

Immunomodulation and anti-inflammatory effects of *Baccharis dracunculifolia* and Brazilian Green Propolis: A integrative literature review

Efeitos imunomoduladores e anti-inflamatórios de *Baccharis dracunculifolia* e própolis verde brasileiro: Revisão integrativa da literatura

Efectos inmunomoduladores y antiinflamatorios de *Baccharis dracunculifolia* y propóleo verde brasileño: Una revisión integrativa de la literatura

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Abstract

Inflammatory and oxidizing factors are important for the triggering of diseases such as arthritis, lupus, and currently, the serious effects of coronavirus disease (COVID-19), which has an increase in inflammatory factors during its development and, consequently, can be mitigated by the beneficial effects of *Baccharis dracunculifolia* (Bd) and Brazilian Green Propolis (BGP). A literature search through PubMed, ResearchGate and HOLLIS Harvard Library Online Catalog was performed from the date of inception until 01/07/2021. A combination of the following keywords was used: propolis and *baccharis dracunculifolia*, anti-inflammatory, antioxidant and immunomodulation. The results of inflammatory and oxidizing factors shown by the study are important for the medical field, in addition to understanding how there are numerous compounds that are not yet known and mainly due to their possible treatments for various diseases. We conclude that BD and BGP are important for the reduction of inflammatory and oxidizing factors, which can be beneficial in immunological diseases and in exorbitant inflammatory factors as observed in COVID-19.

Keywords: *Baccharis dracunculifolia*; Anti-inflammatory; Antioxidant; Immunomodulation.

Resumo

Fatores inflamatórios e oxidantes são importantes para o desencadeamento de doenças como artrite, lúpus e, atualmente, os graves efeitos da doença do coronavírus (COVID-19), que apresenta aumento de fatores inflamatórios durante seu desenvolvimento e, conseqüentemente, pode ser amenizado por os efeitos benéficos da *Baccharis dracunculifolia* (Bd) e da própolis verde brasileira (BGP). Uma pesquisa bibliográfica através do PubMed, ResearchGate e HOLLIS Harvard Library Online Catalog foi realizada desde a data de início até 01/07/2021. Foi utilizada uma combinação das seguintes palavras-chave: própolis e *baccharis dracunculifolia*, anti-inflamatório, antioxidante e imunomodulação. Os resultados dos fatores inflamatórios e oxidantes mostrados pelo estudo são importantes para a área médica, além de entender como existem inúmeros compostos que ainda não são conhecidos e principalmente devido aos seus possíveis tratamentos para diversas doenças. Concluímos que BD e BGP são

importantes para a redução de fatores inflamatórios e oxidantes, o que pode ser benéfico em doenças imunológicas e em fatores inflamatórios exorbitantes como observado na COVID-19.

Palavras-chave: Baccharis dracunculifolia; Anti-inflamatório; Antioxidante; Imuno-modulação.

Resumen

Los factores inflamatorios y oxidantes son importantes para el desencadenamiento de enfermedades como la artritis, el lupus y, actualmente, los graves efectos de la enfermedad por coronavirus (COVID-19), que tiene un aumento de los factores inflamatorios durante su desarrollo y, en consecuencia, puede ser mitigado por los efectos beneficiosos de Baccharis dracunculifolia (Bd) y Propóleo Verde Brasileño (BGP). Se realizó una búsqueda bibliográfica a través de PubMed, ResearchGate y HOLLIS Harvard Library Online Catalog desde la fecha de inicio hasta el 07/01/2021. Se utilizó una combinación de las siguientes palabras clave: propóleo y baccharis dracunculifolia, antiinflamatorio, antioxidante e inmunomodulador. Los resultados de factores inflamatorios y oxidantes que arroja el estudio son importantes para el campo médico, además de entender cómo existen numerosos compuestos que aún no se conocen y principalmente por sus posibles tratamientos para diversas enfermedades. Concluimos que BD y BGP son importantes para la reducción de factores inflamatorios y oxidantes, lo que puede ser beneficioso en enfermedades inmunológicas y en factores inflamatorios exorbitantes como se observa en COVID-19.

Palabras clave: Baccharis dracunculifolia; Anti-inflamatório; Antioxidante; Imuno-modulación.

1. Introduction

Medicinal plants currently represent the origin of 25% of the drugs used, which is due to the immense diversity of the world flora and the important therapeutic properties already marked. There are several studies carried out that contribute to the development and use of these plant species, proving therapeutic effects and enabling their use for the treatment of pathologies (Kalluf et al., 2008).

A food can be considered functional if it is considered that it can beneficially affect one or more target functions in the body, in addition to having nutritional effects, in a way that is both relevant for well-being and health and for risk reduction of a disease (Branco et al., 2012).

Food must have beneficial constituents in addition to the basic nutritional elements, being used in the conventional way in diets, as it has beneficial effects on regular bodily functions, helping to protect against diseases such as: diabetes, hypertension, cancer, osteoporosis and coronary artery disease (Fatehi-Hassanabad et al., 2010).

Diabetes mellitus is characterized by hyperglycemia and increased neuronal or adipose tissue inflammation, which leads the body to reduce hormonal responses. Brazilian Green Propolis (BGP) is a resin produced by honey bees mixing their waxes and saliva with exudate of botanical substances. One of the characteristics of bee propolis is that it is hard and brittle when cold and soft, flexible and very sticky when hot; therefore, it is sometimes called bee glue (Cavaltante et al., 2018). Some plants of the Baccharis genus are popularly used for different purposes and some species have already been affected as a hypoglycemic activity (Pereira and Malfatti, 2012).

The antioxidant activity of BGP is demonstrated in studies that have shown a reduction in oxidative stress markers (Moise et al., 2020; Osés et al. 2016). Inflammation occurs in response to constant exposure to environmental and endogenous stimuli as well as accidental damage. Wound healing is a dynamic and complex process of skin repair that occurs in response to an injury. Inflammation represents its first stage, followed by healing and remodeling (Brandenburg et al, 2020).

2. Methodology

The type of study chosen for this research was developed by an integrative literature review related to the presumed theme. Therefore, the organization of the literature review is an attachment to the main existing knowledge bases (Torraco, 2016).

A literature search through PubMed, ResearchGate and HOLLIS Harvard Library Online Catalog was performed from

the date of inception until 31/08/2021.

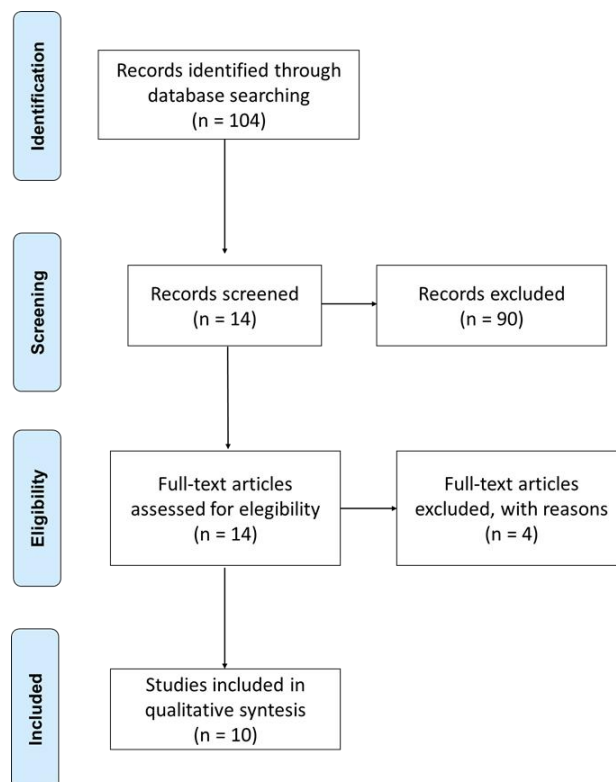
After searching for the articles, the research followed the analysis stage for inclusion and exclusion of the selected materials. Firstly, the titles were analyzed, followed by the analysis of abstracts to verify which articles met the intention of studying the research. After that, the articles in total that had interconnection between the chosen keywords were analyzed. We used the keywords for the research: propolis AND anti-diabetic AND anti-inflammatory.

The analysis of the collected data was expressed in a discursive manner and illustrated utilizing tables. The table contains the title, author's name, objectives, and conclusion of each article. A figure of the knowledge design acquired by schemes was organized in a summarized way and analyzed according to the theoretical framework.

From the searches carried out in the referred databases, 104 articles were found described according to the keywords. According to the digitized titles, ten articles were separated for reading the corresponding summary.

After reading the abstracts, zero articles were discarded because they did not have a central coherence with the theme. Ten articles were selected for a complete and coherent reading for the development of this review.

Figure 1. Flow Diagram.



Source: Authors.

3. Results and Discussion

In the Table 1 lists 10 articles in which they analyzed the exercise link in dopamine and thyroid hormones function.

Figure 1. Selected articles.

Author	Title	Results	Conclusion
<i>Brandenburg et al., 2020.</i>	Baccharis dracunculifolia (Asteraceae) essential oil displays anti-inflammatory activity in models of skin inflammation	B. dracunculifolia essential oil (BdEO) was obtained from leaves and it was analyzed with Gas Chromatograph. Topical anti-inflammatory activity of BdEO (0.1, 0.3 and 1.0 mg/ear) was evaluated in Arachidonic Acid or TPA-induced acute and chronic skin inflammation in mice. Parameters such edema, cell migration and keratinocytes proliferation were evaluated. In addition, safety and a possible mechanism of action for BdEO essential oil were also investigated.	BdEO inhibited inflammatory parameters in skin inflammation: ↓ edema formation (61 at 81%) vs dexamethasone (96%). ↓ cellular influx into the inflamed tissue (64 at 82%) vs dexamethasone (98%) ↓keratinocytes hyperproliferation. (82%) vs dexamethasone (98%) anti-inflammatory effect through a corticosteroid pathway no local or systemic side effects
<i>Figueiredo-Rinhel et al., 2017.</i>	Baccharis dracunculifolia DC (Asteraceae) selectively modulates the effector functions of human neutrophils	In-vitro assays based on chemiluminescence, spectrophotometry, flow cytometry and polarimetry were used, as well as docking calculations.	BdE (1) inhibited NADPH oxidase (60 at 80%) and myeloperoxidase activity (40 at 80%); (2) scavenged H ₂ O ₂ (40 at 80%) and HOCl (20 at 80%); (3) weakly inhibited phagocytosis (18;5%)
<i>Figueiredo-Rinhel, 2018.</i>	Incorporation of Baccharis dracunculifolia DC (Asteraceae) leaf extract into phosphatidylcholine-cholesterol liposomes improves its anti-inflammatory effect in vivo	Prepared biocompatible liposomes of soya phosphatidylcholine and cholesterol with low diameter, homogeneous size distribution, and neutral surface charge. Free BdE decreased joint swelling, total leucocyte and neutrophil infiltration, and the synovial levels of tumour necrosis factor- α and interleukins 6 and 1 β . Incorporation of BdE into liposomes preserved its capacity to inhibit the neutrophil superoxide anion and total reactive oxygen species generation, and improved its anti-inflammatory effect in vivo by decreasing the effective BdE dose by nearly sixfold.	Liposomal BdE and caffeic acid suppressed O ₂ ⁻ generation (↓54.6%).and ROS generation in human neutrophils (↓59.1%) BdE improves anti-inflammatory effect. TNF- α (↓30%) IL-6 (↓26%) IL-1 β (↓22%)
<i>Bachiega et al., 2013.</i>	Immunomodulatory/anti-inflammatory effects of Baccharis dracunculifolia leaves	Cells were incubated with Bd and Ca, and the inhibitory concentrations were tested before or after macrophages challenge with LPS. Bd and Ca stimulated IL-1b and inhibited IL-6 and IL-10 production. In LPS-challenge protocols, Bd prevented LPS action either before or after LPS challenge, whereas Ca prevented LPS effects only after LPS addition.	Bd leaves and Ca showed anti-inflammatory effects in macrophages through inhibiting cytokine production. ↓IL-1b ↓IL-6 ↑IL-10 ↓NF-kB
<i>Figueiredo-Rinhel et al., 2013.</i>	Inhibition of the human neutrophil oxidative metabolism by Baccharis dracunculifolia DC (Asteraceae) is influenced by seasonality and the ratio of caffeic acid to other phenolic compounds	The extracts were obtained from leaf samples collected monthly during one year. The superoxide anion and total ROS generation were assessed by the lucigenin (CL-luc)- and luminol (CL-lum)-enhanced chemiluminescence assays.	- superoxide anion - total ROS production
<i>Kitamura et al., 2018.</i>	Brazilian propolis ethanol extract and its component kaempferol induce myeloid-derived suppressor cells from macrophages of mice in vivo and in vitro	Ethanol extract of Brazilian propolis (PEE; 100 mg/kg i.p., twice a week) was injected into lean or high fat fed obese C57BL/6 mice or C57BL/6 ob/ob mice for one month. Subsequently, immune cells in visceral adipose tissue and the peritoneal cavity were monitored using FACS analysis. Isolated macrophages and the macrophage like cell line J774.1 were treated with PEE and its constituent components, and the expression of immune suppressive myeloid markers were evaluated. Finally, we injected one of the identified compounds, kaempferol, into C57BL/6 mice and performed FACS analysis on the adipose tissue.	Intraperitoneal treatment of propolis induces myeloid-derived suppressor cells (MDSCs) in visceral adipose tissue.

Miranda et al., 2019.	Hydroalcoholic extract of Brazilian green propolis modulates inflammatory process in mice submitted to a low protein diet	subcutaneous implantation of sponge disks as an inflammatory model and the animals were distributed in the following groups: standard protein diet (12% protein content), control treatment; standard protein diet, propolis treatment; low-protein diet (3% protein content), control treatment; low-protein diet, propolis treatment. Propolis was given daily at a dose of 500 mg/kg (p.o.) during a period of 7 or 15 days.	Propolis reduced the inflammatory infiltrate (↓8%).
Guimarães et al., 2012.	Baccharis dracunculifolia, the main source of green propolis, exhibits potent antioxidant activity and prevents oxidative mitochondrial damage	Bd was prepared by fractionated percolation using propylene glycol as solvent. The total phenols and flavonoids, which are substances with recognized antioxidant action, were quantified in GEBd and the phytochemical analysis was carried out by HPLC.	DPPH radicals superoxide anions H ₂ O ₂ generation lipid hydroperoxides (LOOH).
Veiga et al., 2017.	Artepillin C and phenolic compounds responsible for antimicrobial and antioxidant activity of green propolis and Baccharis dracunculifolia DC	The amount of Artepillin C in different extracts was determined by high performance liquid chromatography analysis. Minimum inhibitory concentration 90 (MIC ₉₀) was determined using 40 isolates of <i>S. aureus</i> inoculated in Mueller–Hinton agar culture medium containing the green propolis and <i>B. dracunculifolia</i> DC extracts.	↓DPPH
Bittencourt et al., 2015.	Metabolite profiling, antioxidant and antibacterial activities of Brazilian propolis: Use of correlation and multivariate analyses to identify potential bioactive compounds	Gas chromatography–mass spectrometry was applied for chemical profiling of propolis extracts. Antibacterial activity was assessed against <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , and <i>Micrococcus luteus</i> . Correlation and multivariate statistical analysis were used to identify potential bioactive compounds in the extracts.	Total phenolic compounds and methyl retinoate showed a positive correlation with the antioxidant capacity

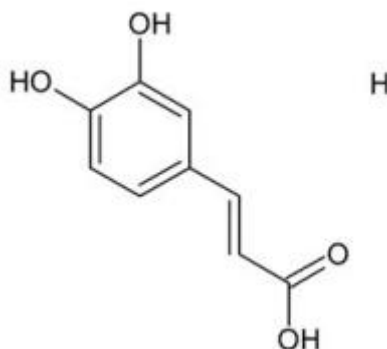
Source: Authors.

BGP treatment for inflammatory disease

Some chronic inflammatory diseases, in particular those mediated by immune complexes, are associated with intense recruitment and activation of neutrophils in tissues. Neutrophils play an important role in host defense and in regulating innate and adaptive immune responses. Once at the site of inflammation, activated neutrophils secrete a variety of pro-inflammatory cytokines, eicosanoids and chemokine and release a large amount of ROS and photolytic enzymes that can damage tissue and favor the development of pain and target organ deformity. Rheumatoid arthritis, glomerulonephritis and vasculitis are some examples of inflammatory diseases mediated by the exacerbated immune system, affecting a significant percentage of the human population and decreasing quality of life and life expectancy (Kolaczowska and Kubek, 2013; Nemeth and Mocsai et al., 2012).

Bd has anti-inflammatory and antioxidant effects due to the amount of compounds in its constitution. One of the main compounds is known as caffeic acid (3,4-dihydroxy cinnamic acid), characterized by HPLC. Caffeic acid is a phenolic acid that has the property of binding itself to other compounds, which makes it with antioxidant capacity and activity. We can see the chemical structure of caffeic acid in the Figure 2.

Figure 2. Chemical structure of caffeic acid isolated from the leaves of *Baccharis dracunculifolia*.



Source: Authors.

Natural products have received great attention in recent years due to the promising anti-inflammatory, immunomodulatory and antioxidant activity of extracts from plants and marine organisms and their isolated compounds. Some of the leading pharmaceutical and research institutions have shown growing interest in researching plants to discover medically useful compounds.

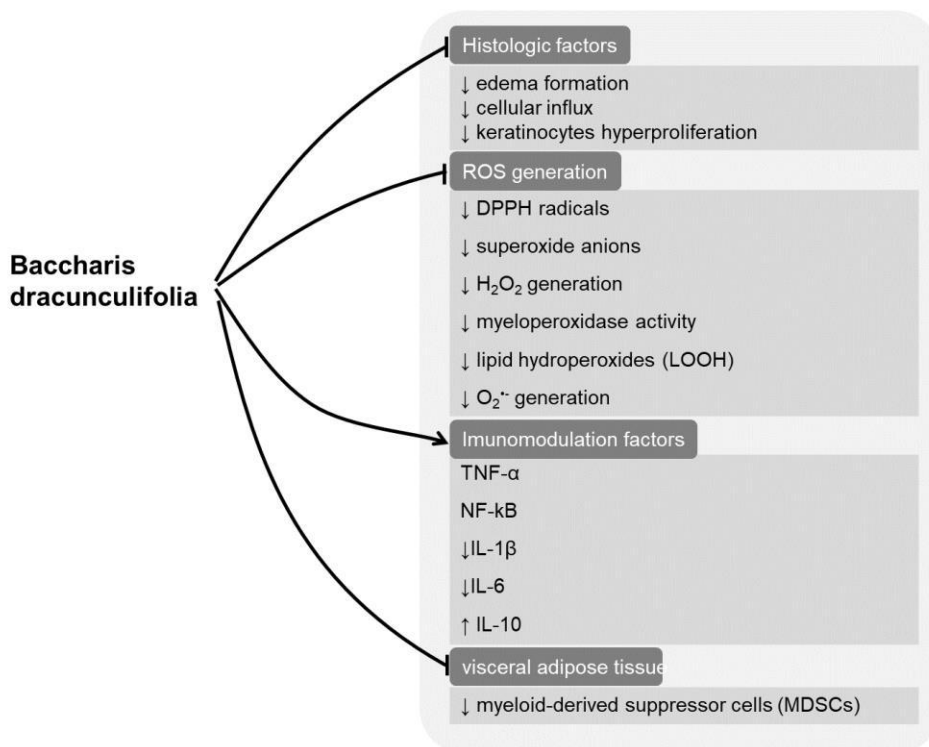
Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus, triggering a series of exacerbated immune responses in the body. This excess response can result in tissue damage, which is seen in the lung of the patient hospitalized with COVID-19 (Gallelli, 2020).

One study was interested in researching the potential antiviral effects of curcumin that may be useful for researchers to further investigate the potency of curcumin against the emerging new infection of SARS-CoV-2 (Zahedipour *et al.*, 2020). Curcumin's ability to modulate a wide range of molecular targets makes it a suitable candidate for controlling coronavirus infection. Thus, a natural product based on curcumin, with anti-oxidant effects, becomes interesting for the treatment of inflammatory diseases.

Studies have shown immunomodulatory effects of BGP by inhibiting the activity of cyclooxygenase-2 and activating the nuclear factor κ B (NF κ B), also modulating the production of cytokines by macrophages and suppressing the effector functions of human neutrophils (Campos *et al.*, 2016).

Such compounds seem to be responsible for the biological activities shared by BGP, like antioxidant, anti-carcinogenic, anti-inflammatory and immunomodulation, observed in Figure 3 (Beserra *et al.*, 2020; Ferreira *et al.*, 2021).

Figure 3. Immunomodulatory and anti-inflammatory effects of *Baccharis dracunculifolia*



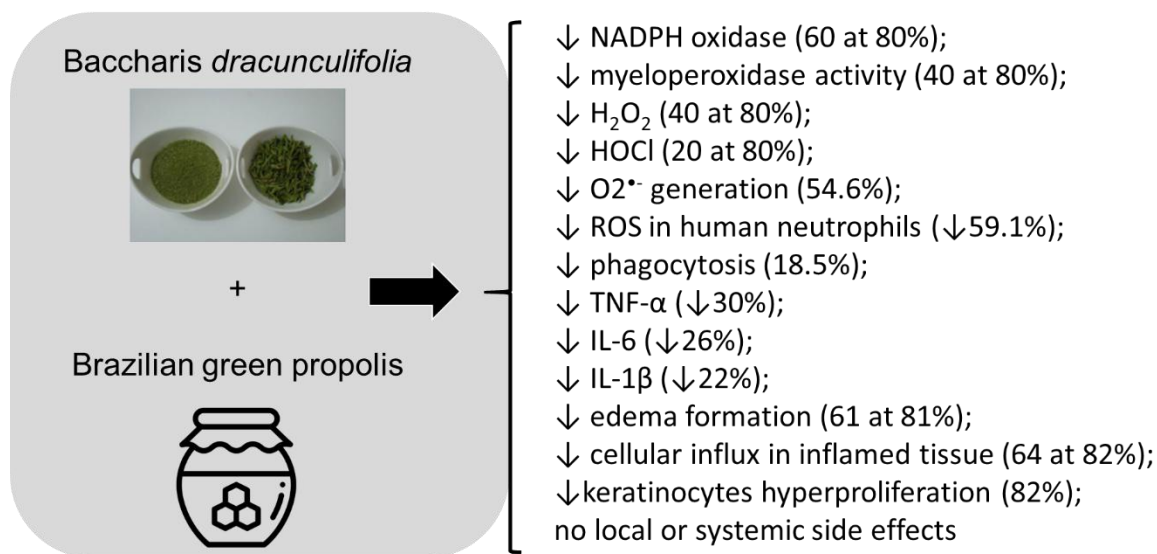
Source: Authors.

The *Baccharis dracunculifolia*, a plant component of BGP, have antioxidant activities were studied by *Hocayen et al.*, (2016), who performed extractions with different solvents (ethanol, methanol and acetone) and presented positive results in all cases, especially in methanol solvent one. The mechanism associated to hyperglycemia and diabetes is complex, but it its being related to oxidative stress and ROS (Lushchak, 2014; Yan, 2014).

Many compounds may be responsible for the antioxidant and anti-inflammatory activities related to *Baccharis* gender, such as: polyphenolics, among them the phenolic acids, coumarins and flavonoids (*Abad and Bermejo, 2007*). Studies have been relating the production of ROS with diabetes *mellitus* observing the fact that lipid peroxidation biomarkers increase, while endogenous antioxidant syntheses decrease (*França et al., 2013*). Thus, a way of avoiding the effects related to ROS in the organism is the treatment with compounds that possess antioxidant activities. Once damages caused by free radicals may be delayed by antioxidants, that react rapidly, even before the radicals could act in the organism (*Fatehi-Hassanabad et al., 2010*).

Thus, it is observed that BD and BGP have a strong influence on inflammatory and oxidative factors. These effects show the link between the effects of products together with their compounds for the treatment of diseases that affect a large part of training today. In addition, a situation that can be improved is one of the most serious diseases that affect humans today, COVID-19, which has an increase in inflammatory during its development and, consequently, can be mitigated by the beneficial effects of BD and BGP. In figure 4, showed main findings on Bd and BGP on inflammatory and oxidant factors.

Figure 4. Main findings on Bd and BGP on inflammatory and oxidant factors.



Source: Authors.

The results of inflammatory and oxidizing factors in the study are important for the medical field, in addition to understanding how there are numerous compounds that are not known yet and mainly due to their possible methods in various diseases.

4. Conclusion

We conclude that BD and BGP are important for the reduction of inflammatory and oxidizing factors which may be beneficial to immunological diseases and exorbitant inflammatory factors as observed in COVID-19.

We understand that new ones are needed to prove the effectiveness of the treatments granted, but the treatment through BD and BGP is fundamental studies so that we can have new scientific evidence and consequently improve the treatment of various diseases that are affecting all people day after day.

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