, N_2O and NO_3--N losses from a pasture soil with urease or nitrification inhibitors and elemental S-amended nitrogenous fertilizers	Biology & Fertility of Soils	2008	158	11.3
6	An inhibitor of urease activity effectively reduces ammonia emissions from soil treated with urea under Mediterranean conditions	Agriculture Ecosystems & Environment	2008	144	10.3

7	Gaseous emissions of N_2O and NO and NO_3^- leaching from urea applied with urease and nitrification inhibitors to a maize (Zea mays) crop	Agriculture Ecosystems & Environment	2012	127	12.7
8	Synthesis, biological assay in vitro and molecular docking studies of new Schiff base derivatives as potential urease inhibitors	European Journal of Medicinal Chemistry	2011	121	11.0
9	Ammonia volatilisation from urease inhibitor-treated urea applied to sugarcane trash blankets	Scientia Agricola	2008	121	8.6
10	An overview on the potential of natural products as ureases inhibitors: A review	Journal of Advanced Research	2015	111	15.9

Table 4: List of top ten journals that published articles on urease inhibitor-related work according to their total publication count

No.	Journal's Title	Publication Count	Publisher	Country	IF	5-year IF
1	Bioorganic Chemistry	29	Elsevier	USA	5.275	5.252
2	Biology and Fertility of Soils	16	Springer	USA	6.432	6.332
3	Agriculture Ecosystems Environment	15	Elsevier	Netherlands	5.567	6.064
4	Bioorganic Medicinal Chemistry	15	Pergamon-Elsevier	England	3.641	3.319
5	Soil Science Society of America Journal	14	Wiley	USA	2.307	2.832
6	Fertilizer Research	12	Kluwer	Netherlands	0.750	-
7	Soil Biology Biochemistry	12	Pergamon-Elsevier	England	7.609	8.312
8	Agronomy Journal	10	Wiley	USA	2.240	2.829
9	European Journal of Medicinal Chemistry	10	Elsevier	France	6.514	6.099
10	Journal of Enzyme Inhibition and Medicinal Chemistry	10	Taylor & Francis	England	5.051	4.598

number of organisations publishing studies involving urease inhibitors in the region, with three each, followed by the United States with two organisations and other countries with one. Through the analysis of 574 articles, the highest number of publications came from the University of Karachi, with 69 articles. Most of the organisations have published more than 500 studies in this topic, ranging from 1 to 5. Furthermore, it has been noted that universities produce the majority of the publications, as opposed to other organisations such as research institution and private labs.

B. Bibliometric Analysis

In this part of analysis, the figures are all displayed in the form of "overlay visualisation", unless stated otherwise. Under this type of

Table 5: Top ten most productive organisations that published articles involving urease inhibitors

Order	Organisation	Country	Number of Articles
1	University of Karachi	Pakistan	69
2	Quaid I Azam University	Pakistan	31
3	Chinese Academy of Sciences	China	25
4	Comsats University Islamabad Cui	Pakistan	25
5	United States Department of Agriculture USDA	United State	21
6	Kongju National University	South Korea	15
7	Nanjing University	China	15
8	Wroclaw University of Science Technology	Poland	15
9	Universiti Teknologi MARA	Malaysia	14
10	Iowa State University	United State	12
10	Shenyang Institute of Applied Ecology Cas	China	12
10	University of Nizwa	Oman	12

visualisation, the colour indicates the score of an item for the analysis being performed. Blue represents the lowest score while yellow the highest score. The colour in between shows the transition scores between high and low. The weight, represented by the size of the circle shows the importance of an item. The larger the circle, the more important an item is. The distance between items shows their relatedness. The closer the two items, the stronger their relatedness.

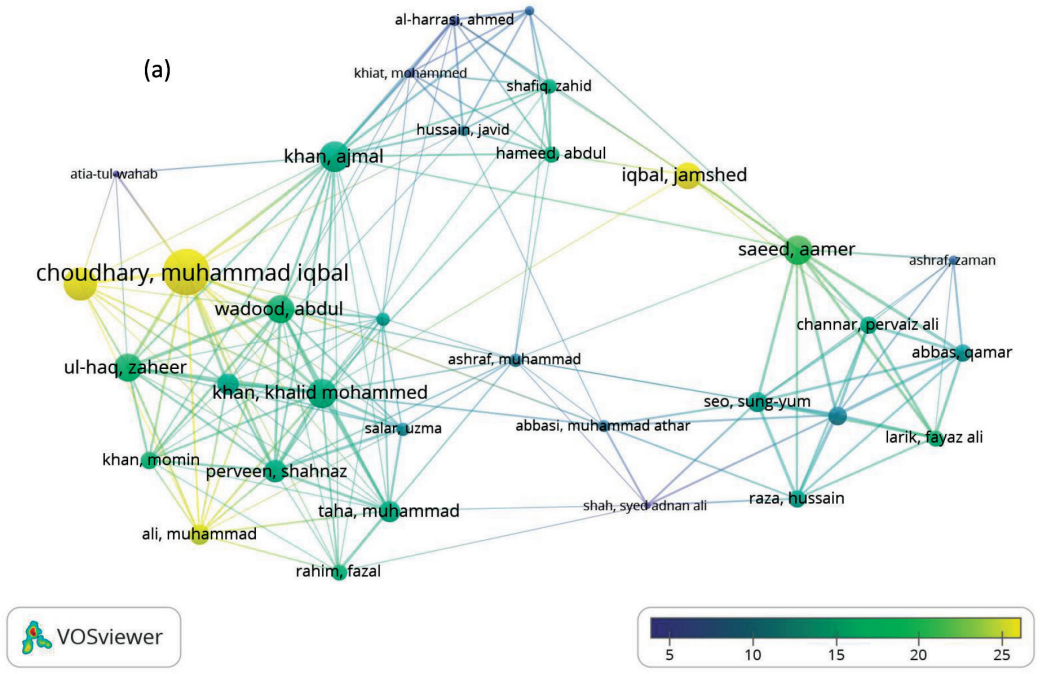
Co-authorship

The analysis of co-authorship is performed in terms of (a) author, (b) organisations and (c) countries, as shown in Figure 11. For the co-authorship links, the line between the items, in this case, the authors, indicate the number of works the two authors have published. In Figure 11 (a), Choudhary is shown as the top researcher. The analysis, as shown in Figure 11 (a), provides further information on the data presented in Figure 9 such as the collaborations between the top researchers in the field. The University of Karachi is shown to be the top organisation in producing urease inhibitor-related publications as shown in Figure 11 (b). The university is also the organisation that Choudhary is affiliated with. The country that has the most co-authorship is Pakistan as shown in Figure 11 (c).

Co-authorship analysis can be used to determine the collaboration and influence among the authors. A big number of co-authored articles indicates a close relationship between authors working in the same subject, which could lead to future research collaboration (Wang *et al.,* 2014).

Co-occurrence of All Keywords

The keywords involved the works on urease inhibitor were analysed using a co-occurrence network analysis tool in the VOSviewer software. In this analysis, the minimum number of occurrences of a keyword in the titles was set at 10. The duplicate terms were filtered using the thesaurus file. Of the 2010 keywords, 82 meet the threshold. The results of keywords co-occurrence analysis are shown in Figure 12. For Cluster 1, "temperature", "volatilization" and "losses" are connected to "hydrolysis",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choudhary, muhammad iqbal
wadood, abdul
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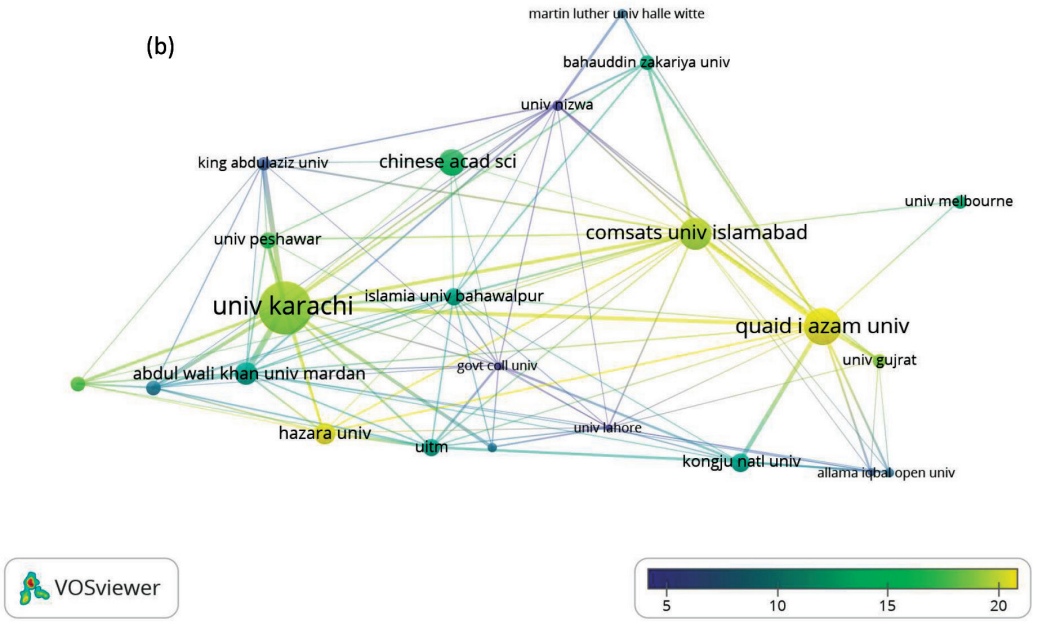
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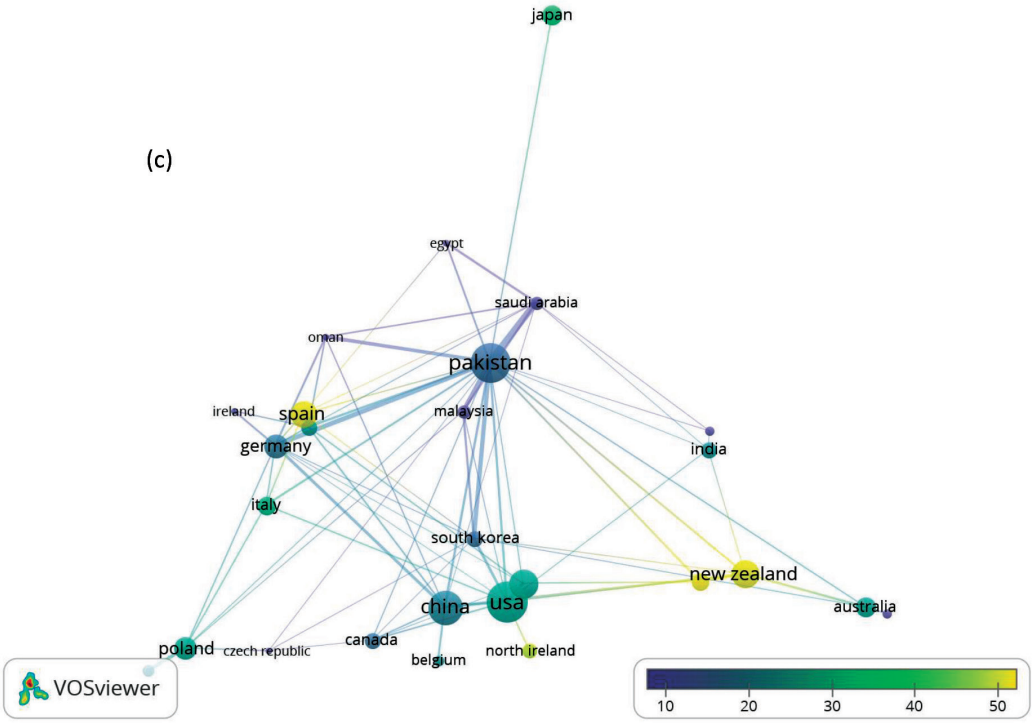

Figure 11: Co-authorship in terms of (a) author, (b) organisations and (c) countries

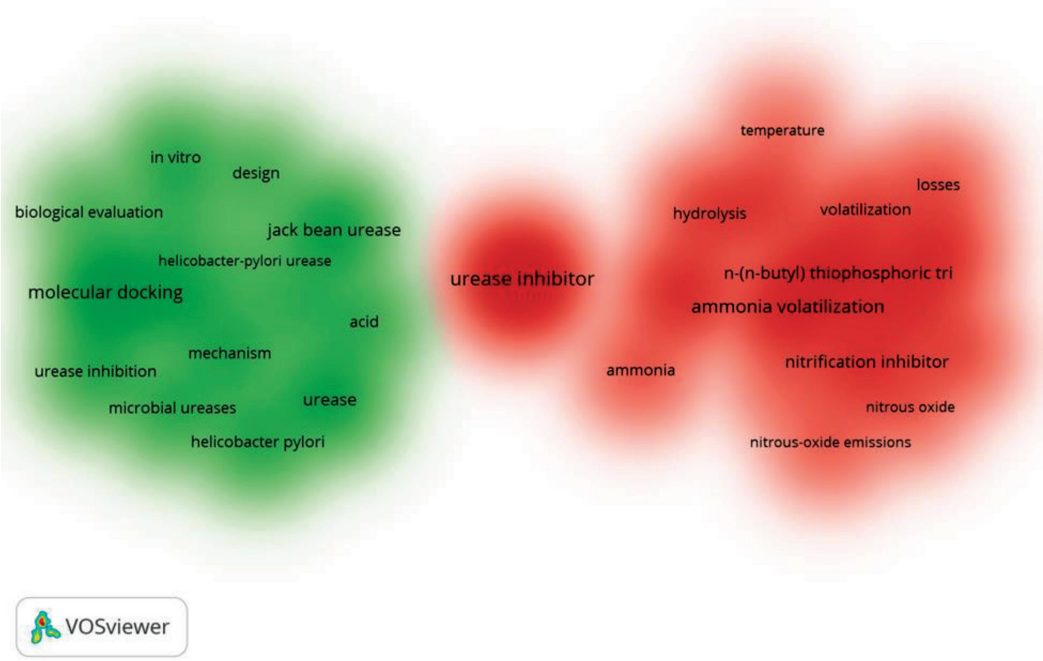

Figure 12: Keywords co-occurrence network analysis using density visualisation

with a total link strength of 125. This can be understood as the works being performed to gauge the effects of the factors on the losses of hydrolysis. Other notable keyword is "ammonia volatilization", as well as the compounds "n-(n-butyl) thiophosphoric triamide" and "nitrification inhibitor". Overall, the keywords in this cluster are more on the chemistry and agricultural side.

Cluster 2 contains chemistry and pharmaceutical-related keywords. Visibly, in this cluster, the keywords "urease inhibitor", "biological evaluation", "design" and "in vitro" are connected to "molecular docking" with a total link strength of 221. However, the frequency of the reported work on "molecular docking" is low when compared with other keywords in Cluster 2.

Even though "urease inhibitor" belongs to Cluster 1, it is positioned at the centre between the clusters and has linkages with keywords in the two clusters. It can be thought of as a common topic that links the two clusters. Additionally, it is also noticed that few new keywords have appeared between 2016 and 2020 such as "molecular docking", "biological evaluation" and "nitrous-oxide emissions".

A common indicator used in judging the quality of publications is the citation count (Aksnes *et al.,* 2019). The 37 cited sources in the co-citation analysis, which met with the criterion set (one source cited by four documents) were classified into three clusters. From Figure 13 (a), the Agriculture, Ecosystems and Environment Journal, the Soil Biology and Biochemistry Journal and the Biology and Fertility of Soils Journal have the highest average number of citations with 68.00, 56.17 and 50.93 citations, respectively. The total link strengths for the top three cited journals are 132, 122 and 109, respectively. Computers and electronics in agriculture covers developments in the use of computer hardware, software, and electronic instrumentation and control systems in agriculture, forestry and allied sectors on a global scale.

The total number of authors involved this study is 2032. Figure 13 (b) shows the overlap mapping of authors with more than ten citations. A total of 15 authors were found to meet this criterion. From the figure, we can assume that Zaman M has the highest number of citations, with 888 citations and 213 total link strengths. Choudhary MI is the second author who was widely cited, with 869 citations and 373 total link strengths.

Even though Choudhary was shown to be the top researcher, in which he has the highest number of publications, the citations are in the third ranking. However, his works were cited by a more diverse pool of researchers compared with the top one.

Discussion

In this study, the bibliographic database from WoS was used; despite extensive comparisons beween the WoS and Scopus databases over the past 15 years, the scientometric community has yet to conclude "which one is better". On the other hand, both databases are constantly improving due to intense competition and the notable transfer of academic activities into a digital internet-based environment. Hence, from our perspective, there is no significant difference to the outcomes if from the Scopus database was used. The use of WoS is just a convenient choice and due to personal sentiment as well.

The analysis have shown that agriculture, chemistry and pharmacy are the three major research fields that have publications related to urease enzyme. The experimental and mixed investigations were always the more popular types of investigations, as shown in Figure 5. The trend where the pharmaceutical field produces a higher number of publications per year, from the mid-2010s (Figure 2), can be attributed to the increase in molecular docking studies, as can be seen from the keywords co-occurrence networks (Figure 12). The availability of powerful workstations, as well as the software to perform simulations are the reason behind the increase in mixed studies in

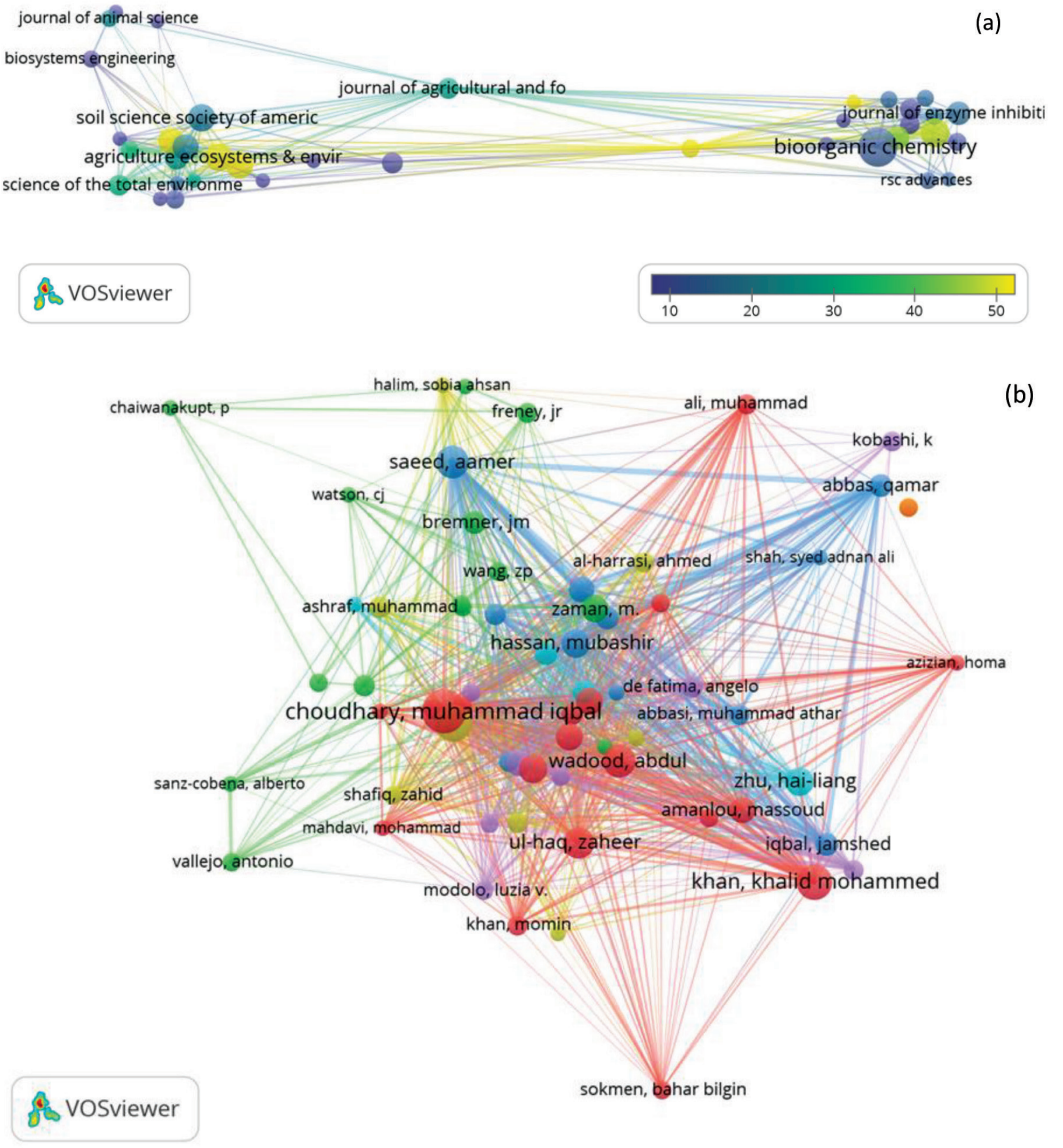

Figure 13: The network visualisation of the number of citations in the published documents by (a) sources and (b) authors

the pharmaceutical field. Molecular docking was usually performed to reveal the binding modes of inhibitors and as virtual screening of potential candidates (Naqvi *et al.,* 2018; Li *et al.,* 2019; Pinzi & Rastelli, 2019; Bhagat *et al.,* 2021), reducing the time and cost involved in the search for suitable compounds to be used in specific functions. Of the 574 records obtained, only two research reported calculations using the density functional theory (Leopoldini *et al.*, 2008; Ali *et al.*, 2020), even though it offers a higher accuracy in terms of molecular interactions. Of these two, only Leopoldini *et al.* (2008) explored the binding of boric acid on the active sites of urease and is completely theoretical.

It is of no surprise that experimental works has a higher percentage, compared with

theoretical works in the fields investigated. In agriculture, field experiments are needed such as the real applications of the fertilisers, monitoring the dependencies of external factors such as soil pH, temperature and irrigation. For the pharmaceutical field, clinical trials are important. Even though simulation software are available, agricultural studies seldom report on molecular docking or use simulations. The Agricultural Production Systems Simulator (Holzworth *et al.,* 2014) and Decision Support System for Agrotechnology Transfer (Jones *et al.,* 2003; Hoogenboom *et al.,* 2019) are popular modelling software in agriculture. However, the software does not have functions to check the effect of different types of fertilisers. This limited capability can be considered as an opportunity for future development in the field.

Citations are considered to be a measure of the scientific impact of a publication. Of the top ten cited articles, the meta-analysis of three popular inhibitors in crop yields (Abalos *et al.,* 2014) has the highest number of citations. The only pharmaceutical field representation in the ten most cited studies is the work by Nagata *et al.* (1993). Review studies are conspicuously absent from the top ten. Based on the data from WoS, the top three cited review articles were Cantarella *et al.* (2018), Modolo *et al.* (2015) and Upadhyay (2012), with average citations per year of 18.25, 16.29 and 9.2, respectively while the work of Abalos *et al.* (2014) has an average of 34. Hence, review articles are not the determining factor in terms of high number of citations. However, even though important publications have more citation than others (Abt, 2000), citation counts are affected by a few factors, including the geographical origin of the publication (West & McIlwaine, 2002). To delve into the citation behaviour between citing and cited articles is out of the scope for the current work.

For the research on urease inhibitors, global collaborations are seen from the points of authors, organizations and countries. International collaborations are a way to share and promote research among nations (Ye *et al.,* 2012) and increase the research quality (Payumo *et al.,* 2017). Based on the results, the main partners to consider for cooperation are those in Pakistan, China, the United States, New Zealand and Spain. To obtain a full picture of the state of urease inhibitors in a country, researchers can perform further studies through collaborations between research institutions and universities (Liu *et al.,* 2012; Coccia & Bozeman, 2016; Huang, 2021).

Conclusion

The search for urease inhibitors is an active field of research. To the best of our knowledge, there has been no bibliometric study on the topic before. This paper focuses on the published works related to urease inhibitors in the span of 50 years. With the data obtained from WoS and processed using Microsoft Excel and VOSviewer, it can be seen that there are increases in publications in the research fields investigated. The increase in mixed and pure theoretical works indicates the acceptance and the role of theoretical work. Furthermore, even though it is a norm for the number of review articles published to be lower than research articles, the trend observed here indicated that the number of review articles can be improved. The involvements of countries can also be intensified through collaborations. It will also be interesting to see more use of computational modelling with high accuracy in the agriculture, pharmaceutical and chemistry fields.

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