Repurposing plant-derived substances as antivirals against sars-cov-2

Redirecionando substâncias derivadas de plantas como antivirais contra Sars-cov-2

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ABSTRACT

The urgent need for effective treatments for COVID-19 has developed, encouraging pharmaceutical companies to develop or redirect substances against SARS-CoV-2. Among them, substances used against worms, malaria, or bacteria were targeted to combat the virus. Such substances have been used in clinical trials and evaluated in vitro and in silico regarding the action on viral proteins, pharmacodynamics and toxicity of drugs. In this study, we conducted a systematic review of peer-reviewed articles involving molecules of plant origin with potential antiviral action on SARS-CoV-2. Reports containing the combinations of key words herbal, medicinal plants, natural products, and SARS-CoV-2 available from 01-01-2019 to 28-08-2020 in the Pubmed Central and World Wide Science sites were selected. A total of 677 items were retrieved. Of these, 170 were excluded because they were not complete, peer reviewed, freely, or related to vegetable products. Of the remaining, 345 were review articles, 23 were discussions, 4 were clinical trials, 14 showed *in vitro* experiments, and 121 were *in silico* studies. The proteins of SARS-CoV-2 considered as the therapeutic targets for the molecular docking were the structural spike glycoprotein (S protein), membrane protein Mpro, papain-*like* protease (PLpro), and RNA-dependent RNA polymerase (RdRp). Also, some studies have addressed the cell receptor ACE2 and natural products interaction. From *in silico* tests, therefore, 149 isolated plant molecules were identified with binding affinity to SARS-CoV-2 Mpro. Also, pharmacokinetic properties and bioavailability of some products were investigated highlighting the products nimbolide, withaferin-A, caffeic acid derivatives, rhamnetin, delta d-Viniferin, myri-citrin, chrysanthemin, myritilin,

taiwanhomoflavone A, lactucopicrin 15-oxalate, nympholide A, afzelin, biorobin, herperidin and phyllaemblicin B, glycyrrhizic acid, and rutin. As reported, rutin may influence viral functional protein assembly and host inflammatory suppression. Its affinity for Mpro and toll like receptors (TLRs) besides *in vivo* results render rutin a potential novel therapeutic anti-coronavirus strategy. This study highlights the *in silico* diversity of plant metabolites with high potential of antiviral activity against SARS-CoV-2 as alternatives in the repurposing course against COVID-19 as well as other viral pandemics that may arise.

Keywords: Coronavirus, Natural products, Medicinal plants, *in silico*.

RESUMO

No último ano, com o advento da pandemia pela COVID-19, doença causada pelo novo coronavírus associado à síndrome respiratória aguda (SARS-CoV-2), houve a necessidade urgente do desenvolvimento de tratamentos eficazes e a agilidade da indústria farmacêutica em desenvolver ou redirecionar substâncias utilizadas contra outros agentes para o combate do SARS-CoV-2. Entre essas substâncias, as empregadas no tratamento anti-helmíntico, anti-malária e antimicrobiano conhecidas foram utilizadas em ensaios clínicos e avaliadas *in vitro* e *in silico* em relação à ação sobre proteínas virais, farmacodinâmica e toxicidade de drogas. Entretanto, até o momento não existe um tratamento em uso, eficaz com ação direta sobre o vírus o que faz com que a busca de novas substâncias com ação seletiva sobre o SARS-CoV-2 continue necessária. Desta feita, neste estudo, realizou-se revisão sistemática de publicações científicas revisadas por pares envolvendo moléculas de origem vegetal com ação antiviral potencial sobre o SARS-CoV-2. Foram selecionados relatos contendo as combinações de palavras-chave *herbal, medicinal plants, natural products* e SARS-CoV-2 disponíveis de 01-01-2019 a 28-08-2020 nos sites Pubmed Central e World Wide Science. Na busca, foram recuperados 677 itens. Destes, 170 foram excluídos porque não estavam completos, não eram revisados por pares, não eram de acesso livre, ou não eram originados de plantas. Dos restantes, 345 eram artigos de revisão, 23 eram discussões, quatro eram ensaios clínicos, 14 mostravam experimentos *in vitro* e 121 eram estudos *in silico*. As proteínas do SARS-CoV-2 consideradas como alvos terapêuticos para o acoplamento molecular foram a glicoproteína estrutural spike (proteína S), proteína de membrana Mpro, protease papaína-*like* (PLpro) e RNA polimerase dependente de RNA (RdRp). Além disso, alguns estudos abordaram a interação entre o receptor celular ACE2 e produtos naturais. A partir de testes *in silico*, portanto, 149 moléculas vegetais isoladas foram identificadas com afinidade de ligação a Mpro do SARS-CoV-2 . Também foram investigadas as propriedades farmacocinéticas e a biodisponibilidade de alguns produtos, destacando-se os produtos nimbolide, withaferin-A, derivados de ácido cafeico, ramnetina, delta d-Viniferina, mircitrina, crisantina, mirtilina, taiwanhomoflavona A, lactupicrina 15-oxalato, ninfolfe A, afzelina, biorobina, herperidina e filaemblicina B, ácido glicirrízico e rutina. Destaca-se a rutina por sua ação tanto na montagem da proteína funcional viral como na supressão da inflamação do hospedeiro. Além disso, sua afinidade com a Mpro, com os receptores *toll-like* (TLRs) além de resultados *in vivo* tornam a rutina candidata à terapêutica anti-coronavírus. Este estudo destaca a diversidade dos metabólitos vegetais com alto potencial de atividade antiviral contra o SARS-CoV-2 identificados *in silico* como alternativas no redirecionamento contra a COVID-19, bem como outras pandemias virais que possam surgir.

Palavras-chave: Coronavírus, Produtos naturais, Plantas medicinais, *in silico*

1 INTRODUCTION

The year 2020 has been marked by the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease-19 (COVID-19). The virus has been spread all over the world and caused a high number of cases and death, becoming one of the most reliable events that affected humanity in the last few decades (Dutra et al., 2020; Lauxmann et al., 2020).

In order to restrain the pandemia, efforts have been made worldwide to efficiently control this health crisis through public health policies such as lockdown, border control, early virus detection, hands hygiene, and face protection usage (WHO, 2020). Meanwhile, although the results of population protection are not conclusive, novel health products such as vaccines against SARS-CoV-2 have been released as a public health emergency measure (WHO, 2021) .

At clinical and hospitalization level controversial treatments were put into question and the focus is mainly on supportive care and symptomatic treatment (Song et al., 2020). Clinical trials have not demonstrated therapeutic advantages over the toxicological risks of the drugs used so far, which demonstrates the need to investigate new therapeutic alternatives (Oroojalian et al., 2020).

Thus, in the search for redirection of substances with antiviral action, researchers have suggested the metabolites of vegetal origin already identified and reported in the literature as an alternative (Azim et al., 2020; Ghosh et al., 2020; Rolta et al., 2020). The molecules of vegetal origin deserve attention in this area since they present molecular structures with great variety and versatility of interactions with other molecules or biological fonctions (Shahzad et al., 2020).

For this, one must take into consideration peculiar characteristics of the new coronavirus that were important in pathogenesis, interspecies infection and in the triggering of the pandemic, such as the large positive sense, single stranded RNA genome and the presence of envelope (Malik, 2020). In addition, there are other viral structures that are also relevant when seeking therapeutic alternatives after infection in individuals in the critical phase of the disease, from which one can highlight the main protein (M), also called 3C-like protease, that is not recognized by any host protease (Mazzini et al., 2020).

Thus, from a networked database available for both substances of plant origin and therapeutic targets, the interaction between the elements is observed. Using virtual tools and empirical rules, information such as degree of interaction, pharmacokinetics,

pharmacodynamics and possible toxicological risks are obtained. Thus, in a short period of time, substances with good affinity score and biological potential can be selected to be tested *in vitro*, *in vivo* and in clinical trials, if they already have previous results *in vivo* for other agents or even viruses.

2 OBJECTIVE

In this context, the objective of the present study was to conduct a systematic review based on peer-reviewed articles containing molecules of plant origin with potential antiviral action on SARS-CoV-2.

3 METHODOLOGY

3.1 DATABASE

Two international databases were used to search scientific publications: PubMed and WorldWide Science. Natural products, medicinal plants, SARS-CoV-2, and herbal were chosen. In order to validate the keywords, they were checked at Medical Subject Headings (MeSH) controlled vocabulary thesaurus used for indexing articles for PubMed.

The search was conducted combining the keywords in the following order: "SARS-CoV-2 and herbal"; "SARS-CoV-2 and medicinal plants"; "SARS-CoV-2 and natural products". In the sequence, each individual search was unified and duplication was verified.

Search filters included date of publication, peer revision, language and type of text available. Thus, peer-reviewed scientific articles retrieved in English between January 1st, 2019 and August 26th, 2020. A date before SARS-CoV-2 notification was established to include reports with other coronaviruses such as SARS-CoV and MERS-CoV or, in the case of WorldWide Science, only the filter 'year' was available. Finally, the articles whose methodology contained *in silico* analysis were selected for the most thorough analysis.

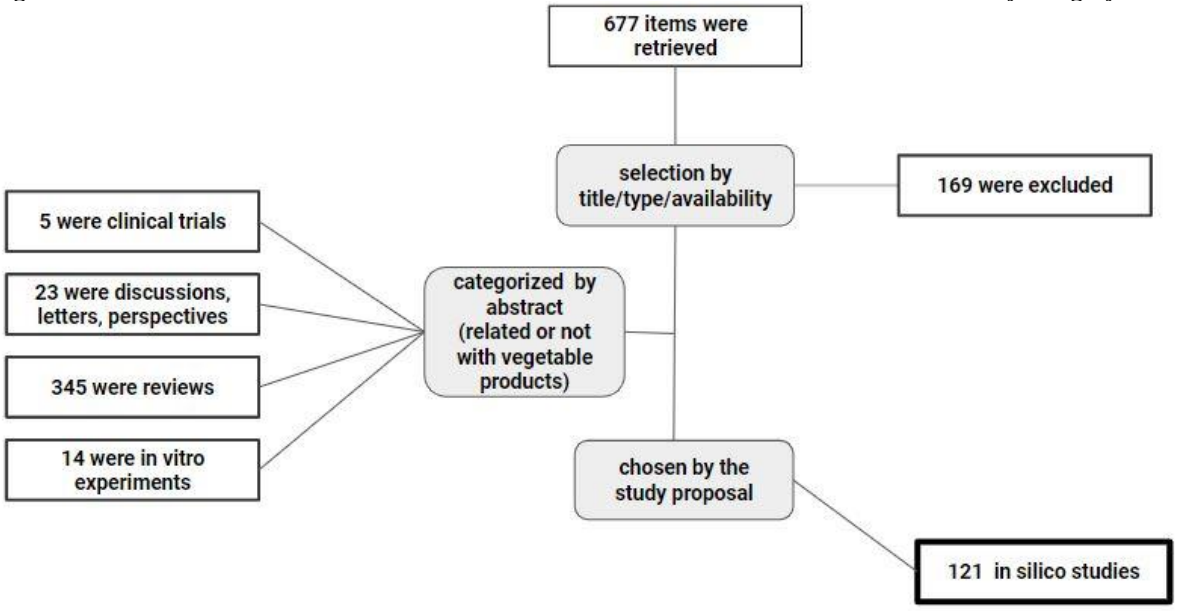
4 RESULTS AND DISCUSSION

The initial search showed 677 articles which were downloaded and organized into categories, according to table 1 and figure 1. Among these, 57 were repeated, as they were found in two or even all the researches performed for each unit.

Table 1. Scientific reports classified by type retrieved from PubMed and WorldWide Science between January 1st, 2019 and August 26th, 2020.

Article type	SARS-CoV-2 and Herbal	SARS-CoV-2 and Medicinal plants	SARS-CoV-2 and Natural products
Meta-Analysis	1	0	0
Review	64	35	74
In vitro	4	3	7
In silico	40	58	24
Discussion, letter, perspectives	5	11	7
Clinical Trial	2	2	1
Not related to natural products	40	31	33
Total	227	213	237

Figure 1. Flowchart of search in PubMed and WorldWide Science and number of articles found by category.



Retrieving *in silico* studies, 121 reports were then selected and throughout analysed. The current pandemic scenario has accelerated the scientific race, so that more agile and economically viable researches, such as *in silico* studies, have been crucial for a possible direction of more costly investigations with greater promise of positive results. The *in silico* methods have advantages in view of the fact that they comprehend computational simulation that aims to model a phenomenon that occurs naturally; it is an alternative for research models that use animal experimentation (Herrman et al., 2019;

Madden et al., 2020); or facilitate rational strategies for drug repurposing and the detection of side effects (Cheng et al., 2018).

In this context, articles retrieved showed simulation of molecular affinity of isolated natural products to molecules involved in SARS-CoV-2 infection. Prediction took into consideration optimal binding temperatures and if the binding strength would be enough to determine the viability or not of these substances as future antivirals. Thus, the natural products with high affinity to molecules involved in SARS-CoV-2 infection tagged *in silico* studies are shown in Table 2.

Table 2. Natural products with high affinity to molecules involved in SARS-CoV-2 infection tagged *in silico* studies.

Products	Molecules	N	References
withaferin A	ACE2/M^{pro}	3	AZIM et al, 2020; MAURYA et al, 2020; SUDEEP et al, 2020.
caffeic acid derivatives	M^{pro}	1	KUMAR et al, 2020.
rhamnetin	M^{pro}	1	FISCHER et al, 2020.
d-Viniferin	M^{pro}	1	JOSHI et al, 2020.
myricitrin	M^{pro}	4	CHIKHALE et al, 2020; GOSH et al, 2020; JOSH et al, 2020; MAHMUD et al, 2020.
taiwanhomoflavone A	M^{pro}	1	JOSHI et al, 2020.
lactucopicrin 15-oxalate	M^{pro}	1	JOSHI et al, 2020.
nympholide A	M^{pro}	1	JOSHI et al, 2020.
afzelin	M^{pro}	1	JOSHI et al, 2020.
biorobin	M^{pro}	1	JOSHI et al, 2020.
hesperidin	M^{pro}/ACE2/ S protein/RdRp	7	BALMEH et al, 2020; DAS et al, 2020; CHIKHALE et al, 2020; GOSH et al, 2020; KODCHAKORN et al, 2020; KOULGI et al, 2020; PANDEY et al, 2020.
phyllaemblicin B	M^{pro}/ACE2	1	JOSHI et al, 2020.
glycyrrhizic acid	M^{pro}/ACE2/NSP1/ RdRp/S protein	3	SHARMA et al, 2020; SINHA et al, 2020; VARDHAN and SAHOO, 2020.
rutin	M^{pro}	5	ALAMRI et al, 2020; DAS et al, 2020; GOSH et al, 2020; HU et al, 2020; XU et al, 2020.

N - number of articles retrieved; M^{pro} - main protein; ACE2 - angiotensin-converting enzyme type II ; RdRp - RNA polymerase RNA dependent; S protein - Spike protein

Between SARS-CoV-2 molecules most studied by this technique were a) the Main protease (M^{pro}) that acts indirectly through the cleavage of polyproteins in smaller structures (He et al., 2020); the external Spike (S) protein related to the virus entry events in the host cell (Huang et al., 2020); and the RNA polymerase RNA dependent (RpRd), an important enzyme for viral RNA synthesis (Aftab et al., 2020).

Besides the molecules mentioned above, some human receptors have also been considered as the target of antiviral action in *in silico* analysis. Here, we highlight the angiotensin-converting enzyme type II (ACE2), a specific cellular receptor that has presented a direct relation with SARS-CoV-2 infection (AZIM et al., 2020; MAURYA et al., 2020; BALMEH et al., 2020).

From the analyzed results, the multiple action of the substances hesperidin and glycyrrhizic acid on both the S (Sinha et al., 2020) and the RpRd proteins of the virus and on the ACE receptor stands out. On the other side, the virus M^{pro} proved to be an excellent target of antiviral therapy by natural products with amplitude of molecules with good score in the compounds sizes, ability to fit into the protein binding pocket and to reach the catalytic dyad (Mazzini et al., 2020), for example.

Another substance that draws attention is rutin. For this dietary polyphenol there are reports of a good affinity score only with M^{pro} (Das et al., 2020) and Toll-like cell receptors involved in the host's cellular inflammatory response (Hu et al., 2020). In addition, rutin has been widely used as an antioxidant in the food processing industry. Therefore, as suggested by Hu et al. (2020), it would be easy to ingest it in daily meals as well as through complex vitamin-based supplements.

5 CONCLUSION

From the systematic review carried out, it can be concluded that *in silico* studies involving products of plant origin reveal a diversity of metabolites with high antiviral potential against SARS-CoV-2.

It is noted that the molecule rutin stands out as a promising antiviral agent. It has potential to act in viral assembling, in suppressing the inflammatory process in the host, and is easily found in food products.

And, finally, the plant substances constitute an excellent alternative in the race to redirect substances with action on SARS-CoV-2, as well as other viral diseases that may arise in the future.

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