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ROMEL JEFFERSON HILGEMBERG JUNIOR

Mapping worldwide productivity on the field of preclinical studies focused on Angiotensin-(1-7) actions on metabolic syndrome risk factors

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Mapping worldwide productivity on the field of preclinical studies focused on Angiotensin-(1-7) actions on metabolic syndrome risk factors

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Short Title: Bibliometric analysis of Ang-(1-7) actions

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“People who perform rarely sit back and leave things happen for them. They leave and make things happen”
Andrea Del Verrocchio

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ABSTRACT

Emerging evidence from primary studies has postulated that Angiotensin (Ang)-(1-7) might be a potential pharmacological strategy to treat cardiovascular and metabolic injuries, such as metabolic syndrome (MetS). In this view, secondary studies play a crucial role, since it provides prospective views of primary data. The present study aimed to map worldwide productivity of preclinical studies related to Ang-(1-7) actions on MetS. Therefore, a search protocol was designed; a comprehensive search on scientific databases was performed, and the bibliometric data was collected from the eligible articles. A total of 2100 articles were initially retrieved, and after screenings, 62 eligible articles were detected, involving 19 countries. The first 2 studies on the field dated in 2003, and the third appeared only in 2009. Peak of publications occurred from 2013 to 2015, with 8 publications per year. The United States was the country with more publications, (n = 21). Differently, Bader, M. (Germany) was the author with more publications, and the most cited author was Dominici, F.P. (Argentina), who was also co-author of the most cited article, published by Giani, JF and colleagues (2009), with 135 citations. Index keywords analysis revealed that mice and rats were the most used animal models, and that the trends in the research differ between those approaches. The first aggregates keywords related to atherosclerosis, vascular functions, and knockout mice; while the second focused on insulin resistance, diets and obesity. Considering that MetS is a global epidemic, the data herein indicates the literature might have few preclinical studies focused on the physiological actions of Ang-(1-7) on MetS risk factors, and the number of publications in the field has also been decreasing in the last years. However, strong international collaborations and publications in high-impact Journals were detected.

INTRODUCTION

Metabolic syndrome (MetS) is currently considered a worldwide health problem, since it increases cardiometabolic risks, and it affects a quarter of global population [1]. Treatment of cardiovascular diseases and type II diabetes is multifactorial. It includes a non-pharmacological approach, involving diet plan for weight reduction, physical exercises, reduction of stressful situations, cessation of smoking and alcohol consumption [2, 3], as well as pharmacological approach, which include medication for hypertension, such as angiotensin converter enzyme (ACE) inhibitors or angiotensin (Ang) II receptor blockade; and for dyslipidemia, such as statins, among others; which difficult patient's adhesion to the appropriate treatment [2, 3].

In this context, Ang-(1-7), a bioactive peptide of the renin angiotensin system (RAS) might confer potential strategy to treat patients with cardiometabolic injuries [4]. Ang-(1-7) is majorly formed through the cleavage of Ang II by the angiotensin II converting enzyme (ACE2) [4], and is classically known by its counter regulatory on Ang II/ AT_1 axis, besides its effects beyond opposing Ang II [4].

Concerning to MetS risk factors, recent data has been shown that acute vasodilator effects of Ang-(1-7) are preserved in obese patients [5]. In addition, interleukin-1 antagonism increased Ang (1–7) levels after 4 weeks of treatment in obese individuals, paralleled by a decrease in peripheral vascular resistance [6]. On the other hand, overweight/ obesity has been associated with higher blood pressure and Ang II levels, but lower Ang-(1-7) levels in adolescents born prematurely [7]. In line, preclinical studies indicates that chronic infusion of Ang-(1-7) ameliorates several risk factor in animal models designed to study this syndrome, such as hypertension [8], insulin resistance [8, 9], and fat deposition [10], while Mas knockout mice display increased blood pressure [11], dyslipidemia and reduced insulin sensitivity [12] and thermogenesis [13], a phenotype that reminds one of MetS condition.

Generally, preclinical studies constitute a key step to scientific knowledge and development of preventive and therapeutic strategies for health issues [14, 15], and this type of research expands greatly worldwide, since the advances in technology and collaborative research and partnership [14]. Despite that, secondary researches, which can provide a prospective trend and metrics of the research in a specific area, are still a growing tool when basic science is concerned [15].

Therefore, the present study mapped the worldwide productivity in the field of preclinical data focused on comprehending Ang-(1-7) actions on MetS risk factors. Bibliometric parameters were assessed, considering co-authorship, scientific citation index, international collaborations, Journals, and affiliations. These findings may provide a better understanding of the trends of global preclinical research in the field of Ang-(-1-7) and MetS, and points the direction of further studies.

METHODS

Study design

Bibliometric analysis was designed to map worldwide productivity on preclinical studies focused on Ang-(1-7) actions on metabolic syndrome risk factors. Data was obtained by a comprehensive search of EMBASE, PubMed, Scopus and Web of Science database. The search strategy was defined in a specific protocol, created by the authors, and published on PROSPERO previously. The protocol presents the aim of a systematic review concerning to the central question: "*What are the effects of angiotensin-(1-7) in animal models to study metabolic syndrome?*", and is available at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019142673. The comprehensive search was performed in July, 2019 and updated in Feb, 2020. Appendix I shows the comprehensive strategy for visualization. All steps were performed by two or three authors, and discrepancies were solved through discussion.

Bibliometric data extraction and analysis

All eligible articles were grouped using Scopus database, and bibliometric information was exported as (.csv) file to VOS Viewer software for visualization of maps and clusters. In addition, the main information of eligible articles was catalogued using Excel software for descriptive analysis, and charts were created using GraphPad Prism software. The worldwide map was created using the Mapchart (https://mapchart.net/world.html). Data was also directly obtained from Scopus database analyzer.

RESULTS

General information

A total of 62 publications were eligible for the present study (Appendix II). General information was summarized in Table 01.

Table 01 – General information

Data	Total
Publications	62
Authors	349
Mean citation per article	34,91
Mean articles per author	1,69
Journals	36
Author keywords	138
All kyewords	1145

The first two studies in the field dated in 2003 by Rodgers, KE and colleagues. A gap of 5 years with no publications was observed. A slow grow in publication was observed between 2009 and 2012, reaching the greatest peak in the field between 2013 and 2015, with 8 publications per year. Then, the number of annual publications decreased again, having a second peak in 2019, with 7 publications (Figure 01).

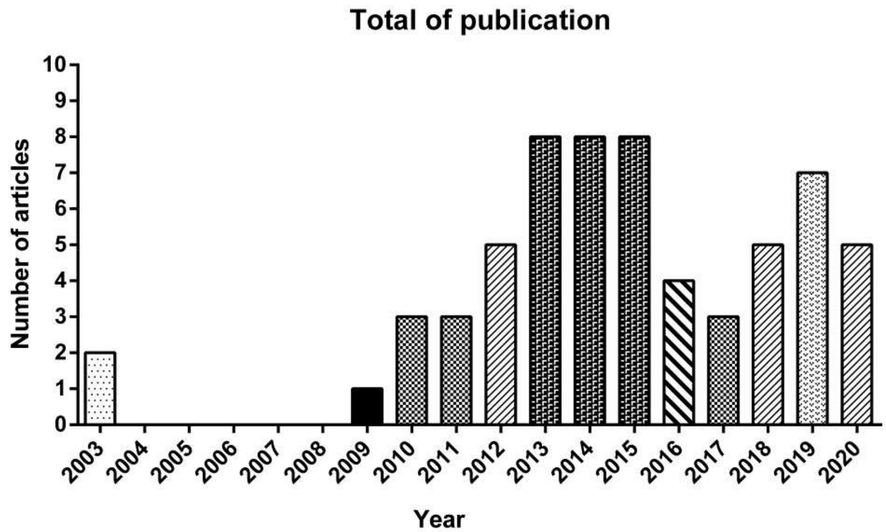

Figure 01 – Total number of annual publication in the field.

Bibliometric variables

The bibliometric variables analysis considered all authors on manuscripts, their affiliations and countries. As for the total number of publications, the most productive country was the United States (USA; 21 articles), followed by Brazil (15 articles), China (11 articles), and Germany (9 articles; Figures 02 and 03). In line, the United States was also the most cited country, when the total of citations was used as reference, followed by Brazil, Argentina and Canada, respectively (Table 02). Remarkably, analyzing the mean number of citations per published article, the most productive country was Austria, followed by Canada, which has only 1 and 4 publications respectively (Table 02).

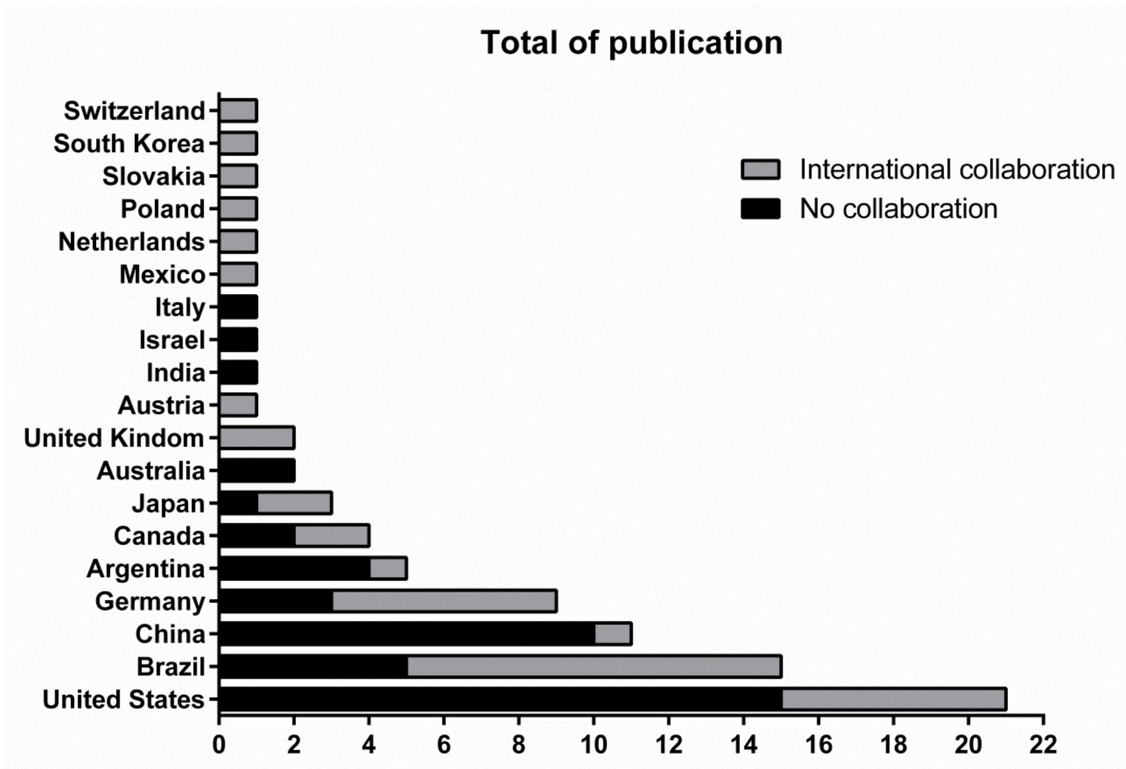

Figure 02 – Total number of publication by country.

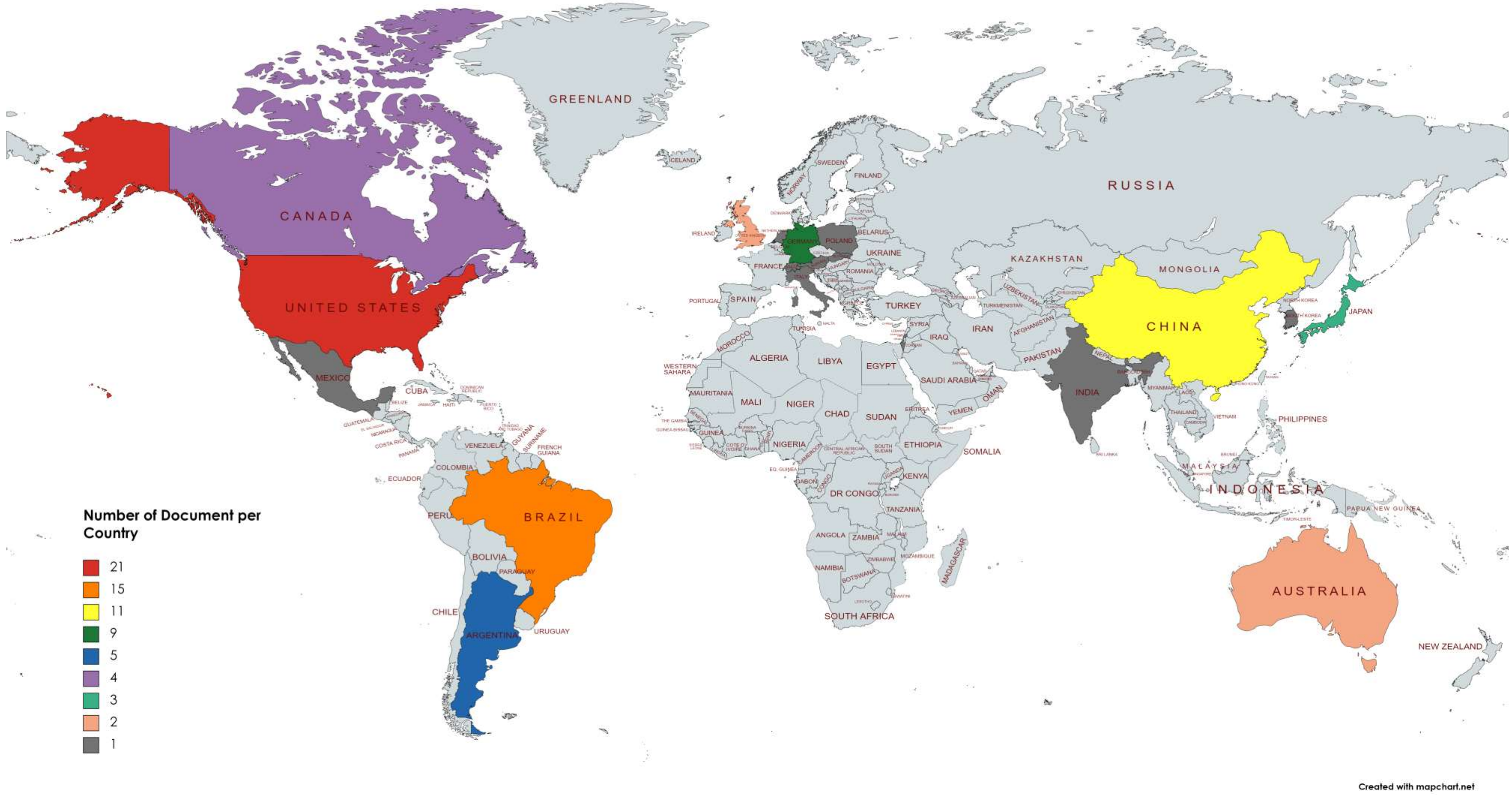

Figure 03. Worldwide map showing geographic distribution of publications of preclinical data related to Ang-(1-7) actions on metabolic syndrome risk factors.

Table 02 – Ranking of country citations considering the mean number of citations per article

Ranking	Country	Total of publications	Total of citations	Mean number of citations per article
1	Áustria	1	100	100
2	Canada	4	296	74
3	Argentina	5	360	72
4	Austrália	2	144	72
5	South Korea	1	67	67
6	Israel	1	54	54
7	United States	21	886	42.2
8	Índia	1	37	37
9	Japan	3	91	30.3
10	Brazil	15	445	29.7
11	Switzerland	1	26	26
12	Germany	9	227	25.2
13	Italy	1	13	13
14	China	11	133	12.1
15	Netherlands	1	9	9
16	Mexico	1	5	5
17	United Kingdom	2	9	4.5
18	Poland	1	3	3
19	Slovakia	1	3	3

Interestingly, as shown in Figure 04, the top 5 institutions with the highest number of publications were the Universidade Federal de Minas Gerais (UFMG; Brazil, 14 publications), Max Delbruck Center for Molecular Medicine (Germany, 7 publications); University of Southern California (United States, 6 publications) and the Universidad de Buenos Aires (Argentina, 5 publications).

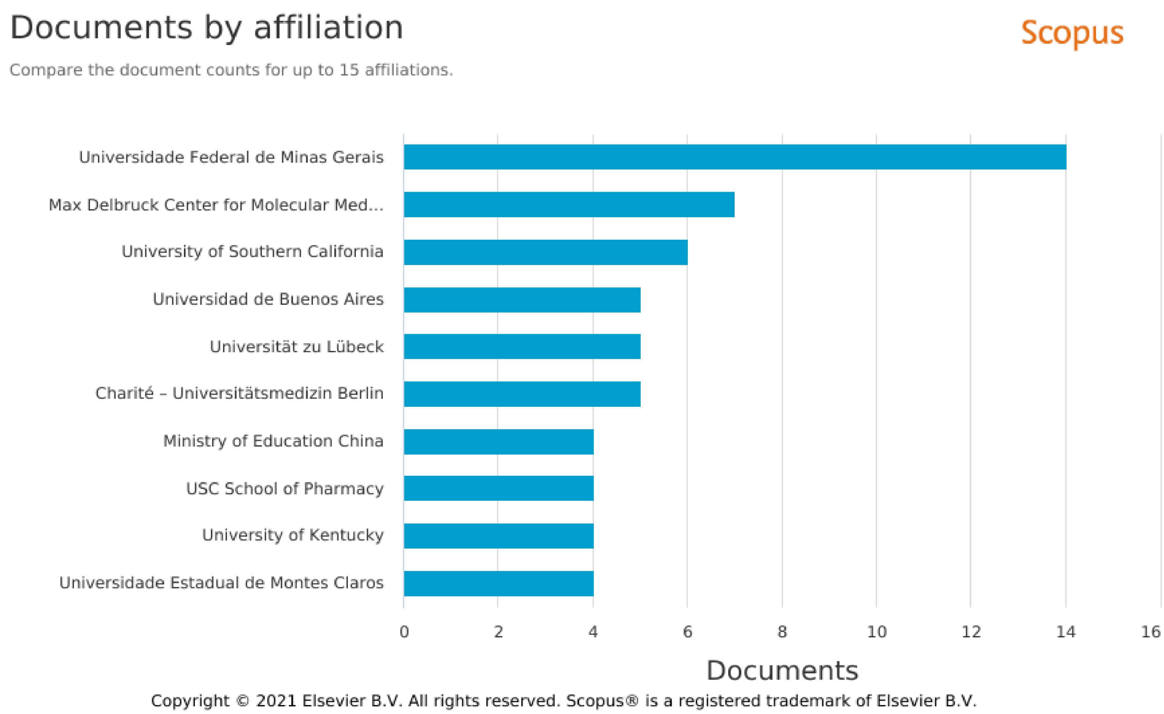

Figure 04 – Ranking of the number of publications by affiliation.

In contrast, the most productive author was Bader, M, from the Max Delbruck Center for Molecular Medicine, with 7 publications; followed by Rodgers, KE; Santos, RAS; and Santos, SHS, with 6 publications each one; and then by Dominici, FP; and Giani, JF, with 5 publications each one (Table 03). Differently, the most cited authors were Dominici, FP and Giani JF, with 360 citations each one, followed by Santos SHS, with 335 citations (Table 04). In line, the most cited article was *Chronic infusion of Angiotensin-(1-7) improves insulin resistance and hypertension induced by a high-fructose diet in rats*, published by Giani, JF and colleagues in the American Journal of Physiology – Endocrinology and Metabolism (2009), with 135 citations (Table 05).

Table 03 – Ranking of the most productive authors (total of publications) and the number of citations.

Author	Articles	Total of Citation
Bader M.	7	161
Santos S.H.S.	6	335
Santos R.A.S.	6	275
Rodgers K.E.	6	163
Dominici F.P.	5	360
Giani J.F.	5	360
De Paula A. M.B.	4	187
Guimarães A.L.S.	4	187
Campagnole-Santos M.J.	4	194
Raasch W.	4	41
Muñoz M.C.	4	305
Mori J.	4	296
Oudit G.Y.	4	296

Table 04 - Ranking of the most cited authors (total of citations)

Author	Articles	Total of citation
Dominici F.P.	5	360
Giani J.F.	5	360
Santos S.H.S.	6	335
Muñoz M.C.	4	305
Mori J.	4	296
Oudit G.Y.	4	296
Lopaschuk G.D.	3	280
Patel V.B.	3	280
Santos R.A.S.	6	275
Turyn D.	3	262
Mayer M. A.	3	237
Taira C.A.	3	237
Sinisterra R.D.M.	3	203
Souza F.B.	3	203
Campagnole-Santos M.J.	4	194
Cassis L.A.	3	193
De Paula A.M.B.	4	187
Guimarães A.L.S.	4	187
Zhang X.	3	181
Andrade J.M.O.	3	176
Feltenberger J.D.	3	176
Burghi V.	3	166
Shoemaker R.	3	166
Rodgers K.E.	6	163
Bader M.	7	161

Table 05 – Ranking of the top 5 most cited manuscripts.

Manuscript	Total of citation	Affiliation	Country
Giani, J.F.; Marcos A. Mayer; Marina C. Muñoz; Ezequiel A. Silberman; Chrstian Hocht; Carlos A. Taira; Mariela M. Gironacci; Daniel Turyn; Fernando Pablo Dominici. *Chronic infusion of angiotensin-(1-7) improves insulin resistance and hypertension induced by a high-fructose diet in rats* (Am J Physiol Endocrinol Metab, 2009)	135	Universidade de Buenos Aires	Argentina
Bindom, S.M.; Chetan P. Hans; Huijing Xia; A. Hamid Boulares; Eric Lazartigues. *Angiotensin I–Converting Enzyme Type 2 (ACE2) Gene Therapy Improves Glycemic Control in Diabetic Mice.*(Diabetes, 2010)	129	Louisiana State University	United States
Tesanovic, S.; Antony Vinh; Tracey A. Gaspari; David Casley; Robert E. Widdop. *Vasoprotective and Atheroprotective Effects of Angiotensin (1-7) in Apolipoprotein E–Deficient Mice.* (Atherosclerosis, Trombosis and Vascular Biology,2010)	124	Monash university	Australia
Gupte, M.; Sean E. Thatcher; Carine M. Boustany-Kari; Robin Shoemaker; Frederique Yiannikouris; Xuan Zhang; Michel Karounos; Lisa A. Cassis. *Angiotensin Converting Enzyme 2 Contributes to Sex Differences in the Development of Obesity Hypertension in C57BL/6 Mice.* (Atherosclerosis, Trombosis and Vascular Biology, 2012)	119	University of Kentuck	United States
Mori, J.; Vaibhav B. Patel; Osama Abo Alrob; Ratnadeep Basu; Tariq Altamimi; Jessica DesAulniers; Cory S. Wagg; Zamaneh Kassiri; Gary D. Lopaschuk; Gavin Y. Oudit.*Angiotensin 1–7 Ameliorates Diabetic Cardiomyopathyand Diastolic Dysfunction in db/db Mice by ReducingLipotoxicity and Inflammation.*(Circulation:Heart Failure, 2014)	105	University of Alberta	Canada

Interestingly, mapping the co-authorship network between the most productive authors (5 to 7 publications), it was possible to observe that 3 clusters were formed, in which Rodgers KE does not have collaboration with the other two, and that all 5 remaining authors collaborate to each other (Figure 05). Network map shows that Bader, Santos RAS and Santos SHS share the same cluster, while Dominici FP and Giani JF, the other one. Moreover, the overlay visualization points that Bader, M is a key author between these two groups since recent publications together (Figure 06).

Figure 05 – Network map of co-authorship between the authors with more number of publications.

Figure 06 – Overlay map of co-authorship between the authors with more number of publications.

A total of 84 authors shared 2 or more publications, and formed 11 research groups (Figure 07). However, only 35 authors, distributed into 4 research groups, are connected to each other (Figures 07 and 08). Among the last, Santos, RAS appears as a key author between all groups. Santos, RAS links the UFMG group (red cluster; Figure 08) that holds studies during the peak of annual publications in the field (2014) with the one headed by Alzamora, AC from Universidade Federal de Ouro Preto (UFOP), Brazil (yellow cluster, Figure 08) that holds the more recent publications (2019 and 2020; Figure 09). In addition, he has strong collaboration with Bader, M and Giani FP groups. For details, see Figures 08 and 09. Another interestingly observation is that the remaining most cited authors (top 10 cited arthors; Table 04) appear in the same cluster, indicating a strong co-authorship between them (Figure 10).

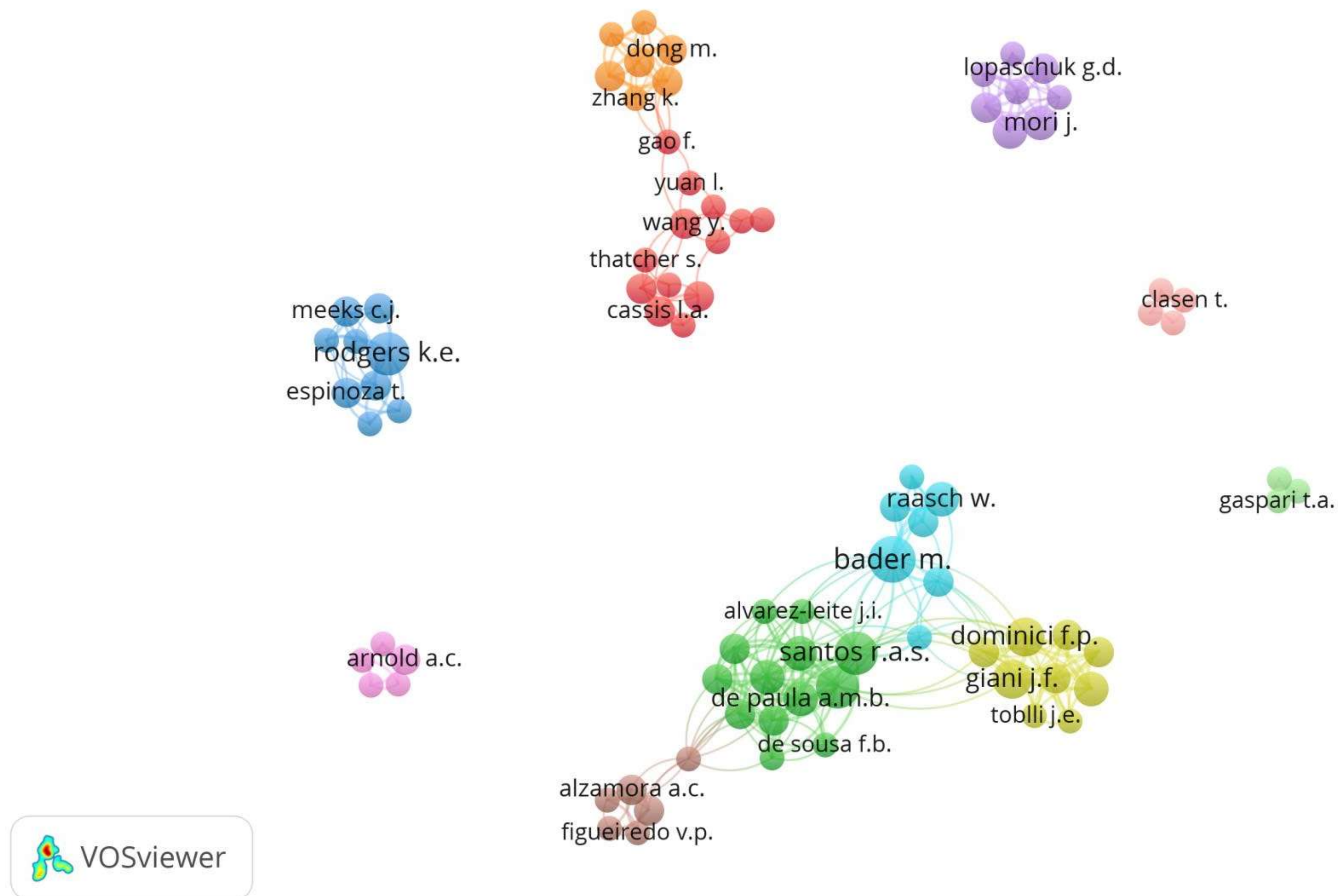

Figure 07 – Network map of the 84 authors that shared at least 2 publications, in which a total of 11 research groups were formed.

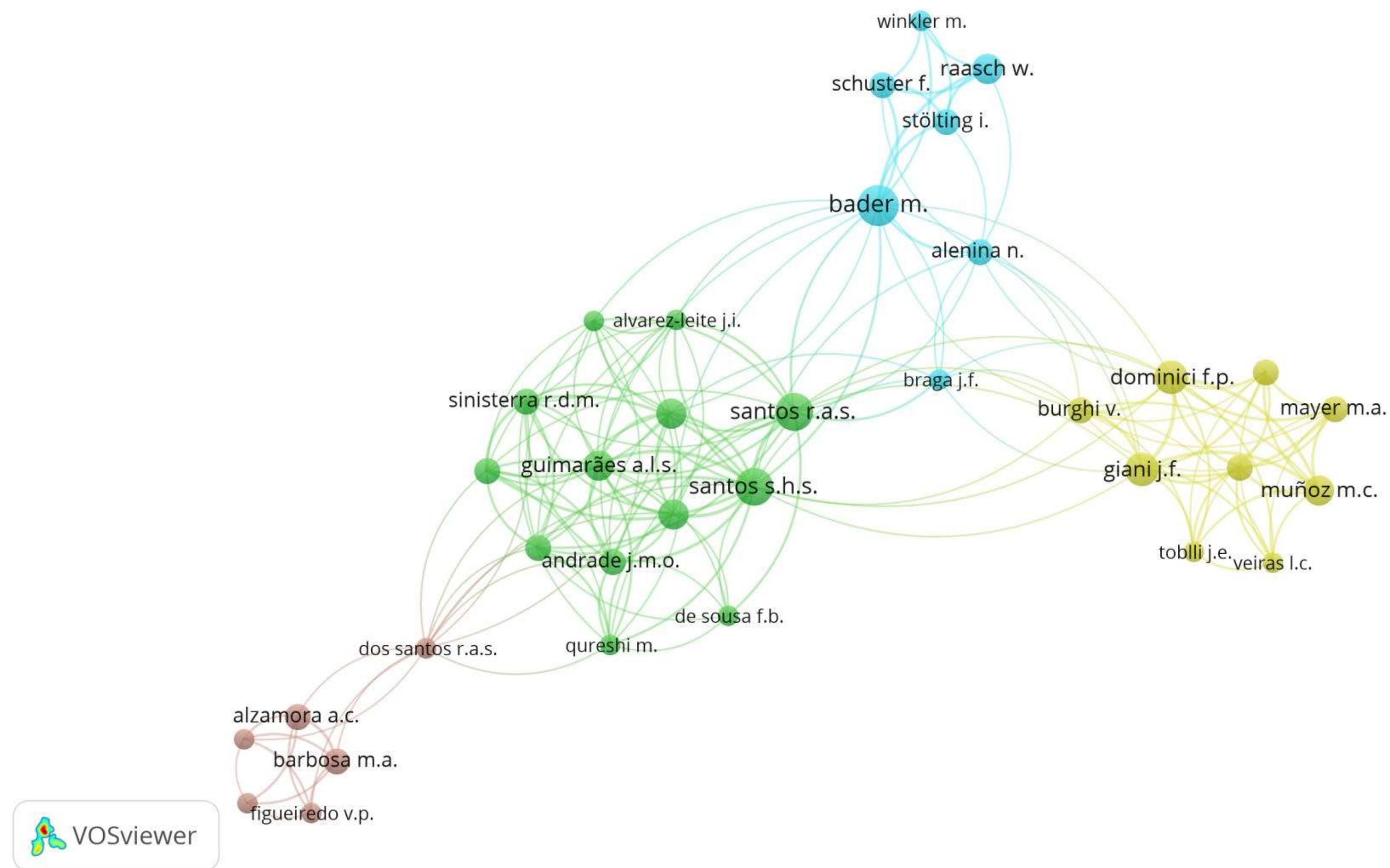

Figure 08 – Network map of the 35 authors that shared at least 2 publications, in which a total of 04 research groups were formed.

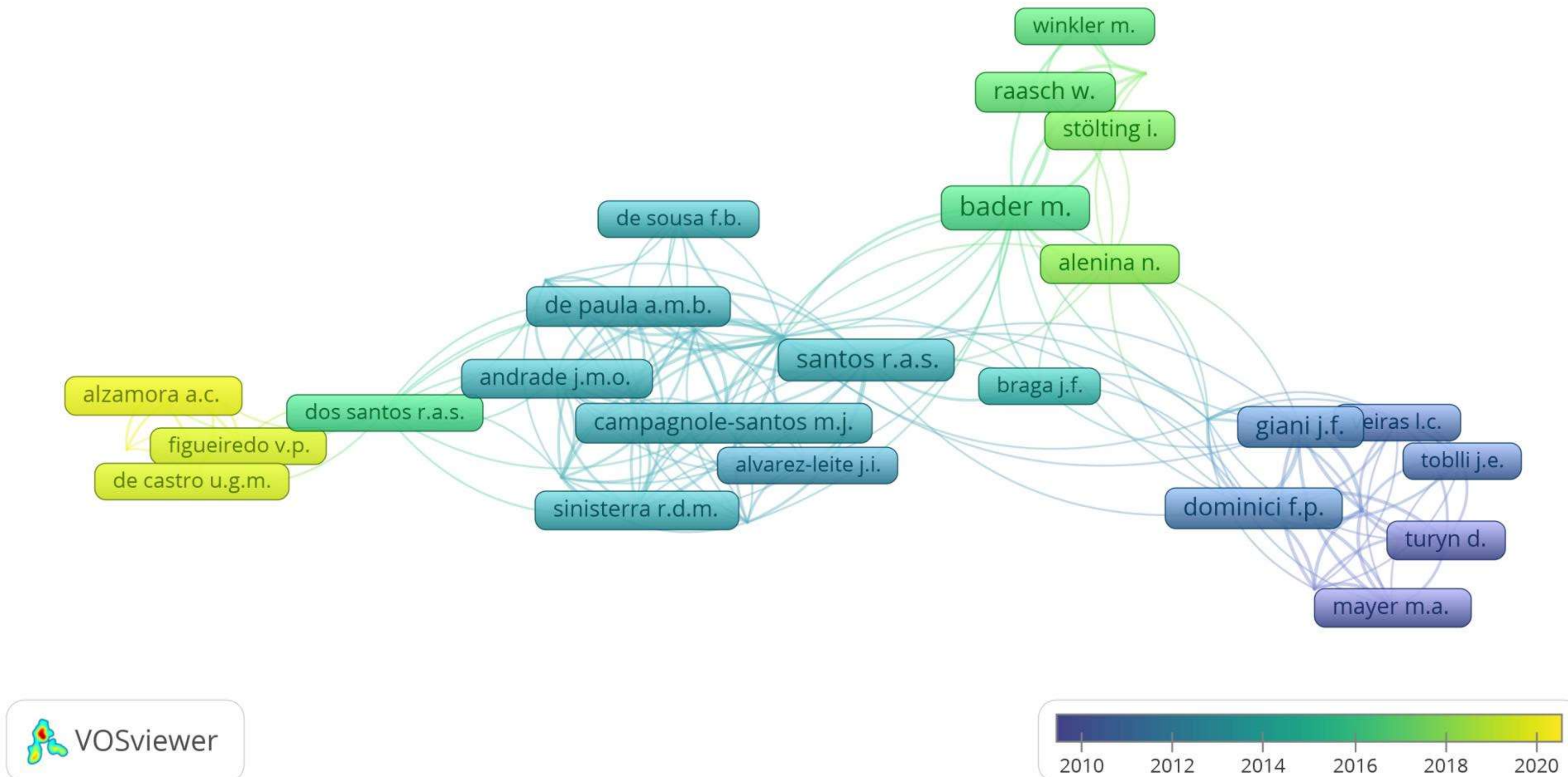

Figure 09 – Overlay map of the 35 authors that shared at least 2 publications.

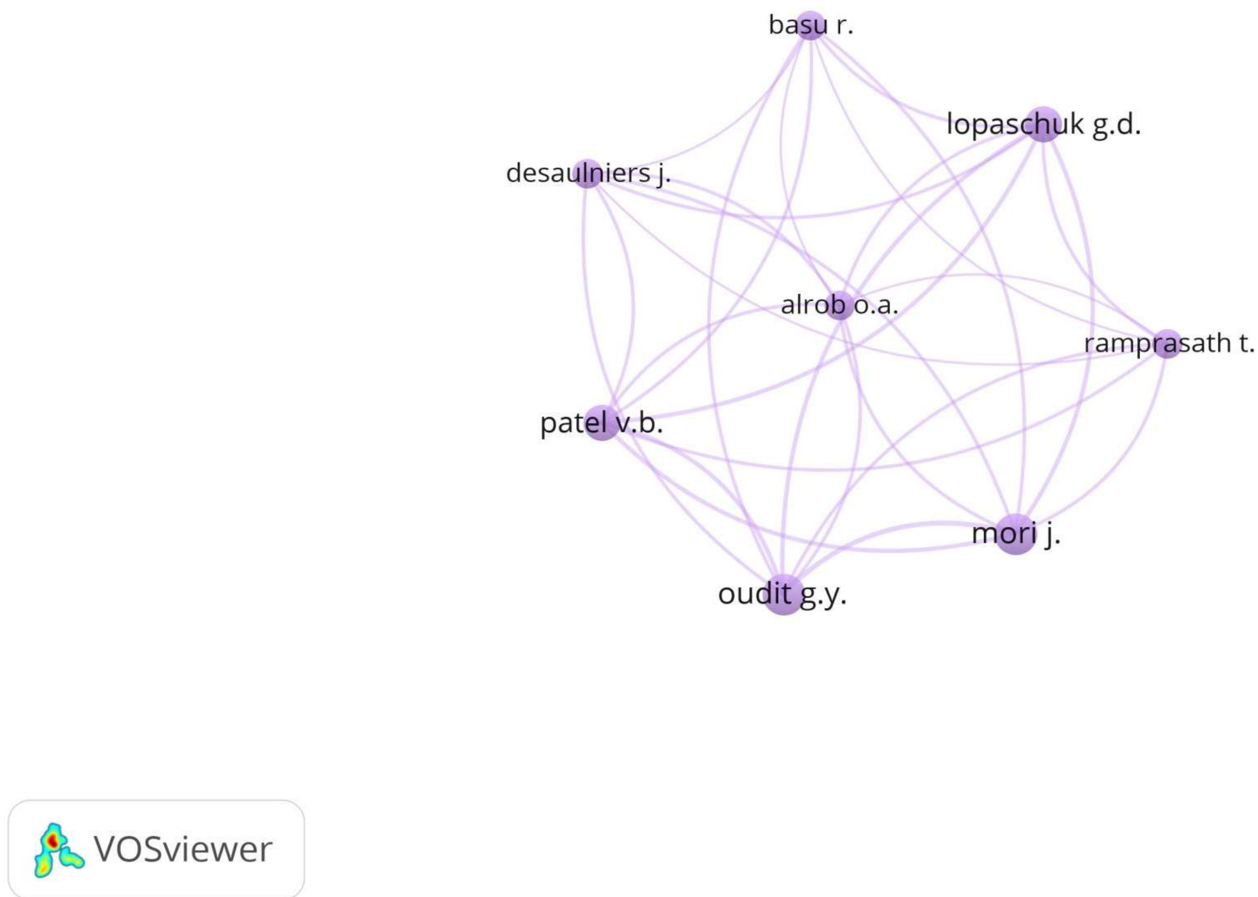

Figure 10 – Network map headed by Oudit, G. Y. and Mori, J.

The Journals with more publications (n = 4; Table 06) were the *American Journal of Physiology (AJP) – Endocrinology and Metabolism, Hypertension, Peptides, Diabetes and the Arteriosclerosis, Trombosis, and Vascular Biology (ATVB)*. In which, the *Arteriosclerosis Thrombosis and Vascular Biology* Journal was the one with the highest number of citations (341 citations), followed by *Diabetes* (320 citations); the *American Journal of Physiology – Renal Physiology* (290 citations), the *American Journal of Physiology - Endocrinology and Metabolism* (192 citations); and then by *Peptides* (163 citations). Interestingly, as shown in Table 06, normalizing the number of citations by the number of publications, the Journal *Circulation: Heart Failure* headed the list, with 1 Canadian publication with 105 citations from Mori, J and colleagues (2014).

Table 06 – Ranking of the Journals with more number of publications in the field.

Ranking	Journal	Number of publications	Number of citation	Mean citation per article
1	AJP- Endocrinology	4	192	48
2	Hypertension	4	133	33.3
3	Peptides	4	163	40.8
4	Diabetes	4	320	80
5	Arteriosclerosis,thrombosis and vascular biology	4	341	85.3
6	British Journal of Pharmacology	3	111	37
7	Oxidative Medicine and Cellular Longevity	3	14	4.7
8	AJP- Renal Physiology	3	210	70
9	AJP- Heart and Circulation	2	77	38.5
10	Regulatory Peptides	2	103	51.5

Table 07 – Ranking of the Journals considering the total number of citation

Ranking	Journal	Number of documents	Total number of citations
1	ATVB	4	341
2	Diabetes	4	320
3	Am. Journal of Physiology-Renal Physiology	3	210
4	Am. Journal of Physiology-Endocrinology and Metabology	4	192
5	Peptides	4	163
6	Hypertension	4	133
7	British Journal of Phamacology	3	111
8	Circulation: Heart Failure	1	105
9	Regulatory Peptides	2	103
10	Am. Journal Of physiology-heart and Circulation	2	77

Table 08 – Ranking of the Journals considering the mean number of citation per article

Ranking	Journal	Number of documents	Total number of citations	Mean citation per article
1	Circulation: Heart Failure	1	105	105
2	ATVB	4	341	85.3
3	Diabetes	4	320	80
4	Am. Journal of Physiology-Renal Physiology	3	210	70
5	Regulatory Peptides	2	103	51.5
6	Am. Journal of Physiology-Endocrinology and Metabology	4	192	48
7	Peptides	4	163	40.8
8	Am. Journal Of physiology-heart and Circulation	2	77	38,5
9	British Journal of Phamacology	3	111	37
10	Hypertension	4	133	33.3

The author keywords analysis revealed a total of 138 keywords were used, in which only 7 keywords occurred at least 5 times, which were *obesity, angiotensin-(1-7), renin-angiotensin system, insulin resistance, atherosclerosis, angiotensin II, and hypertension*, being the first two the most common, with 12 occurrences. A total of 25 author keywords occurred at least 2 times, and 6 clusters were formed, focused on *diabetes*, *atherosclerosis*, insulin resistance and oxidative stress, inflammation, metabolic syndrome and hypertension, and obesity (Figure 11).

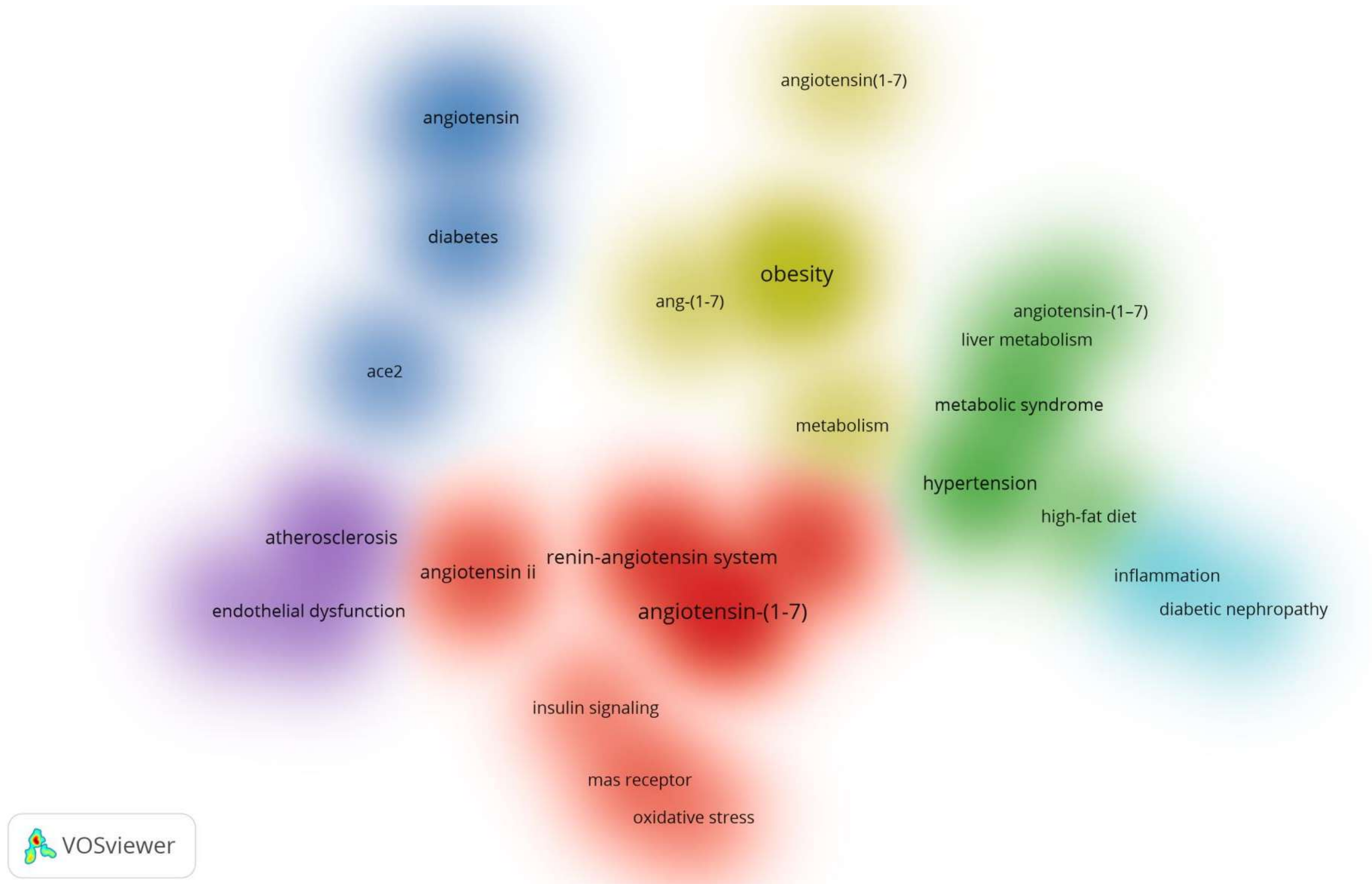

Figure 11 - Cluster map of the 25 author keywords, that occurred at least in 2 publications

As for the index keywords, a total of 1071 were used. Among those, 262 keywords appeared at least 3 times, forming a total of 6 clusters of networks (Figure 12). Interestingly, 2 clusters clearly show keywords that appear along with animal models. The red cluster, which is the one with the most intense colour, shows the following as keywords with more frequency: *mice, mouse, inbred c57bl, alipoprotein e, aterosclerosis, knockout mice, enzyme activity, cell proliferation, vasodilator agents, and nitric oxide*. On the other hand, the light purple cluster shows the following as keywords with more frequency: *rat, rats, insulin, hypertension, fructose, enzyme phosphorylation, metabolic syndrome x, and glucose tolerance test*.

Interesting, the remaining clusters, which are also lightly coloured, display keywords that are not strongly related to the others. Moreover, the timeline overlay visualization clearly shows a trend in the indexation in not specifying the animal strain, e.g. *animal;* and the emphasis on keywords, such as *obesity*, *lipid diet*, *energy expenditure*, *inflammation* and *oncoprotein* (Figure 13).

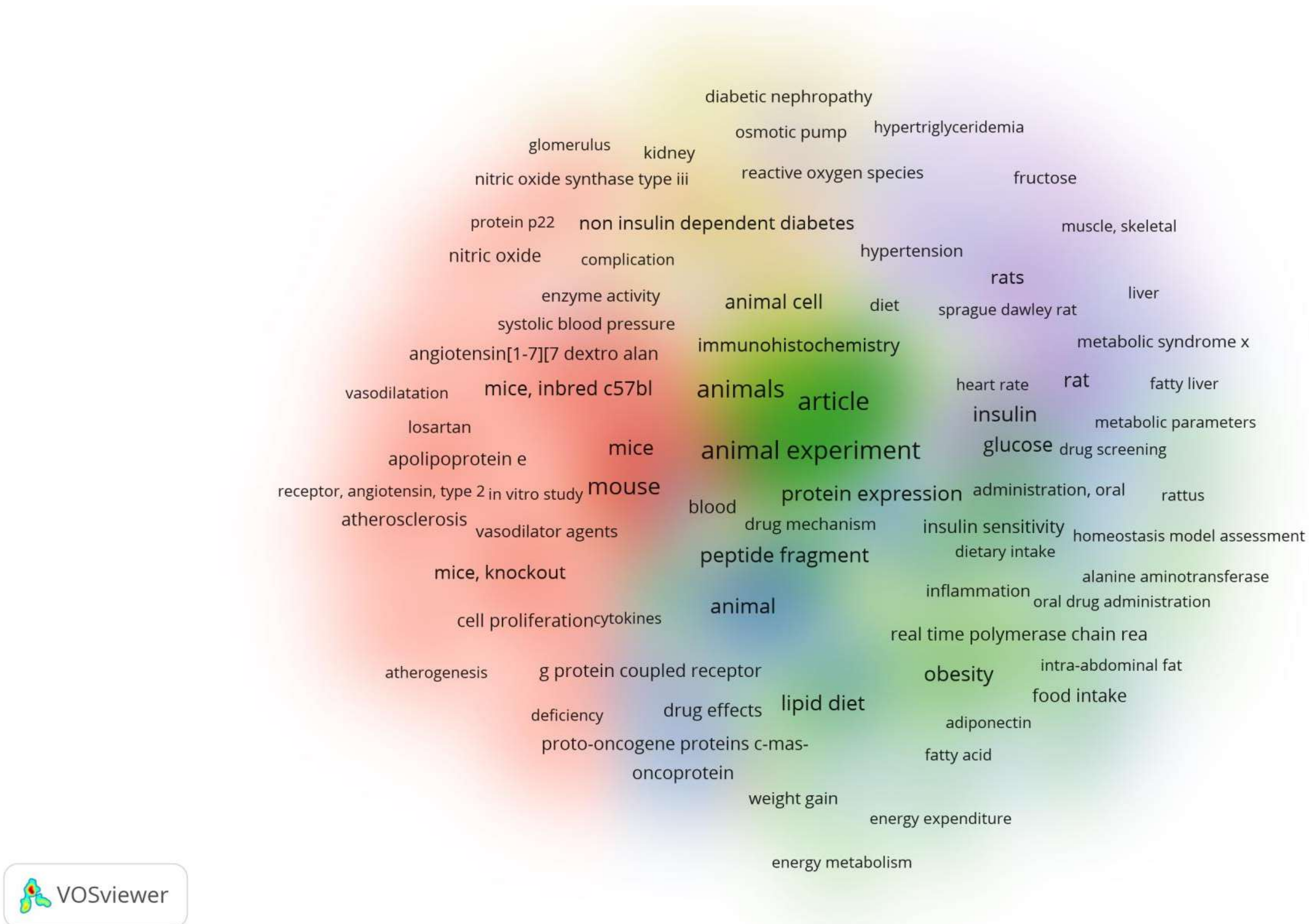

Figure 12 – Cluster density of the 262 index keywords, which occurred at least in 3 publications.

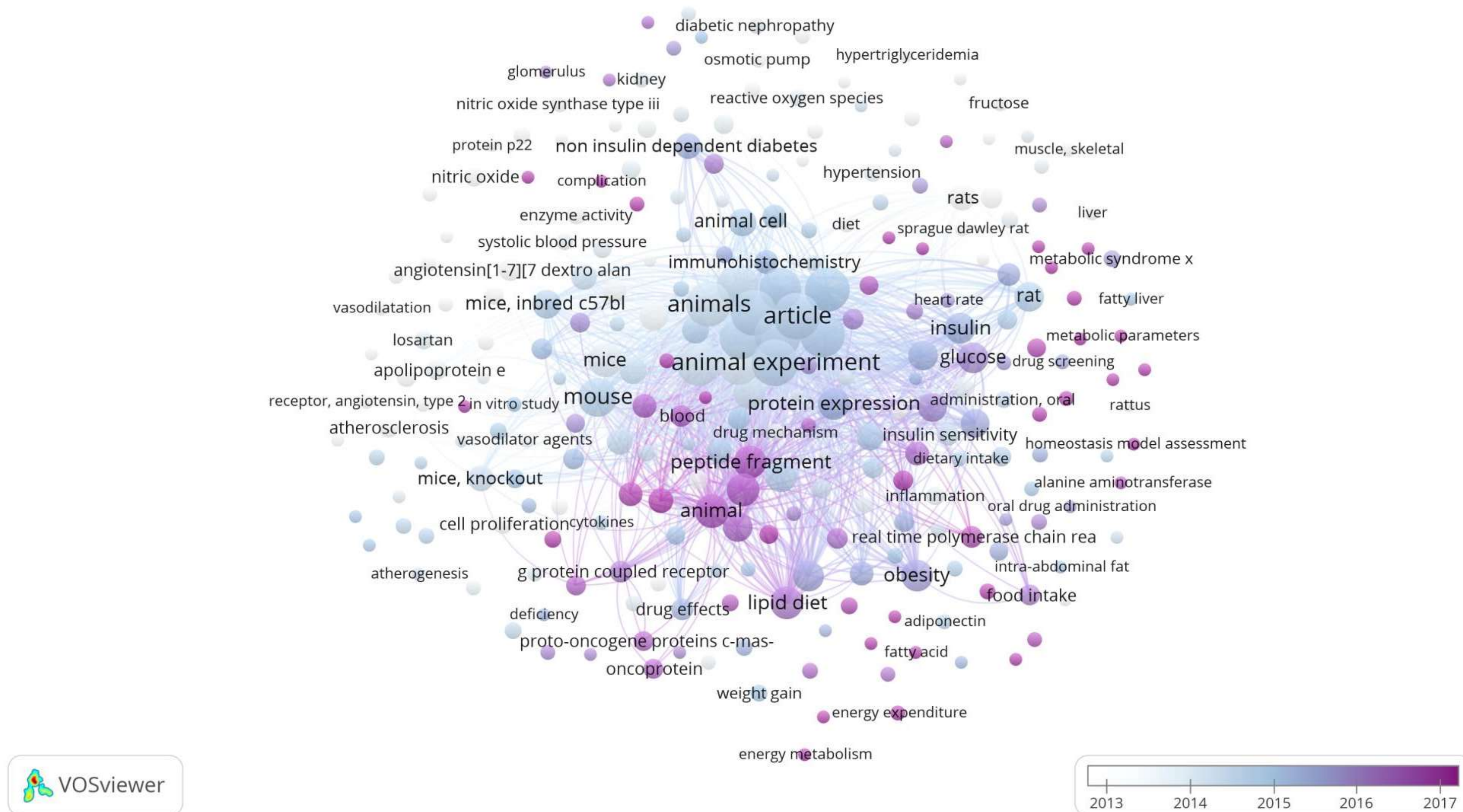

Figure 13 – timeline overlay visualization of the 262 index keywords, which occurred at least in 3 publications.

DISCUSSION

The present study aimed to map the worldwide productivity in the field of preclinical data of angiotensin-(1-7) effects on metabolic syndrome. The main findings were that the first manuscript in the field was published in 2003, and the literature displays a total of 62 original preclinical studies, wherein a third is from the United States (USA), which is the most cited country, as well. Differently, the most productive institution is the *Universidade Federal de Minas Gerais* (UFMG), from Brazil, with a total of 14 publications. Moreover, two researchers from UFMG are listed at the top of the most productive ones, along with Rodgers K.E. from the University of Southern California, USA. Despite that, the most cited article in the field is from the *Universidad de Buenos Aires*, Argentina, published by Giani and colleagues in 2009, in the *American Journal of Physiology (AJP) – Endocrinology and Metabolism*. In line, this Journal is one of those that held the highest number of publications, but it is not the most cited one. The keywords *obesity* and *angiotensin-(1-7)* were the most used by authors, while *animal experiment*, *article* and *nonhuman* were the most used index words. Moreover, two clusters were clearly formed considering the index keywords that include animal models, one relating to atherosclerosis and mice, and the other, insulin sensitivity and rats.

Data from the World Health Organization (2000 to 2019) show that ischaemic heart disease (1^{st}) and stroke (2^{nd}) still head the top 10 causes of global death, leading to most of 14 million deaths, along with diabetes mellitus (9^{th}) and kidney diseases (10^{th}) [16]. In this context, MetS highlights as a global epidemic, since it is likely that a quarter of global population are affected with this syndrome [1], and it increases the risk of a person having cardiovascular and renal diseases, as well as type II diabetes [1].

In order to elucidate the pathophysiology and the worsening mechanisms underlying MetS, several induction methods have been used in animals in order to replicate MetS phenotype, such as high caloric diets (sugar or fat), or transgenic approaches (e.g.: *ob/ob*, *db/db*, or ApoE^{-} mice; Zucker rats) [17 - 21]. In this concern, there still no uniformed guidelines to fully replicate the syndrome in animals as observed in humans; however, preclinical studies in the field have been highlighting possible intracellular mechanisms [17, 22], neuronal dysfunction [18], and potential non-pharmacological [23] and pharmacological approaches to ameliorates MetS, as Ang-(1-7) [8, 9, 17 – 22].

Ang-(1-7) is a bioactive heptapeptide of the renin angiotensin system, mainly known by its counter regulatory effects, through Mas receptor, on the exacerbated and non appropriated function of Ang II/ AT_1 receptor axis in several pathophysiological conditions [4], which confers to this peptide high potential of being considered as a new strategy on the treatment of several diseases in the practice of medicine [4].

In the present study, we sought to elucidate the bibliometric data concerning to preclinical studies focused on Ang-(1-7) actions on experimental models to study MetS. The first two preclinical studies in the literature relating Ang-(1-7) and MetS were from the United States, published by Rodgers K.E., in 2003, and focused on wound repair in *ob/ob* mice, using topic and systemic treatment with an analog of Ang-(1-7), the NorLeu – A(1-7) [24, 25]. After that, a gap in the literature was observed, and the third study came from Argentina in 2009, by Giani JF and colleagues, who sought to elucidate Ang-(1-7) actions on insulin resistance, using fructose-fed rats as MetS model [9].

Besides being the pioneer in the field, the United States headed as the most productive and the most cited country, followed by Brazil. Differently, other countries did not match such rankings, such as China, which holds the 3rd position in the number of publication, but is the 7th in citation; and Australia, which published only 2 articles and is ahead of China in citation ranking. On the other hand, most of China manuscripts (9 from 11) were published later than the ones from Australia, which may also account for the differences in citation ranking. Also, considering that China has few contact nodes with other countries, keeping itself far from the most productive nuclei, in which USA and Brazil are inserted, it is possible that a new reference nucleus in the field may appear in the future. Certainly, the next publications in the field and the number of citations will take part on that. In contrast, normalizing the number of citation by the total number of publications the most cited country was Austria, with 1 article, followed by Canada, with 4; Argentina (5 articles) and Australia (5 articles). Such data highlights the relevance of the impact of the research rather than the number of publications solely to future studies.

Supporting this notion, the Institution heading the number of publications in the field was the UFMG (Brazil), followed by Max Delbruck Center of Molecular Medicine (Germany), University of Southern California (USA) and Universidad de Buenos Aires (Argentina). The last one is the affiliation of the most cited manuscript in the field (135 citations), as mentioned above, published by Giani JF and colleagues in 2009, in the *AJP – Endocrinology and Metabolism*, which might be due to the fact that this was the first study to approach the perspective of Ang-(1-7) as a potential drug to attenuate MetS risk factors.

Such discrepancies were also observed when the rankings of authors and journals were analyzed. As for the authors, the most productive author (number of articles) was Bader, M, from the Max Delbruck Center for Molecular Medicine, from Germany; followed by Rodgers, KE (USA); Santos, RAS (Brazil); and Santos, SHS (Brazil); and then by Dominici, FP; and Giani, JF (both from Argentina). Differently, the most cited authors were Dominici, FP and Giani JF; followed by Santos SHS, when the total of citations was used as reference. Differently, normalizing total citations by the number of articles published by an author, Munoz, M.C. (Argentina), become the most cited one, and Dominici and Giani were the 3rd ones. Such differences in authors rankings corroborate the idea that impact of the research rather than the number of publications itself might be a more valuable tool to measure the contribution of an author in a research field.

Also, our data show that 3 clusters were formed when co-authorship network of the most productive authors was analyzed, in which Rodgers, K.E. does not have collaboration with the other two in this field, and that all 5 remaining authors collaborate to each other. Moreover, Bader, M.; Santos RAS and Santos SHS share the same cluster, while Dominici FP and Giani JF the other one. Besides that, Bader, M. is a key author between these two groups considering the recent publication [26]. Taking all this into account, it is likely that such collaborations may also contribute to the results obtained here for Institution and Authors Rankings, in which Brazil and Germany are in the spotlight. In fact, two third of the publications from Brazil or Germany were performed with international collaboration, while only 1 in 5 articles from Argentina was made in collaboration, which was with Brazil and Germany.

In addition, our study showed that there are 349 authors distributed into 11 research groups in the field, in which 84 authors have, at least, 2 publications together. Among these, only 35 are, in fact, related to each other, corresponding to a total of 4 research groups, wherein Santos, R.A.S. appears as a key author between all groups, supporting the position of UFMG as the most productive Institution in the field, since he links the groups that contributed to the area during the peak of publications (UFMG; 2013 to 2015) to the group that has been publishing more recently (UFOP; 2019 and 2020), and has also collaborations with Bader, M. and Giani, J.F. groups. Moreover, the remaining most cited authors (top 10 list) are clustered together, indicating a strong co-authorship between them.

As observed in Journal Rankings, *ATVB* heads both the number of publication and citation rankings, with 4 publications that occurred between 2010 and 2013 and 314 citations. However, such matching does not apply to other journals. For instance, while *Hypertension* is one of the journals with more number of publications in the field, along with *ATVB*, *Peptides* and *AJP – Endocrinology and Metabolism*; the *AJP – Renal Physiology* is more cited, suggesting that the articles published in the last have more impact to the design of future studies. Also, it is worth to mention that *Regulatory Peptides*, which is the 8th most cited journal is not publishing since 2015, and it contains only 2 manuscripts in the field, published by 2 of the top 5 most cited authors ([15, 16]). Remarkably, normalizing the number of citations by the number of publications, the *Circulation: Heart Failure* Journal headed the list, with 1 Canadian publication with 105 citations from Mori, J and colleagues (2014), which approached the benefic effects of chronic administration of Ang-(1-7) on diabetic cardiomyopathy and diastolic dysfunction in transgenic *db/db* mice [27].

Interestingly, author keyworks analysis revealed that *angiotensin-(1-7)* and *obesity* were the most used ones, having 12 occurrences each one. Other 23 keywords appear at least in 2 articles, in which *renin angiotensin system* (n=7), *insulin resistance* (n=6), *atherosclerosis* (n=6), *hypertension* (n=5), and *angiotensin ii* (n=5) were the most prevalent ones. Corroborating and extending these data, index keywords analysis revealed some clusters, in which two clearly show the animal models used and the direction of research in each one.

The red cluster, which is the most intense coloured cluster, includes *mice* and *mouse*, has also *mice, knockout*; *apolipoprotein e*; *mice, inbred c57bl*; *disease models*; *angiotensin 2 receptor*; *enzyme activity*; *cell proliferation*; and *vascular smooth muscle* as strong keywords. These data suggest that mice, and specially knockout mice, constitute the major animal model that has been used to elucidate vascular dysfunction in MetS. In contrast, the light purple cluster has *rat* and *rats* as strong keywords, suggesting it as an animal model, as well. Along with, keywords such as *insulin*; *hypertension*; *glucose tolerance test*; *insulin release*; *fructose*; and *enzyme phosphorylation*; among others, appear as strong keywords in the last. Such observation suggest that preclinical studies using rats as a model to study MetS might have been more directed to the use of non transgenic strains, subjected to diets and focused on ameliorating hypertension and insulin resistance, and the underlying mechanisms.

The remain clusters, which were lightly coloured as well, bring keywords such as *diabetic nephropathy*, *reactive oxygen species*, *non insulin dependent diabetes*, *drug effects*, *lipid diet*, *obesity*, *energy metabolism*, *weight gain*, and *food intake*. Such words were not directed connected to a keyword related to animal strain though. However, taking a close view on the timeline overlay visualization; one can clearly see that those keywords appeared in a different time course, and also have weak (or no) connections with the most common keywords which are displayed in the center of the map (Figure 13), except for *lipid diet*, and *obesity*, suggesting that trends in the research may have been changing in the past 5 years, since the strain animal and the most keywords clustered in red were not being indexed lately.

Conclusion

In summary, the present bibliometric analysis suggest that preclinical studies concerning to the Ang-(1-7) action on experimental models to study MetS have been performed for several countries. Considering the overall number of publications and citations, the United States is the most productive and cited country in the world. In contrast, the most cited article in the field is from Giani and colleagues in 2009, published in the AJP – Endocrinology and Metabolism [9]. Finally, despite not presenting a clear grow in publications along the years; the available data addressed relevant topics in the field, such as atherosclerosis and insulin resistance.

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APPENDIX 1

Frame 1. Search components in regarding to research database.

Base de dados	Search Component (SC)	Estratégia de busca
EMBASE	SC1: angiotensin-1-7	'angiotensin[1-7]'/exp OR 'angiotensin[1-7][7 dextro alanine]'/exp OR (angiotensin-:ab,ti AND '1 7':ab,ti) OR (angiotensin:ab,ti AND '1 7':ab,ti) OR 'angiotensin-1-7':ab,ti OR 'ang 1-7':ab,ti OR 'ang-1-7':ab,ti OR ('angiotensin ii':ab,ti AND '1 7':ab,ti) OR 'asp arg val tyr ile his pro':ab,ti OR 'aspartylarginylvalyltyrosylisoleucylhistidylproline':ab,ti OR 'txa 127':ab,ti OR 'txa127':ab,ti OR 'a779':ab,ti OR 'a 779':ab,ti OR 'a-779':ab,ti OR '7 d ala angiotensin [1-7]':ab,ti OR '7 d alanine angiotensin [1-7]':ab,ti OR '7 dextro alanine angiotensin [1-7]':ab,ti OR 'angiotensin [1-7] [7 d ala]':ab,ti OR 'angiotensin [1-7] [7 d alanine]':ab,ti OR 'asp arg val tyr ile his d ala':ab,ti OR 'aspartylarginylvalyltyrosinylisoleucylhistidyl dextro alanine':ab,ti OR 'mas receptor':ab,ti OR 'receptor mas':ab,ti OR 'proto oncogene proteins c mas 1':ab,ti OR 'proto-oncogene proteins c-mas-1':ab,ti OR (angiotensin:ab,ti AND 1–7:ab,ti AND receptor:ab,ti) OR 'g protein coupled receptor mas':ab,ti
	SC2: metabolic syndrome	'metabolic syndrome x'/exp OR 'diabetic hypertension'/exp OR 'obesity'/exp OR 'experimental obesity'/exp OR 'diet induced obesity'/exp OR 'dyslipidemia'/exp OR 'hyperglycemia'/exp OR 'glucose intolerance'/exp OR 'insulin resistance'/exp OR 'hyperinsulinism'/exp OR 'hyperinsulinemia'/exp OR 'diet'/exp OR 'carbohydrate diet'/exp OR 'high-fructose diet'/exp OR 'dietary intake'/exp OR 'carbohydrate intake'/exp OR 'sugar intake'/exp OR 'fructose'/exp OR 'metabolic disorder'/exp OR 'cardiometabolic risk'/exp OR 'cholesterol'/exp OR 'insulin'/exp OR 'glycogen'/exp OR 'triacylglycerol'/exp OR 'hypertriglyceridemia'/exp OR 'glucose metabolism disorders':ab,ti OR hyperinsulinism:ab,ti OR obesity:ab,ti OR 'obesity, abdominal':ab,ti OR hyperglycemia:ab,ti OR 'glucose intolerance':ab,ti OR dyslipidemias:ab,ti OR diet:ab,ti OR 'diet, western':ab,ti OR 'diet, high-fat':ab,ti OR 'high fructose corn syrup':ab,ti OR 'nutritive sweeteners':ab,ti OR 'nutritional physiological phenomena':ab,ti OR insulin:ab,ti OR 'dietary carbohydrates':ab,ti OR 'insulin resistance':ab,ti OR 'metabolic diseases':ab,ti OR 'metabolic syndrome':ab,ti OR fructose:ab,ti OR glycogen:ab,ti OR cholesterol:ab,ti OR hypertriglyceridemia:ab,ti OR 'metabolic syndromes':ab,ti OR 'metabolic syndrome x':ab,ti OR 'metabolic cardiovascular syndrome':ab,ti OR 'cardiometabolic syndrome':ab,ti OR 'plurimetabolic syndrome':ab,ti OR 'high-fat':ab,ti OR 'fructose diet':ab,ti OR 'fructose intake':ab,ti OR 'fructose-fed':ab,ti OR 'cafeteria diet':ab,ti OR hypercaloric:ab,ti OR obese:ab,ti OR 'western type diet':ab,ti OR 'western diet':ab,ti OR 'insulin signaling':ab,ti OR sucrose:ab,ti OR 'obesity-induced

		hypertension':ab,ti OR 'obesity hypertension':ab,ti OR 'type 2 diabetes':ab,ti OR 'diabetes':ab,ti OR 'hfd':ab,ti OR 'diet-induced':ab,ti OR overfed:ab,ti OR overfeeding:ab,ti OR 'diet intake':ab,ti OR 'glucose metabolism':ab,ti OR dyslipidemia:ab,ti OR glycemia:ab,ti OR 'sugar intake':ab,ti OR 'insulin resistance syndrome':ab,ti OR 'syndrome x, metabolic':ab,ti OR 'hypertension in diabetes':ab,ti OR 'adipose tissue hyperplasia':ab,ti OR adipositas:ab,ti OR adiposity:ab,ti OR 'alimentary obesity':ab,ti OR 'body weight, excess':ab,ti OR corpulency:ab,ti OR 'fat overload syndrome':ab,ti OR 'nutritional obesity; obesitas':ab,ti OR overweight:ab,ti OR 'experimental adiposity':ab,ti OR 'experimentally induced adiposity':ab,ti OR 'experimentally induced obesity':ab,ti OR 'diet induced obese animal':ab,ti OR 'diet induced obese mice':ab,ti OR 'diet induced obese mouse':ab,ti OR 'diet induced obese rat':ab,ti OR 'dietary induced obesity':ab,ti OR 'dio animal':ab,ti OR 'dio mice':ab,ti OR 'dio mouse':ab,ti OR 'dio rat':ab,ti OR 'hfd-induced adiposity':ab,ti OR 'hfd-induced obesity':ab,ti OR 'high fat diet-induced adiposity':ab,ti OR 'high fat diet-induced obesity':ab,ti OR ('high-fat diet':ab,ti AND hfd:ab,ti AND 'induced obesity':ab,ti) OR dyslipaemia:ab,ti OR dyslipemia:ab,ti OR dyslipidaemia:ab,ti OR dyslipidaemias:ab,ti OR 'lipidaemia, dys':ab,ti OR 'lipidemia, dys':ab,ti OR 'glucose blood level, elevated':ab,ti OR 'glycemia, hyper':ab,ti OR hyperglucemia:ab,ti OR hyperglycaemia:ab,ti OR 'hyperglycemic syndrome':ab,ti OR 'resistance, insuline':ab,ti OR hyperinsulinaemia:ab,ti OR hyperinsulinema:ab,ti OR 'diet influence':ab,ti OR 'diet regimen':ab,ti OR 'diet surveys':ab,ti OR 'dietary effect':ab,ti OR 'dietary influence':ab,ti OR 'dietary survey':ab,ti OR 'dietary surveys':ab,ti OR dieting:ab,ti OR 'diet, carbohydrate':ab,ti OR 'diet, high carbohydrate':ab,ti OR 'dietary carbohydrate':ab,ti OR 'high carbohydrate diet':ab,ti OR 'fructose enriched diet':ab,ti OR 'fructose-rich diet':ab,ti OR 'nutritional intake':ab,ti OR 'alimentary carbohydrate':ab,ti OR 'carbohydrate, alimentary':ab,ti OR 'carbohydrate, dietary':ab,ti OR 'diet carbohydrate':ab,ti OR 'saccharide intake':ab,ti OR 'dietary sucrose':ab,ti OR 'dietary sugar':ab,ti OR 'dietary sugars':ab,ti OR 'sucrose intake':ab,ti OR 'sugar consumption':ab,ti OR 'sugar diet':ab,ti OR 'sugar feeding':ab,ti OR 'd fructose':ab,ti OR 'dextro fructose':ab,ti OR dextrofructose:ab,ti OR diabetin:ab,ti OR 'fructose load':ab,ti OR 'fructose solution':ab,ti OR 'fruit sugar':ab,ti OR 'hypertonic fructose':ab,ti OR 'laevoral; laevoran':ab,ti OR 'laevosan; laevulose':ab,ti OR 'levo fructose':ab,ti OR levugen:ab,ti OR levulose:ab,ti OR 'vmine laevulose':ab,ti OR 'vmine levulose':ab,ti OR 'metabolic disease':ab,ti OR 'metabolic disturbance':ab,ti OR 'metabolic error':ab,ti OR 'metabolism disorder':ab,ti OR (nutritional:ab,ti AND 'metabolic diseases':ab,ti) OR 'water-electrolyte imbalance':ab,ti OR glucogen:ab,ti OR 'acylglycerol, tri':ab,ti OR 'fatty acid triglyceride':ab,ti OR 'triacyl glyceride':ab,ti OR triglyceride:ab,ti OR triglycerides:ab,ti OR hypertriglyceridaemia:ab,ti OR 'triglyceride storage disease':ab,ti OR triglyceridemia:ab,ti

	SC3: animal models	'animals':ab,ti OR 'non human primate':ab,ti OR 'animal':ab,ti OR 'mice':ab,ti OR 'mus':ab,ti OR 'mouse':ab,ti OR 'murine':ab,ti OR 'woodmouse':ab,ti OR 'rats':ab,ti OR 'rat':ab,ti OR 'murinae':ab,ti OR 'muridae':ab,ti OR 'cottonrat':ab,ti OR 'cottonrats':ab,ti OR 'hamster':ab,ti OR 'hamsters':ab,ti OR 'cricetinae':ab,ti OR 'rodentia':ab,ti OR 'rodent':ab,ti OR 'rodents':ab,ti OR 'pigs':ab,ti OR 'pig':ab,ti OR 'swine':ab,ti OR 'swines':ab,ti OR 'piglets':ab,ti OR 'piglet':ab,ti OR 'boar':ab,ti OR 'boars':ab,ti OR 'sus scrofa':ab,ti OR 'ferrets':ab,ti OR 'ferret':ab,ti OR 'polecat':ab,ti OR 'polecats':ab,ti OR 'mustela putorius':ab,ti OR 'guinea pigs':ab,ti OR 'guinea pig':ab,ti OR 'cavia':ab,ti OR 'callithrix':ab,ti OR 'marmoset':ab,ti OR 'marmosets':ab,ti OR 'cebuella':ab,ti OR 'hapale':ab,ti OR 'octodon':ab,ti OR 'chinchilla':ab,ti OR 'chinchillas':ab,ti OR 'gerbillinae':ab,ti OR 'gerbil':ab,ti OR 'gerbils':ab,ti OR 'jird':ab,ti OR 'jirds':ab,ti OR 'merione':ab,ti OR 'meriones':ab,ti OR 'rabbits':ab,ti OR 'rabbit':ab,ti OR 'hares':ab,ti OR 'hare':ab,ti OR 'cats':ab,ti OR 'cat':ab,ti OR 'carus':ab,ti OR 'felis':ab,ti OR 'dogs':ab,ti OR 'dog':ab,ti OR 'canine':ab,ti OR 'canines':ab,ti OR 'canis':ab,ti OR 'sheep':ab,ti OR 'sheeps':ab,ti OR 'mouflon':ab,ti OR 'mouflons':ab,ti OR 'ovis':ab,ti OR 'goats':ab,ti OR 'goat':ab,ti OR 'capra':ab,ti OR 'capras':ab,ti OR 'rupicapra':ab,ti OR 'chamois':ab,ti OR 'haplorhini':ab,ti OR 'monkey':ab,ti OR 'monkeys':ab,ti OR 'anthropoidea':ab,ti OR 'anthropoids':ab,ti OR 'saguinus':ab,ti OR 'tamarin':ab,ti OR 'tamarins':ab,ti OR 'leontopithecus':ab,ti OR 'hominidae':ab,ti OR 'ape':ab,ti OR 'apes':ab,ti OR 'pan':ab,ti OR 'paniscus':ab,ti OR 'pan paniscus':ab,ti OR 'bonobo':ab,ti OR 'bonobos':ab,ti OR 'troglodytes':ab,ti OR 'pan troglodytes':ab,ti OR 'gibbon':ab,ti OR 'gibbons':ab,ti OR 'siamang':ab,ti OR 'siamangs':ab,ti OR 'nomascus':ab,ti OR 'symphalangus':ab,ti OR 'chimpanzee':ab,ti OR 'chimpanzees':ab,ti OR 'prosimians':ab,ti OR 'bush baby':ab,ti OR 'prosimian':ab,ti OR 'bush babies':ab,ti OR 'galagos':ab,ti OR 'galago':ab,ti OR 'pongidae':ab,ti OR 'gorilla':ab,ti OR 'gorillas':ab,ti OR 'pongo pygmaeus':ab,ti OR 'orangutans':ab,ti OR 'pygmaeus':ab,ti OR 'lemur':ab,ti OR 'lemurs':ab,ti OR 'lemuridae':ab,ti OR 'horse':ab,ti OR 'horses':ab,ti OR 'pongo':ab,ti OR 'equus':ab,ti OR 'cow':ab,ti OR 'calf':ab,ti OR 'bull':ab,ti OR 'sciuridae':ab,ti OR 'squirrel':ab,ti OR 'squirrels':ab,ti OR 'chipmunk':ab,ti OR 'chipmunks':ab,ti OR 'suslik':ab,ti OR 'susliks':ab,ti OR 'vole':ab,ti OR 'voles':ab,ti OR 'lemming':ab,ti OR 'lemmings':ab,ti OR 'muskrat':ab,ti OR 'muskrats':ab,ti OR 'lemmus':ab,ti OR 'otter':ab,ti OR 'otters':ab,ti OR 'marten':ab,ti OR 'martens':ab,ti OR 'martes':ab,ti OR 'weasel':ab,ti OR 'badger':ab,ti OR 'badgers':ab,ti OR 'ermine':ab,ti OR 'mink':ab,ti OR 'sable':ab,ti OR 'sables':ab,ti OR 'gulo':ab,ti OR 'gulos':ab,ti OR 'wolverine':ab,ti OR 'wolverines':ab,ti OR 'minks':ab,ti OR 'mustela':ab,ti OR 'llama':ab,ti OR 'llamas':ab,ti OR 'alpaca':ab,ti OR 'alpacas':ab,ti OR 'camelid':ab,ti OR 'camelids':ab,ti OR 'guanaco':ab,ti OR 'guanacos':ab,ti OR 'chiroptera':ab,ti OR 'chiropteras':ab,ti OR 'bat':ab,ti OR 'bats':ab,ti OR 'fox':ab,ti OR 'foxes':ab,ti OR 'donkey':ab,ti OR 'donkeys':ab,ti OR 'mule':ab,ti OR 'mules':ab,ti OR

		'zebra':ab,ti OR 'zebras':ab,ti OR 'shrew':ab,ti OR 'shrews':ab,ti OR 'bison':ab,ti OR 'bisons':ab,ti OR 'buffalo':ab,ti OR 'buffaloes':ab,ti OR 'deer':ab,ti OR 'deers':ab,ti OR 'bear':ab,ti OR 'bears':ab,ti OR 'panda':ab,ti OR 'pandas':ab,ti OR 'wild hog':ab,ti OR 'wild boar':ab,ti OR 'fitchew':ab,ti OR 'fitch':ab,ti OR 'beaver':ab,ti OR 'beavers':ab,ti OR 'jerboa':ab,ti OR 'jerboas':ab,ti OR 'capybara':ab,ti OR 'capybaras':ab,ti
Base de dados	Search Component (SC)	Estratégia de busca
PUBMED	SC1: angiotensin-1-7	(“angiotensin-(1-7)” [title/abstract] OR “angiotensin (1-7)” [title/abstract] OR “angiotensin 1-7” [title/abstract] OR “angiotensin-1-7” [title/abstract] OR “ang 1-7” [title/abstract] OR “ang-1-7” [title/abstract] OR “angiotensin II (1-7)” [title/abstract] OR “A779” [title/abstract] OR “A 779” [title/abstract] OR “A-779” [title/abstract] OR “MAS receptor” [title/abstract] OR “Mas receptor” [title/abstract] OR “receptor Mas” [title/abstract] OR “receptor MAS” [title/abstract])
	SC2: metabolic syndrome	(“glucose metabolism disorders” [mesh] OR “hyperinsulinism” [mesh] OR “obesity” [mesh] OR “obesity, abdominal” [mesh] OR “hyperglycemia” [mesh] OR “glucose intolerance” [mesh] OR “dyslipidemias” [mesh] OR “diet” [mesh] OR “diet, western” [mesh] OR “diet, high-fat” [mesh] OR “high fructose corn syrup” [mesh] OR “dietary sugars” [mesh] OR “nutritive sweeteners” [mesh] OR “nutritional physiological phenomena” [mesh] OR “insulin” [mesh] OR “dietary carbohydrates” [mesh] OR “insulin resistance” [mesh] OR “metabolic diseases” [mesh] OR “metabolic syndrome” [mesh] OR “fructose” [mesh] OR “glycogen” [mesh] OR “cholesterol” [mesh] OR “triglycerides” [mesh] OR “hypertriglyceridemia” [mesh] OR “metabolic syndrome” [title/abstract] OR “metabolic syndromes” [title/abstract] OR “metabolic syndrome X” [title/abstract] OR “metabolic cardiovascular syndrome” [title/abstract] OR “cardiometabolic syndrome” [title/abstract] OR “plurimetabolic syndrome” [title/abstract] OR “high-fat” [title/abstract] OR “fructose diet” [title/abstract] OR “fructose intake” [title/abstract] OR “fructose-fed” [title/abstract] OR “cafeteria diet” [title/abstract] OR “hypercaloric” [title/abstract] OR “obese” [title/abstract] OR “obesity” [title/abstract] OR “western-type diet” [title/abstract] OR “western diet” [title/abstract] OR “insulin resistance” [title/abstract] OR “insulin” [title/abstract] OR “insulin signaling” [title/abstract] OR “fructose” [title/abstract] OR “sucrose” [title/abstract] OR “obesity-induced hypertension” [title/abstract] OR “obesity hypertension” [title/abstract] OR “type 2 diabetes” [title/abstract] OR “diabetes” [title/abstract] OR “HFD” [title/abstract] OR “diet-induced” [title/abstract] OR “overfed” [title/abstract] OR “overfeeding” [title/abstract] OR “diet intake” [title/abstract] OR “glucose metabolism” [title/abstract] OR “glucose intolerance” [title/abstract] OR

		“dyslipidemia” [title/abstract] OR “dyslipidemias” [title/abstract] OR “cholesterol” [title/abstract] OR “glycemia” [title/abstract] OR “sugar intake” [title/abstract])
	SC3: animal models	((animals[tw] OR non human primate*[tw] OR animal[tw] OR mice[tw] OR mus[tw] OR mouse[tw] OR murine[tw] OR woodmouse[tw] OR rats[tw] OR rat[tw] OR murinae[tw] OR muridae[tw] OR cottonrat[tw] OR cottonrats[tw] OR hamster[tw] OR hamsters[tw] OR cricetinae[tw] OR rodentia[tw] OR rodent[tw] OR rodents[tw] OR pigs[tw] OR pig[tw] OR swine[tw] OR swines[tw] OR piglets[tw] OR piglet[tw] OR boar[tw] OR boars[tw] OR "sus scrofa"[tw] OR ferrets[tw] OR ferret[tw] OR polecat[tw] OR polecats[tw] OR "mustela putorius"[tw] OR "guinea pigs"[tw] OR "guinea pig"[tw] OR cavia[tw] OR callithrix[tw] OR marmoset[tw] OR marmosets[tw] OR cebuella[tw] OR hapale[tw] OR octodon[tw] OR chinchilla[tw] OR chinchillas[tw] OR gerbillinae[tw] OR gerbil[tw] OR gerbils[tw] OR jird[tw] OR jirds[tw] OR merione[tw] OR meriones[tw] OR rabbits[tw] OR rabbit[tw] OR hares[tw] OR hare[tw] OR cats[tw] OR cat[tw] OR carus[tw] OR felis[tw] OR dogs[tw] OR dog[tw] OR canine[tw] OR canines[tw] OR canis[tw] OR sheep[tw] OR sheeps[tw] OR mouflon[tw] OR mouflons[tw] OR ovis[tw] OR goats[tw] OR goat[tw] OR capra[tw] OR capras[tw] OR rupicapra[tw] OR chamois[tw] OR haplorhini[tw] OR monkey[tw] OR monkeys[tw] OR anthropoidea[tw] OR anthropoids[tw] OR saguinus[tw] OR tamarin[tw] OR tamarins[tw] OR leontopithecus[tw] OR hominidae[tw] OR ape[tw] OR apes[tw] OR pan[tw] OR paniscus[tw] OR "pan paniscus"[tw] OR bonobo[tw] OR bonobos[tw] OR troglodytes[tw] OR "pan troglodytes"[tw] OR gibbon[tw] OR gibbons[tw] OR siamang[tw] OR siamangs[tw] OR nomascus[tw] OR symphalangus[tw] OR chimpanzee[tw] OR chimpanzees[tw] OR prosimians[tw] OR "bush baby"[tw] OR prosimian[tw] OR bush babies[tw] OR galagos[tw] OR galago[tw] OR pongidae[tw] OR gorilla[tw] OR gorillas[tw] OR pongo[tw] OR pygmaeus[tw] OR "pongo pygmaeus"[tw] OR orangutans[tw] OR pygmaeus[tw] OR lemur[tw] OR lemurs[tw] OR lemuridae[tw] OR horse[tw] OR horses[tw] OR pongo[tw] OR equus[tw] OR cow[tw] OR calf[tw] OR bull[tw] OR sciuridae[tw] OR squirrel[tw] OR squirrels[tw] OR chipmunk[tw] OR chipmunks[tw] OR suslik[tw] OR susliks[tw] OR vole[tw] OR voles[tw] OR lemming[tw] OR lemmings[tw] OR muskrat[tw] OR muskrats[tw] OR lemmus[tw] OR otter[tw] OR otters[tw] OR marten[tw] OR martens[tw] OR martes[tw] OR weasel[tw] OR badger[tw] OR badgers[tw] OR ermine[tw] OR mink[tw] OR minks[tw] OR sable[tw] OR sables[tw] OR gulo[tw] OR gulos[tw] OR wolverine[tw] OR wolverines[tw] OR minks[tw] OR mustela[tw] OR llama[tw] OR llamas[tw] OR alpaca[tw] OR alpacas[tw] OR camelid[tw] OR camelids[tw] OR guanaco[tw] OR guanacos[tw] OR chiroptera[tw] OR chiropteras[tw] OR bat[tw] OR bats[tw] OR fox[tw] OR foxes[tw] OR donkey[tw] OR donkeys[tw] OR mule[tw] OR mules[tw] OR zebra[tw] OR zebras[tw] OR shrew[tw] OR shrews[tw] OR bison[tw] OR bisons[tw] OR buffalo[tw] OR buffaloes[tw] OR deer[tw] OR

		deers[tw] OR bear[tw] OR bears[tw] OR panda[tw] OR pandas[tw] OR "wild hog"[tw] OR "wild boar"[tw] OR fitchew[tw] OR fitch[tw] OR beaver[tw] OR beavers[tw] OR jerboa[tw] OR jerboas[tw] OR capybara[tw] OR capybaras[tw]))
Base de dados	Search Component (SC)	Estratégia de busca
SCOPUS	SC1: angiotensin-1-7	TITLE-ABS-KEY ("angiotensin-(1-7)" OR "angiotensin (1-7)" OR "angiotensin 1-7" OR "angiotensin-1-7" OR "ang 1-7" OR "ang-1-7" OR "angiotensin II (1-7)" OR "A779" OR "A 779" OR "A-779" OR "MAS receptor" OR "Mas receptor" OR "receptor Mas" OR "receptor MAS")
	SC2: metabolic syndrome	TITLE-ABS-KEY ("glucose metabolism disorders" OR "hyperinsulinism" OR "obesity" OR "obesity, abdominal" OR "hyperglycemia" OR "glucose intolerance" OR "dyslipidemias" OR "diet" OR "diet, western" OR "diet, high-fat" OR "high fructose corn syrup" OR "dietary sugars" OR "nutritive sweeteners" OR "nutritional physiological phenomena" OR "insulin" OR "dietary carbohydrates" OR "insulin resistance" OR "metabolic diseases" OR "metabolic syndrome" OR "fructose" OR "glycogen" OR "cholesterol" OR "triglycerides" OR "hypertriglyceridemia" OR "metabolic syndrome" OR "metabolic syndromes" OR "metabolic syndrome X" OR "metabolic cardiovascular syndrome" OR "cardiometabolic syndrome" OR "plurimetabolic syndrome" OR "high-fat" OR "fructose diet" OR "fructose intake" OR "fructose-fed" OR "cafeteria diet" OR "hypercaloric" OR "obese" OR "obesity" OR "western-type diet" OR "western diet" OR "insulin resistance" OR "insulin" OR "insulin signaling" OR "fructose" OR "obesity-induced hypertension" OR "obesity hypertension" OR "type 2 diabetes" OR "diabetes" OR "HFD" OR "diet-induced" OR "overfed" OR "overfeeding" OR "diet intake" OR "glucose metabolism" OR "glucose intolerance" OR "dyslipidemia" OR "dyslipidemias" OR "cholesterol" OR "glycemia" OR "sucrose" OR "sugar intake")
	SC3: animal models	"animals" OR "non human primate" OR "animal" OR "mice" OR "mus" OR "mouse" OR "murine" OR "woodmouse" OR "rats" OR "rat" OR "murinae" OR "muridae" OR "cottonrat" OR "cottonrats" OR "hamster" OR "hamsters" OR "cricetinae" OR "rodentia" OR "rodent" OR "rodents" OR "pigs" OR "pig" OR "swine" OR "swines" OR "piglets" OR "piglet" OR "boar" OR "boars" OR "sus scrofa" OR "ferrets" OR "ferret" OR "polecat" OR "polecats" OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR "cavia" OR "callithrix" OR "marmoset" OR "marmosets" OR "cebuella" OR "hapale" OR "octodon" OR "chinchilla" OR "chinchillas" OR "gerbillinae" OR "gerbil" OR "gerbils" OR "jird" OR "jirds" OR

		"merione" OR "meriones" OR "rabbits" OR "rabbit" OR "hares" OR "hare" OR "cats" OR "cat" OR "carus" OR "felis" OR "dogs" OR "dog" OR "canine" OR "canines" OR "canis" OR "sheep" OR "sheeps" OR "mouflon" OR "mouflons" OR "ovis" OR "goats" OR "goat" OR "capra" OR "capras" OR "rupicapra" OR "chamois" OR "haplorhini" OR "monkey" OR "monkeys" OR "anthropoidea" OR "anthropoids" OR "saguinus" OR "tamarin" OR "tamarins" OR "leontopithecus" OR "hominidae" OR "ape" OR "apes" OR "pan" OR "paniscus" OR "pan paniscus" OR "bonobo" OR "bonobos" OR "troglodytes" OR "pan troglodytes" OR "gibbon" OR "gibbons" OR "siamang" OR "siamangs" OR "nomascus" OR "symphalangus" OR "chimpanzee" OR "chimpanzees" OR "prosimians" OR "bush baby" OR "prosimian" OR "bush babies" OR "galagos" OR "galago" OR "pongidae" OR "gorilla" OR "gorillas" OR "pongo" OR "pygmaeus" OR "pongo pygmaeus" OR "orangutans" OR "pygmaeus" OR "lemur" OR "lemurs" OR "lemuridae" OR "horse" OR "horses" OR "pongo" OR "equus" OR "cow" OR "calf" OR "bull" OR "sciuridae" OR "squirrel" OR "squirrels" OR "chipmunk" OR "chipmunks" OR "suslik" OR "susliks" OR "vole" OR "voles" OR "lemming" OR "lemmings" OR "muskrat" OR "muskrats" OR "lemmus" OR "otter" OR "otters" OR "marten" OR "martens" OR "martes" OR "weasel" OR "badger" OR "badgers" OR "ermine" OR "mink" OR "minks" OR "sable" OR "sables" OR "gulo" OR "gulos" OR "wolverine" OR "wolverines" OR "minks" OR "mustela" OR "llama" OR "llamas" OR "alpaca" OR "alpacas" OR "camelid" OR "camelids" OR "guanaco" OR "guanacos" OR "chiroptera" OR "chiropteras" OR "bat" OR "bats" OR "fox" OR "foxes" OR "donkey" OR "donkeys" OR "mule" OR "mules" OR "zebra" OR "zebras" OR "shrew" OR "shrews" OR "bison" OR "bisons" OR "buffalo" OR "buffaloes" OR "deer" OR "deers" OR "bear" OR "bears" OR "panda" OR "pandas" OR "wild hog" OR "wild boar" OR "fitchew" OR "fitch" OR "beaver" OR "beavers" OR "jerboa" OR "jerboas" OR "capybara" OR "capybaras"
Base de dados	Search Component (SC)	Estratégia de busca
WEB OF SCIENCE	SC1: angiotensin-1-7	TS=((angiotensin-(1-7)) OR (angiotensin (1-7)) OR (angiotensin 1-7) OR (angiotensin-1-7) OR (ang 1-7) OR (ang-1-7) OR (angiotensin II (1-7)) OR (A779) OR (A 779) OR (A-779) OR (MAS receptor) OR (Mas receptor) OR (receptor Mas) OR (receptor MAS))
	SC2: metabolic syndrome	TS=((glucose metabolism disorders) OR (hyperinsulinism) OR (obesity) OR (obesity, abdominal) OR (hyperglycemia) OR (glucose intolerance) OR (dyslipidemias) OR (diet) OR (diet, western) OR (diet, high-fat) OR (high fructose corn syrup) OR (dietary sugars) OR (nutritive sweeteners) OR (nutritional physiological phenomena)

		OR (insulin) OR (dietary carbohydrates) OR (insulin resistance) OR (metabolic diseases) OR (metabolic syndrome) OR (fructose) OR (glycogen) OR (cholesterol) OR (triglycerides) OR (hypertriglyceridemia) OR (metabolic syndrome) OR (metabolic syndromes) OR (metabolic syndrome X) OR (metabolic cardiovascular syndrome) OR (cardiometabolic syndrome) OR (plurimetabolic syndrome) OR (high-fat) OR (fructose diet) OR (fructose intake) OR (fructose-fed) OR (cafeteria diet) OR (hypercaloric) OR (obese) OR (obesity) OR (western-type diet) OR (western diet) OR (insulin resistance) OR (insulin) OR (insulin signaling) OR (fructose) OR (sucrose) OR (obesity-induced hypertension) OR (obesity hypertension) OR (type 2 diabetes) OR (diabetes) OR (HFD) OR (diet-induced) OR (overfed) OR (overfeeding) OR (diet intake) OR (glucose metabolism) OR (glucose intolerance) OR (dyslipidemia) OR (dyslipidemias) OR (cholesterol) OR (glycemia) OR (sugar intake))
	SC3: animal models	TS=((animals) OR (non human primate) OR (animal) OR (mice) OR (mus) OR (mouse) OR (murine) OR (woodmouse) OR (rats) OR (rat) OR (murinae) OR (muridae) OR (cottonrat) OR (cottonrats) OR (hamster) OR (hamsters) OR (cricetinae) OR (rodentia) OR (rodent) OR (rodents) OR (pigs) OR (pig) OR (swine) OR (swines) OR (piglets) OR (piglet) OR (boar) OR (boars) OR (sus scrofa) OR (ferrets) OR (ferret) OR (polecat) OR (polecats) OR (mustela putorius) OR (guinea pigs) OR (guinea pig) OR (cavia) OR (callithrix) OR (marmoset) OR (marmosets) OR (cebuella) OR (hapale) OR (octodon) OR (chinchilla) OR (chinchillas) OR (gerbillinae) OR (gerbil) OR (gerbils) OR (jird) OR (jirds) OR (merione) OR (meriones) OR (rabbits) OR (rabbit) OR (hares) OR (hare) OR (cats) OR (cat) OR (carus) OR (felis) OR (dogs) OR (dog) OR (canine) OR (canines) OR (canis) OR (sheep) OR (sheeps) OR (mouflon) OR (mouflons) OR (ovis) OR (goats) OR (goat) OR (capra) OR (capras) OR (rupicapra) OR (chamois) OR (haplorhini) OR (monkey) OR (monkeys) OR (anthropoidea) OR (anthropoids) OR (saguinus) OR (tamarin) OR (tamarins) OR (leontopithecus) OR (hominidae) OR (ape) OR (apes) OR (pan) OR (paniscus) OR (pan paniscus) OR (bonobo) OR (bonobos) OR (troglodytes) OR (pan troglodytes) OR (gibbon) OR (gibbons) OR (siamang) OR (siamangs) OR (nomascus) OR (symphalangus) OR (chimpanzee) OR (chimpanzees) OR (prosimians) OR (bush baby) OR (prosimian) OR (bush babies) OR (galagos) OR (galago) OR (pongidae) OR (gorilla) OR (gorillas) OR (pongo) OR (pygmaeus) OR (pongo) (pygmaeus) OR (orangutans) OR (pygmaeus) OR (lemur) OR (lemurs) OR (lemuridae) OR (horse) OR (horses) OR (pongo) OR (equus) OR (cow) OR (calf) OR (bull) OR (sciuridae) OR (squirrel) OR (squirrels) OR (chipmunk) OR (chipmunks) OR (suslik) OR (susliks) OR (vole) OR (voles) OR (lemming) OR (lemmings) OR (muskrat) OR (muskrats) OR (lemmus) OR (otter) OR (otters) OR (marten) OR (martens) OR (martes) OR (weasel) OR (badger) OR (badgers) OR (ermine) OR (mink) OR (minks) OR (sable) OR (sables) OR (gulo) OR (gulos) OR (wolverine) OR (wolverines) OR (minks) OR (mustela) OR (llama) OR (llamas) OR (alpaca) OR (alpacas) OR (camelid) OR (camelids) OR (guanaco) OR

		(guanacos) OR (chiroptera) OR (chiropteras) OR (bat) OR (bats) OR (fox) OR (foxes) OR (donkey) OR (donkeys) OR (mule) OR (mules) OR (zebra) OR (zebras) OR (shrew) OR (shrews) OR (bison) OR (bisons) OR (buffalo) OR (buffaloes) OR (deer) OR (deers) OR (bear) OR (bears) OR (panda) OR (pandas) OR (wild hog) OR (wild boar) OR (fitchew) OR (fitch) OR (beaver) OR (beavers) OR (jerboa) OR (jerboas) OR (capybara) OR (capybaras))

APPENDIX 2

Frame 2. List of eligible articles in timeline order.

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