

The Intestinal Perspective of COVID-19: *NOS2* and *AOC1* Genes as Epidemiological Factors, and a Homeopathic Approach to their Functional Improvement

Á. Millán Macías¹

¹ School of Integrative Veterinary Medicine (Escuela de Medicina Veterinaria Integrativa, EMVI), Barcelona, Spain

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Address for correspondence Álvaro Millán Macías, DVM, CVA, Vet natura Veterinary Centre, Jerónimo Hernández Street, Number 22, Seville 41003, Spain
(e-mail: alvaro.millan.macias.81@gmail.com).

Abstract

The new pandemic disease COVID-19 has wreaked havoc worldwide. Its infectious agent, SARS-CoV-2, uses two key human enzymes called angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) to invade body cells. The first one is encoded by the *ACE2* gene and the second by the *TMPRSS2* gene. Both have an outstanding expression of RNA and proteins in the small intestine compared with other tissues. This prominent location may be related to the main entry route of SARS-CoV-2 into the organism. In the process of infection, two other genes can play a fundamental role: *NOS2*, which expresses inducible nitric oxide synthase (iNOS), and *AOC1*, which encodes diamine oxidase (DAO). Both also highlight in the small intestine and are involved in polyamine metabolism. These biogenic amines are important for viral replication, being enhanced when *NOS2* and *AOC1* genes are downregulated. In addition, *NOS2* shows a negative correlation with ACE2 and TMPRSS2, while nondegraded histamine by DAO can lead to an upregulation of both genes on which the virus depends. Taken together, these data suggest that inhibition or underexpression of *NOS2* and *AOC1* determines the susceptibility to get sick, increasing the risk of infection. On the other hand, a therapeutic approach to the disease could be made with homeopathic medicines. Experiments show the remedies' ability to stimulate gene and protein expression, but a correlation between the symptoms of each drug and these expressions has not yet been established. Here an analysis of the pathogenesis of *Silicea terra* and *Arsenicum album* supported on the scientific literature is done. The objective is to propose a theory about their relationship with key genes whose protein expressed in deficiency can give rise to the chain of events that imbalance the internal environment (homeostasis) and allow the development of symptoms. *Silicea* seems to be related to *NOS2* (gene)/iNOS (protein) and *Arsenicum* with *AOC1* (gene)/DAO (protein), being necessary to carry out studies to corroborate these links. Therefore, the aim of this article is to show the importance of *NOS2* and *AOC1* genes in the development of COVID-19 and to propose a line of investigation to evaluate if homeopathy can improve their protein expression.

Keywords

- COVID-19
- ACE2
- TMPRSS2
- NOS2
- AOC1
- *Silicea terra*
- *Arsenicum album*

Introduction

SARS-CoV-2 is the causal agent of coronavirus disease 19 (COVID-19).¹ It has been evidenced that the virus needs angiotensin-converting enzyme 2 (ACE2), which allows the conversion of angiotensin-II into angiotensin (1–7),² to enter the human cells with its spike (S) protein. SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming.³ Other associated proteases for SARS-CoV-2 entry into cells are cathepsins B and L, which are encoded by the respective *CTSB* and *CTSL* genes,⁴ but they are not indispensable as TMPRSS2.³ Although the disease is primarily a severe acute respiratory syndrome (SARS) with symptoms ranging from mild influenza to critical pneumonia, the presentation of intestinal disturbances as the first manifestation of the disease has been reported.⁵

Approaching the illness from the patient is a good way to understand his susceptibility. *ACE2* and *TMPRSS2* are genes with an outstanding expression of RNA and proteins in the small intestine compared with the rest of the body tissues,⁶ even more than in the kidney and large intestine where virus replication can also take place according to the pathophysiological model that will be discussed later. *ACE2* attracts researchers' attention because the virus needs to enter the cells.³ Interestingly, *ACE2* has a negative correlation with the *NOS2* gene, which encodes inducible nitric oxide synthase (iNOS; producer of nitric oxide) and whose mRNA is enhanced in the same intestinal tissue.⁶ Said correlation has been observed in experiments with angiotensin II, which is produced by *ACE1* from angiotensin I. Angiotensin II exerts a proinflammatory response in vascular smooth muscle cells through the activation of NADPH oxidase and nuclear factor (NF)- κ B, and the induction of nitric oxide from *NOS2*.⁷ Upregulation of *ACE2* decreases the expression of the previous ones because angiotensin (1–7) reduces NADPH oxidase activity, prevents NF- κ B activation, and hence inhibits the induction of iNOS.⁷ Although *NOS2* modulates inflammatory reactions and the immune response,⁸ its frequent involvement in the pathophysiology of inflammation⁹ makes iNO a target for pharmacological inhibition.^{7,10} In addition, the vascular protective activity of *ACE2*^{11,12} invites to its pharmacological stimulation, which can result in a combined downregulation of *NOS2* and upregulation of *ACE2* as is pointed out in the referred study.⁷

AOC1 gene encodes diamine oxidase (DAO; before histaminase). This is a copper-containing enzyme with high expression in the small intestine. Its function is to deaminate biogenic amines proceeding from food.¹³ Its main substrate is peripheral and extracellular histamine, in contrast with the central nervous and intracellular degrading enzyme histamine N-methyl transferase (HNMT).¹⁴ However, DAO also catabolizes 1-methylhistamine, agmatine, cadaverine, and the so-called polyamines putrescine, spermidine, and spermine.¹⁵ Polyamines are necessary for viral replication¹⁶; so, the importance of the peripheral histaminase is that it plays a role in regulating the amount of polyamines in the body. Histamine should also be regulated, assuming a modulation in signalling for a proper immune response, which will all together reduce the risk of infections.¹⁷

As iNOS and DAO are involved in the metabolism of polyamines,^{18,19} this article aims to build a pathophysiological model for COVID-19 based on the relationship between the *ACE*, *ACE2*, *TMPRSS2*, *NOS2*, and *AOC1* genes. For this, the different sections of the article discuss the following issues:

- The biological basis for the development of the disease from the underexpression or inhibition of the *NOS2* gene or the *AOC1* gene, and the genetic and environmental factors that favour the said functional deficiencies.
- The common physiological characteristics of *NOS2* and *AOC1* to understand the infection beyond polyamines metabolism.
- The pathophysiology on a genomic scale model derived from the previous points, where the interferon (IFN) family can make the difference between the *NOS2* and *AOC1* genes in relation to SARS-CoV-2 infection.
- The homeopathic medicines whose pathogenesis show a correlation with the disabilities of iNO and DAO, and would serve to treat COVID-19 along with basic measures (diet, healthy habits and so on).

Section 1

The Importance of GENREs, Polymorphisms, Epigenetics and Environmental Factors that Interact with *NOS2* and *AOC1* or Their End Products for the Development of Infections after Gene Underexpression or Inhibition (Functional Deficiency)

Genome-scale metabolic reconstructions (GENREs) constitute a fundamental tool for understanding physiology and biochemistry through gene and protein expression. This allows us to understand the function of the human body and other living organisms for which there are GENREs studies.²⁰ These investigations facilitate the understanding of a protein function by analysing the tissues of the body where the gene that encodes it is expressed. Thus, the development of a disease can be explained by building the process from the organ or cells where such RNA and protein highlight. In summary, it helps establish pathogenesis and pathophysiology.

The construction of the present disease development model begins with the proposition of the existence of a basic or primary functional deficiency, which would correspond to one of the *NOS2* or *AOC1* genes and which would result in a state of inhibition, blockade or underexpression that leads to the functional disability of iNOS or DAO. This approach results from the combination between the perspective of the disease as a deficiency state in traditional Chinese medicine²¹ and the unicist homeopathic medical current of assigning a single ultra-diluted remedy to the patient to resolve all his symptoms.²² In the author's experience, the fusion of said therapeutic systems, already reflected in medical manuals,^{23,24} improves clinical efficacy because it helps diagnose based on a better understanding of the most probable way in which pathological processes should happen. In the last section of the article about the homeopathic treatment proposed to fight coronavirus infection, information on how to establish the relationship of the drugs with the genes to be stimulated will be expanded.

Continuing with the explanations, since Dr. Samuel Hahnemann laid the foundations of homeopathy, a chronic disease is a pathological condition which results from a previous state of weakness. Such debility constitutes a diathesis or predisposition to get sick in a certain way.²⁵ This susceptibility makes possible the development of acute processes, because the sensitivity to environmental factors is increased. The concept is brightly summarized in paragraph 31 of the *Organon*²⁶ and deeply explained in Hahnemann's *Treatise of Chronic Diseases*, establishing the relationship between the constitutional weakness and the most ancient infectious miasma called Psora.²⁷ In the same line, Dr. James Tyler Kent tries to clear in his *Homeopathic Philosophy* how the complex and contagious psoric disease has been able to cause the general susceptibility of the human being to develop sickness in multiple ways since ancient times. For this famous homeopath, the constitutional weakness is the result of bad habits and unhealthy lifestyles.²⁸ Although he did not try to bind science and religion, some people link his statements to the original sin.²⁹ Time has proved Dr. Tyler Kent was right, as biologist Richard Dawkins explains in his famous book *The Selfish Gene* that memes are the cultural and educational factors that influence genetic inheritance.³⁰ Taking all these together and considering that all body functions are regulated by proteins,³¹ the transition from the physiological state to the pathological condition can be supported by a preexisting functional deficiency in terms of downregulated genes that result in less mRNA and protein expression. As homeostasis is a state of balance,³² its disturbance in the form of protein downregulation is usually accompanied by an overexpression of other substances as compensatory mechanism that take part in the clinical picture. In the case of *NOS2*, iNOS inhibition results in upregulation of arginase pathway due to substrate competition,³³ while *AOC1/DAO* suppression leads to an increase in biogenic amines bioavailability (mainly histamine and polyamines).³⁴

Reached this point, how a specific functional deficiency develops? The downregulation of RNA and protein expression for a certain gene is related to an essential biological concept: the phenotype is the sum of the genotype and the environment.^{35,36} As we have a unique DNA, the way to get sick is also individual.³⁷ Therefore, genetic and environmental factors determine functional deficiencies. The main genetic ones that define the idiosyncrasy of diseases are gene polymorphisms and epigenetic agents.^{38,39} Polymorphisms are little changes in the sequence of nucleotides that can modify the functionality of the gene promoting or reducing its activity, although there can also exist structural alterations without influence in the function.⁴⁰ Epigenetic agents are environmental factors, such as DNA binding substances or climatic variables, that also modulates gene expression through its downregulation or upregulation.⁴¹ Without going into technical aspects, both genetic factors are the basis of evolution and condition of health and disease creating advantages, susceptibilities or predispositions depending on the circumstances.⁴²

There are studies on *NOS2* polymorphisms in terms of overexpression and underexpression. Upregulation of promot-

er regions with a pathological increase of nitric oxide has been seen in diseases like asthma, rheumatoid arthritis, cardiovascular injuries, and cancer.⁴³ On the other hand, and favouring the purpose of this article, iNOS-downregulation polymorphisms alter the protecting role of iNO against infectious diseases, such as tuberculosis, hepatitis C and malaria.⁴³ Researches about these genetic variabilities reveal their existence or absence according to racial type,⁴³ which can be used to understand population morbidity and mortality. Regarding epigenetics for *NOS2*, examples of positive regulation of iNO are hypomethylation⁴⁴ and phosphorylation,⁴⁵ while negative regulation occurs by hypermethylation,⁴⁶ ubiquitylation,⁴⁷ SUMOylating⁴⁸ and, in relation to macrophages competency against infections, acetylation.^{49,50} Single nucleotide polymorphism (SNP) is the variant for *AOC1/DAO* deficiency that explains the so-called disease histamine intolerance.⁵¹ Its clinical picture is constituted by several symptoms mediated by histamine receptors (H1R, H2R, H3R, H4R), among which are respiratory disturbances such as congestion of the nose, rhinorrhoea, sneezing, cough, bronchoconstriction and dyspnoea.⁵²

Although susceptibility to getting sick (diathesis) is genetic, polymorphisms and epigenetic interact with environmental factors to cause disease.⁵³ **Tables 1 and 2** list some of these factors that can inhibit iNOS and DAO in different ways. Some comments on the referenced studies have been added to highlight their importance. Perhaps, those which are common for both enzymes could be more relevant for coronavirus infection due to double protein subexpression. This is not an attack against the cited factors since a varied selection has been made to reflect the possible abuses in a global consumer society. Therefore, the problem is the quantity, sum and combination of them. Surely the reader can think in many more, whether from the West, the East, natural medicine or conventional medicine. Another detail regarding the tables is the way in which the environmental factors affect gene expression. The regulation of *NOS2* is mainly transcriptional and post-transcriptional,⁵⁴ although it can also be translational⁵⁵ and post-translational.⁵⁶ On the other hand, DAO activity can take place without expression of the *AOC1* gene. The enzyme is stored in plasma membrane-associated vesicular structures of epithelial cells and can be activated if any stimulus causes the release of histamine.⁵⁷ For this reason, environmental factors for *AOC1/DAO* are enzymatic inhibitors or enhancers of the bioavailability of biogenic amines. An example of increased concentration of histamine and polyamines in the body is spoiled food poisoning. In this case, a polymorphism of histamine intolerance is not essential to develop symptoms since DAO and histamine N-methyltransferase (HNMT) cannot process as many substrates without injury.⁵⁸ However, the combination of factors of **Table 2** could generate an acquired intolerance to biogenic amines that ends up leaving a genetic footprint over time, that is, affecting the expression of the *AOC1* gene. In the case of *NOS2*, metabolites of the arginase pathway that competitively inhibit iNO, including biogenic amines, are also present in **Table 1**. In this sense, the gene shares problem with *AOC1*: the epigenetic character of polyamines.⁵⁹

Table 1 Environmental factors that can inhibit NOS2/iNOS

Environmental factors for NOS2 Gene—iNOS	Studies (reference number at the end of the comments)
Alcohol ethanol (dose-dependent manner)	- Inhibition of iNOS mRNA due to blockade of NF-κB suppresses the activation of STAT-1⁶⁰ - Inhibition of iNOS at transcriptional and posttranscriptional level in rat lung alveolar macrophages in vivo when stimulated by LPS and DB-cAMP⁶¹ - Inhibition of iNOS mRNA expression induced by IL-1β in isolated rat superior mesenteric arteries⁶²
Nonsteroidal anti-inflammatory drugs (NSAIDs; dose-dependent manner)	- Acetylsalicylic acid, ibuprofen and its analogues inhibit cytokines, LPS or IL-1β induced iNOS at the transcriptional level, stopping the activation of the NF-κB. Examples of these evidences for aspirin are experiments with human endothelial progenitor cells,⁶³ ovarian rat in vitro,⁶⁴ bovine vascular smooth muscle cells,⁶⁵ rat cardiac fibroblasts,⁶⁶ and mouse hepatocytes and macrophages RAW 264.7.⁶⁷ Studies for ibuprofen and analogues are the last one,⁶⁷ rat cerebellar glial cells⁶⁸ and rabbit articular chondrocytes⁶⁹
Corticosteroids (dose-dependent manner)	- Hydrocortisone and dexamethasone decrease iNOS-dependent NO production by destabilizing iNOS mRNA in LPS and/or IFN-γ-treated cells by a mechanism that requires de novo protein synthesis in porcine vascular endothelial cells⁷⁰ and murine macrophages J774.⁷¹ Glucocorticoids can also regulate cytokines-activated iNOS and NO production limiting cofactor tetrahydrobiopterin (BH4) and substrate L-arginine availability⁷²
Antibiotics (dose-dependent manner)	- Tetracyclines doxycycline and CMT-3 increase iNOS mRNA degradation and decrease iNOS protein expression and NO production in LPS-stimulated murine macrophages⁷³ - Macrolides clarithromycin and azithromycin inhibit NO production and iNOS mRNA and protein expression in rat spinal cord and mononuclear cells culture in vivo and in vitro⁷⁴ - Polymyxin B blocks iNOS production in murine macrophages RAW 264.7 exposed to IFN-γ and LPS⁷⁵
Zinc (dose-dependent manner; to consider for its presence in supplements, enriched food and as an excipient in medications ⁷⁶)	- Downregulation of iNOS mRNA and protein expression, and reduction of cytokine-mediated activation of the iNOS promoter. Zinc-mediated regulation of iNOS expression is due to inhibition of NF-κB transactivation activity in rat aorta endothelial cells⁷⁷
Jeju plants (dose-dependent manner; to consider for their use as phytotherapeutic in traditional oriental medicines ⁷⁸)	- Inhibition of NO production in LPS-activated murine macrophages RAW 264.7. Among the 260 kinds of plant extract tested, 122 showed potent inhibitory activity toward NO production. Plants such as <i>Malus sieboldii</i>, <i>Vaccinium oldhamii</i>, <i>Corylus halleasanensis</i>, <i>Carpinus laxiflora</i>, <i>Styrax obassia</i> and <i>Securinega suffruticosa</i> had the most potent inhibition⁷⁹
Artemisia plants (dose-dependent manner; to consider for their use as phytotherapeutic in natural medicine ⁸⁰)	- Suppression of iNOS by sesquiterpenes from several <i>Artemisia</i> species in LPS-stimulated murine macrophages J774A.¹⁸¹ - Inhibition of iNOS and NF-κB activation by sesquiterpene lactones such as artemisinin and parthenolide in cytokine-stimulated human astrocytoma T67 cells⁸² - Suppression of NF-κB activation, iNOS gene expression and NO production by <i>Artemisia annua</i> herba in lipopolysaccharide-stimulated murine macrophages RAW 264.7⁸³
- Food (dose-dependent manner)	- Inhibition of iNOS expression and NO production by biogenic amines (agmatine, putrescine, spermidine, spermine), which are abundant in fermented foods (sausages, anchovies, smoked products, raw milk, cheeses, yogurts, yeast sourdough, kefir, tofu, other vegetable ferments, sauces, wines, beers and alcohols in general).⁸⁴ Examples of the inhibitory effect are experiments with models of hypoxia and LPS/cytokine in murine astrocytes, microglia and RAW 264.7 cells for agmatine.^{85–87} model of LPS/cytokine in rat hepatocytes for polyamines (putrescine, spermidine, spermine)⁸⁸ and model of <i>Helicobacter pylori</i> in murine macrophages RAW 264.7 for spermine⁸⁹ - Inhibition of iNOS protein expression by extracts of eggplants species <i>Solanum melongena</i> and <i>Solanum macrocarpon</i> in murine macrophages RAW 264.7. The process is potentiated by ethanol⁹⁰ - Inhibition of iNOS at the substrate binding site by specific compounds of natural sources (berries, cherries, peanuts and milk thistle as the most important). Note that silibinin from milk thistle is used in phytotherapy⁹¹ - Inhibition of iNOS by curcumin, from turmeric, at transcriptional and posttranslational level in different cell lines^{92,93}

Abbreviations: DB-cAMP, dibutyryl cyclic AMP; IFN- γ , interferon-gamma; IL, interleukin; LPS, lipopolysaccharide; NF- κ B, nuclear transcription factor-kappa B; NO, nitric oxide; STAT-1, signal transducer and activator of transcription-1.

Notes: It has been specified in each factor that the process depends on the dose; so, it is understood that the problem is the sum and combination of factors, that is, the abuse of substances that are widely consumed in society. In fact, some studies aim to stand out the good properties of the inhibitors, because inducible nitric oxide is involved in several pathophysiological processes. Therefore, it can be deduced that what is important is the balance between biological compounds to make homeostasis possible.

Table 2 Environmental factors that can inhibit AOC1/DAO

Environmental factors for AOC1 gene—DAO	Studies (reference numbers at the end of the comments)
Alcohol ethanol (dose-dependent manner)	- Wine and other alcoholic drinks inhibit diamine oxidase and competes as a substrate for the enzyme aldehyde dehydrogenase, which is involved in the histamine catabolic pathway⁹⁴
Enzyme inhibitor drugs (dose-dependent manner)	- Antiarrhythmics (verapamil, propafenone, quinidine), antibiotics (cefuroxime, cefotiam, clavulanic acid, doxycycline, isoniazid, framycetin, pentamidine), analgesics (morphine, pethidine, nonsteroidal anti-inflammatory drugs, acetylsalicylic acid, metamizole), antidepressants/neuroleptics (amitriptyline, tranylcypromine, diazepam, MAO inhibitors, haloperidol), antiemetics/prokinetics (metoclopramide), antihistamines (promethazine, cimetidine, diphenhydramine), antihypertensive drugs (verapamil, alprenolol, diltiazem), antiinflammatories (acetaminophen), antimalarials (chloroquine), bronchodilators (aminophylline, theophylline), diuretics (furosemide, amiloride), mucolytics/expectorants (N-acetylcysteine, ambroxol), muscle relaxants (alcuronium, pancuronium, D-tubocurarine), narcotics (thiopental), local anaesthetics (prilocaine), cardiotoxic agents (dobutamine), antiseptics (acriflavine)^{52,58,95} - Among the strongest inhibitors are chloroquine, clavulanic acid, cimetidine, verapamil, D-tubocurarine, pancuronium, alcuronium, cefotiam and cefuroxime^{96,97}
Pyridoxine (vitamin B6) inactivating drugs (dose-dependent manner)	- Antihypertensive drugs (hydralazine), antibiotics (D-cycloserine, isoniazid), hormonal contraceptives (containing oestrogens).⁵⁸ - Vitamin B6, vitamin C, copper and zinc are cofactors for DAO synthesis⁹⁸
Histamine-releasing drugs (dose-dependent manner)	- Analgesics/anti-inflammatory (acetylsalicylic acid, meclofenamic acid, mefenamic acid, diclofenac, indomethacin, ketoprofen, flurbiprofen, meperidine, morphine, pethidine, metamizole, naproxen), antibiotics (D-cycloserine, pentamidine), antimalarials (chloroquine), cardiotonic agents (dobutamine), antihypertensive drugs (verapamil, alprenolol), antitussives (codeine), cytostatics (cyclophosphamide), diuretics (amiloride), iodine-containing contrast medium, anaesthetics/narcotics (mesocaine, procaine, bupivacaine, prilocaine, thiopental, barbiturates), mucolytics/expectorants (N-acetylcysteine, ambroxol), muscle relaxants (D-tubocurarine, alcuronium)^{58,95} - Histamine release can also occur in the presence of allergens (immunological stimuli) or by hyperosmolarity (glucose/sodium chloride), hypoxia, trauma, extreme temperatures, and stress (non-immunological stimuli)^{99,100}
Food (dose-dependent manner)	- All fermented food (sausages, anchovies, smoked products, raw milk, cheeses, yogurts, kefir, tofu, other vegetable ferments, sauces, wines, beers and alcohols in general) have high quantities of biogenic amines.^{58,101} The same decarboxylation reactions of bacteria used in the food industry to ferment food can spoil meals and lead to poisoning.¹⁰¹ While histamine content safety levels have been established for many foods, not all biogenic amines are typed and there is also no control over the total amount of fermented products that a person can consume without suffering harmful effects.^{58,101–103} ->Eggplant, tomato, spinach, avocado, blue fish and seafood are natural ingredients with the highest quantities of histamine. All these foods can provoke the release of histamine together with citrus fruit, tropical fruit, nuts, peanut, cocoa, pork, egg white, additives and spices^{52,58,104}

Notes: It has been specified in each factor that the process depends on the dose; so it is understood that the problem is the sum and combination of factors, that is, the abuse of substances that are widely consumed in society. This is even more important when histamine intolerance is acquired or inherited.^{52,58}

Section 2

Common Functional Characteristics and Contribution to Body Physiology and the Protection against Infections from the Small Intestine of the *NOS2* and *AOC1* Genes, Happening through Their Respective Protein End Products—Inducible Nitric Oxide Synthase/Nitric Oxide and Diamine Oxidase

The *NOS2* and *AOC1* genes encode their respective enzymes iNOS and DAO, with common functional characteristics that contribute in an essential way to body physiology and the protection against infections. From the perspective of GENREs studies, the outstanding expression of a gene and its protein end product in a tissue indicates the prominent importance of their function in that part of the body. However, minor expression of the gene and protein can happen in other type of organs and cells, pointing out their involvement in physiological processes that do not necessarily have to be related to the enriched tissue.¹⁰⁵ In this sense, an imbalance in the organism can develop after starting in the highlighting location or may occur in secondary places. This will depend on the environmental factors that cause the disease, being something well known in homeopathic medicine through the concept “disorder by (plus the stimulus that triggers the symptoms).”¹⁰⁶

Here a set of functions of iNO and DAO is discussed that have common characteristics and influence the rest of the body from the small intestine, although additional data linked to other organic systems are added. The goal is to support the pathophysiology of COVID-19 that will be discussed in the next section.

1. **Maintenance of the structure, integrity and functionality of the intestinal tract:** Proteins expressed in the intestinal epithelium to perform their functions, such as DAO and iNOS, are often used as biomarkers of the structural integrity of the organ.^{107–109} Furthermore, both DAO and iNOS regulate the absorptive function of the small intestine. On the one hand, a correlation between low serum DAO activity and carbohydrate malabsorption has been published.¹¹⁰ On the other hand, DAO controls the activity of histamine over H1R and H2R digestive receptors to guarantee that the involvement of the biogenic amine in the assimilation of lipids do not become into an aberrant signalling with muscle cramps, pain and diarrhoea.^{57,111} iNO may help in this modulating role because it has suppressive effects over histamine secreted by mucosal mast cells.¹⁰⁹ In addition, this vasodilator gas increases the permeability of the intestinal epithelial cells for nutrient absorption, while also acting as a sentinel, triggering an inflammatory defence mechanism in response to cytokines and lipopolysaccharides (LPS) to prevent harmful effects of microbial toxins or bacterial translocation.¹¹² The involvement of *NOS2* in the absorptive function of the small intestine is controversial due to its inducible character linked to immunological stimuli. But this is compatible with nutrient assimilation because the interaction of the gut with the bacterial flora

during digestion leads to the expression of cytokines. Among them we can find tumour necrosis factor- α (TNF- α), interferon-gamma (IFN- γ) and interleukin-22 (IL-22), which induce iNOS^{113,114} and increase the intestinal permeability.¹¹⁵ It is comprehensible that a proper expression of all the above for gut barrier permeability regulation, integrity and assimilative functionality depends on the balance with the intestinal microbiota.^{116,117}

2. **Influence on local and systemic protein metabolism:** For the structural integrity of the digestive system to be maintained, DAO and iNOS participate in the protein metabolism of the enterocytes and this affects the rest of the body. DAO transforms histamine into imidazole-4-acetaldehyde, which leads to alanine and glutamate metabolism when it is transformed by the enzyme aldehyde dehydrogenase into imidazole-acetic acid (IAA) and then aspartate is formed.¹¹⁸ It is usual to give IAA little anabolic value, considering that its habitual destination is elimination through urine.¹¹⁹ However, patients with DAO deficiency will have altered protein turnover due to reduced intestinal integrity and absorptive capacity,^{52,58} and this makes a metabolic route involved in body homeostasis important. Moreover, aspartate, alanine and glutamate metabolism connect to the iNO pathway.¹²⁰ When there is a deficient expression of iNOS, arginase is upregulated because it is the competitive enzyme for arginine.¹²¹ This leads to the replenishment of the common substrate through the degradation of other amino acids (glutamine, glutamate, alanine, aspartate, proline and citrulline),¹²⁰ resulting in an increase in protein catabolism similar to that of DAO deficiency.
3. **Regulation of histamine and polyamines levels and bioavailability:** It has already been commented that DAO catabolizes biogenic amines from food, but its regulatory role in this metabolic route does not end here. It has been shown that when intestinal cells produce putrescine from ornithine through the enzyme ornithine decarboxylase (ODC), the latter stimulates DAO activation.¹²² Considering that putrescine generates the polyamines spermidine and spermine with the common goal of adhering to DNA for cell proliferation or apoptosis,¹²³ the *AOC1* gene is important in limiting the activity of endogenous biogenic amines. If these are overexpressed, aberrant responses can occur, such as necrosis,¹²⁴ cancer^{125,126} and, in the present case, an advantage for viral replication.¹²⁷ To this we must add that histamine and the others have synergy and capacity to potentiate their biological effects mutually.¹²⁸ The relationship of the *NOS2* gene with the aforementioned metabolic routes is that upregulation of the arginase pathway by inhibition of iNOS allows the production of ornithine from arginine, activating ODC and forming putrescine.¹²⁰
4. **Cushion the impact of exogenous toxins over the cleansing organs and the remaining tissues:** The three great “filters” of the body (liver, kidney, lung) have DAO and iNOS activity.^{13,129} This is a second opportunity to clearance biogenic amines from the organism, while it allows to neutralise pathogens and toxic debris that overcome the

gut barrier. The problem is that an inhibition of the aforementioned enzymes in the cells with the highest expression, that is the enterocytes,⁶ supposes a significant reduction of the protection against translocation through the loss of influence in zonulin balance by DAO¹³⁰ and the reduction of tight junctions regulation by iNO.¹¹² If any of the inhibitory factors cited in **Tables 1** and **2** extend their suppressive action to the liver thanks to its close anatomic relationship with the intestinal tract, the consequences will be worse, and even more if genetic predisposition to gene underexpression exists. It is true that the body has compensatory mechanisms to metabolise exogenous biogenic amines when they are too much, but an excess from food can inhibit both histaminase enzymes DAO and HNMT and exert harmful effects on all organic systems.¹³¹

5. **Participation in neurological balance and nervous activity:** It has been suggested that iNOS can affect synaptic transmission through astrocytes in the central nervous system.¹³² Although the transcriptional induction of this nitric oxide seems to be “too slow” to modulate neuronal activity and synaptic plasticity, experiments with NOS2 knockout mice show an inadequate adaptation response to environmental stimuli.^{133,134} iNO can also react in response to infection in the brain, existing a regulatory pathway to avoid overexpression and injuries. It consists of the activation of the third possible route of arginine metabolism, different from arginase and iNOS. This one is the conversion of arginine into agmatine by arginine decarboxylase. The biogenic amine reduces the formation of nitric oxide in the form of aldehyde, for which DAO is necessary.¹³⁵ It is widely accepted that HNMT is the main catabolic enzyme for histamine in the central nervous system,¹³⁶ but DAO has protein expression in the brain⁶ and compensate HNMT if it is deficient.¹³⁷ Furthermore, an increase in the bioavailability of biogenic amines due to DAO or iNOS inhibition improves their vasoactive activity and they can reach the central nervous system in different possible ways to alter the nervous centres.^{138–142} Some of the impairments are seizures and tremors through histamine H3R receptors¹⁴³ and polyamines NMDA receptors.¹⁴⁴ Additional pro-convulsive mechanisms for NOS2 will be discussed in next sections.

6. **Contribution to cardiovascular function:** Western modern science and traditional Chinese medicine coincide in admitting the existence of a heart–intestine axis.^{145–147} This should not be uncommon when intestinal cells have a high expression of RNA and proteins for genes with end-products active in the cardiovascular system, as is the case of serotonin formed from tryptophan hydroxylase 1 (TPH1) or angiotensin II and angiotensin (1–7) produced from the respective ACE1 and ACE2.⁶ In this same sense, NOS2 and AOC1 influence circulatory physiology. iNO stimulates vascular endothelial growth factor (VEGF),¹⁴⁸ which is essential for angiogenesis that leads to tissue growth, development, and repair. This process does not only occur in response to trauma or endotoxins¹⁴⁹ but also happens in physiological conditions such as tooth erup-

tion,^{150,151} ovulation,¹⁵² and placentation.¹⁵³ For its part, DAO participates too in the establishment of the maternal-filial circulation¹⁵⁴ and constitutes a biomarker of haemorrhagic shock.¹⁵⁵ Moreover, both iNOS and DAO control the vasoactive activity of histamine, but in different ways. While the former inhibits its release from mucosal mast cells,¹⁰⁹ the latter is more important because it stops its signalling by catching the biogenic amine from H1R to H4R binding receptors.¹⁵⁶

7. **Modulation of the immune response:** iNO and DAO can have either positive and negative regulation in immune processes.^{8,157,158} While the NOS2 gene is expressed in response to mediators of inflammation, ischaemia or bacterial toxins,^{159,160} AOC1 does so in relation to histamine release by similar stimuli (in addition to non-immunological liberators).^{99,100} The biogenic amine is again in the connection between the end-products of the genes. iNO is necessary for phagocytosis by M1 macrophages, which activate lymphocytes T helper type 1 (Th1) for removing pathogens.¹⁶¹ Th1 can be upregulated by histamine binding directly to its H1R receptor or through dendritic cells type 1 (CD1), with the same classic receptor. The pathway implicates phospholipase C and NF-κB, leading to nitric oxide induction.¹⁶² DAO is essential to avoid an aberrant response due to too strong or prolonged signalling on the H1R receptor. The aforementioned ability of histamine to enhance the action of other biogenic amines connects with infectious agents that are favoured by the arginase pathway, highlighting among them hepatitis C virus, *Helicobacter pylori*, *Salmonella enterica* serovar Typhimurium, *Mycobacterium tuberculosis*, *Candida albicans*, *Leishmania* sp., *Trypanosoma cruzi*, *Trypanosoma brucei*, *Toxoplasma gondii*, *Schistosoma mansoni*, and *Giardia lamblia*. As with coronaviruses,¹⁶ polyamines act as growth factors.^{163,164} In this sense, the iNOS and DAO enzymes are important for substrate control and a proper immune response.

Section 3

Pathophysiological Model for COVID-19 on a Genomic Scale with the ACE, ACE2, TMPRSS2, NOS2 and AOC1 genes—The Interferon Family Could Make the Difference between iNOS and DAO Deficiency in SARS-CoV-2 Infection

So far, what we know is that SARS-CoV-2 depends on ACE2 and TMPRSS2 to infect epithelial cells of the airways and the gut.¹⁶⁵ To make invasion possible, other genes may play an essential role. ACE, the one that encodes the ACE,¹⁶⁶ participates in the process because ACE2 competes for its substrate angiotensin I and the end-product angiotensin II to produce angiotensin (1–9) and angiotensin (1–7), respectively.¹⁶⁷ This supposes a negative correlation between both, where the upregulation of ACE2 means the downregulation of ACE. On the other hand, TMPRSS2 seems to be enhanced by interleukin-13 (IL-13),¹⁶⁸ which is a cytokine produced by lymphocytes Th2 cells, lymphocytes B (B-cells), mast cells, eosinophils, basophils,

and alveolar macrophages (M2 cells)¹⁶⁹; so, there should be an increase in the activity of these immune cells during the infection. In addition, a recent study referring to the relationship between TMPRSS2 and IL-13 demonstrates the implication of the IFN family in the improvement of ACE2 for the virus to enter into nasal goblet secretory cells, lung type II pneumocytes, and ileal absorptive enterocytes.¹⁷⁰ A remarkably interesting extra datum from this research is that the airway epithelial cells used to evidence the positive regulation of ACE2 when the samples are cultivated with IFN- γ proceed from asthmatic patients. This pathological condition could make the difference and create a divergence between iNO and DAO in relation to the IFN family if DAO deficiency underlies the asthma (see – Figs. 2 and 3 to compare data). Therefore, the connection of all the aforementioned points together with the augmented bioavailability of polyamines for viral replication can be done through NOS2 or AOC1 gene underexpression, as we will be discussing in the following paragraphs.

The construction of the pathophysiological model for COVID-19 begins with the linkage of ACE, ACE2, TMPRSS2, NOS2 and AOC1 to specific organs. – Table 3 shows the main places of the body where the five genes and their enzymatic end-products related to SARS-CoV-2 infection have a prominent expression of RNA and proteins. Obviously, NOS2 and AOC1 are the new proposals. Consensus data come from the Human Protein Atlas version 19.⁶ Common tissues with the most prominent expression are highlighted in bold.

As can be seen, the small intestine, the large intestine and the kidney constitute key tissues which can be interpreted as three important places for viral replication, but considering that

reaching the nephrons means overcoming the enterocytes. Tissue enrichment for the five genes and their encoded enzymes is greater in the small intestine compared with the large intestine (graphics in the Human Protein Atlas version 19⁶), and for this reason the former is a more important gateway to the body for SARS-CoV-2 than the latter. Although in the Human Protein Atlas version 19 there is variability in the tissue hierarchy related to the expression of RNA and proteins, a global interpretation of the data allows to build the infectious process following the order of small intestine > large intestine > kidney.

The logical question about how the gut can be the main front door to the body for the virus when respiratory symptoms predominate in the clinical picture needs some explanations. First, we must consider the fact that gene and protein expression also occurs in other organs. The airways manifest ACE2 and TMPRSS2,¹⁷⁰ and iNOS and DAO are present in all the epithelia, not only in the intestinal one (DAO reaches mucosal surfaces through serum after AOC1 gene expression in the bowel, kidney and placenta).^{6,107,172} In all mucous membranes, the functional deficiency of both enzymes will lead to similar impairments as those that would develop in the bowel. What it is suggested here is that the outstanding abundance of all the cited genes and their enzymes in the same tissue has a significant influence on other parts of the organism, conditioning the working capacity of the remaining cells. Therefore, the more enriched the organ is, the more important it is in the function related to the expressed genes and the more responsibility it has in the associated metabolism, even in distant areas of the body (there is a reason for a tissue to express one gene more than

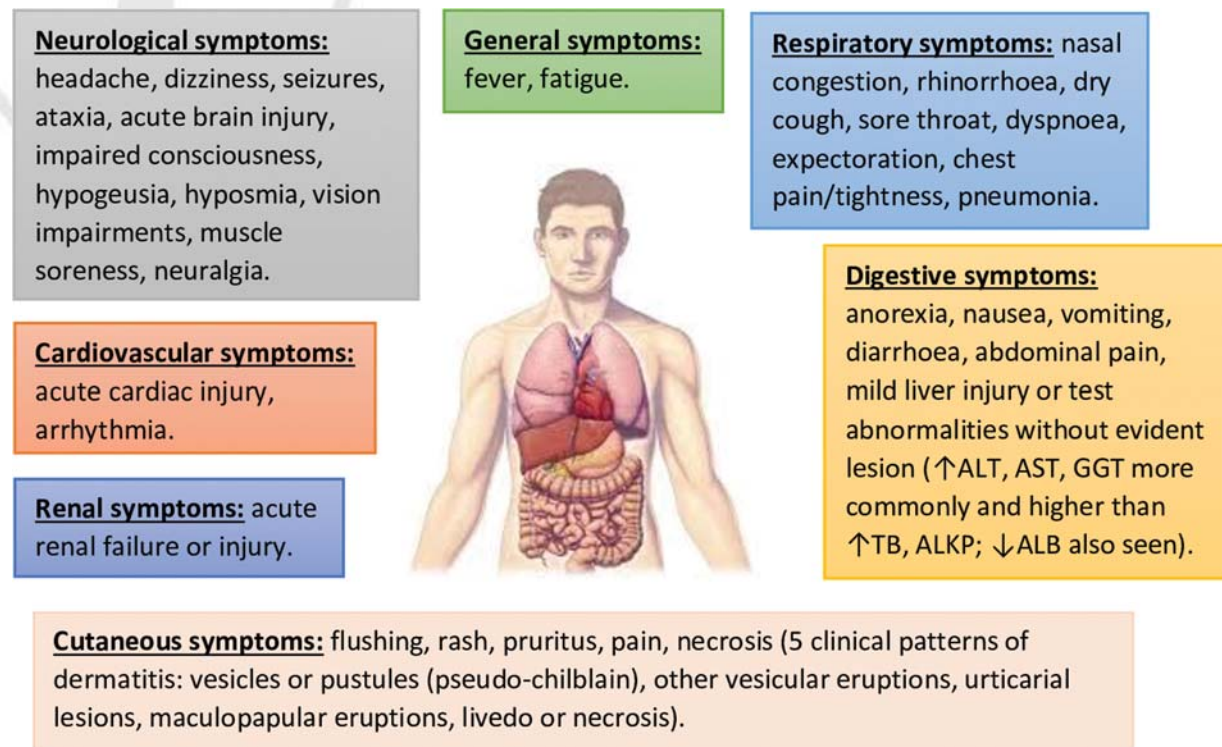


Fig. 1 Symptoms of COVID-19 recorded in scientific publications. The clinical manifestations are grouped by organic systems and their references are the following: general and respiratory symptoms^{5,177–181,188,189}; digestive symptoms^{5,177–180,188,189}; cutaneous symptoms¹⁸⁷; renal symptoms^{180,181,190,191}; cardiovascular symptoms^{181,182}; neurological symptoms.^{177,183–186}

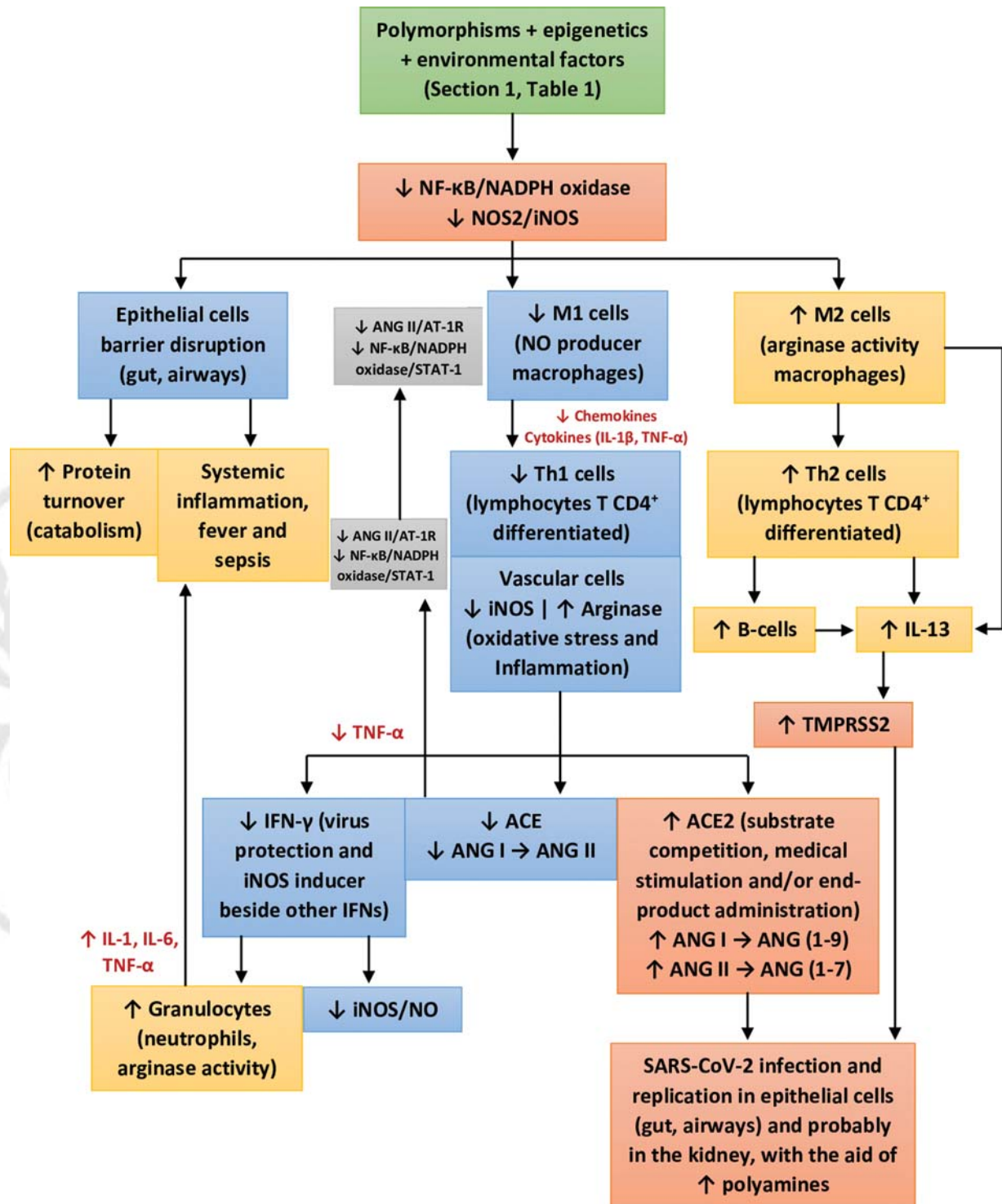


Fig. 2 Enhancement of ACE2 and TMPRSS2 for cell infection by SARS-CoV-2 beginning with the inhibition of NOS2/iNOS after exposition to certain environmental factors and with the help of gene polymorphisms and epigenetics. Green box = unique in this colour to symbolize the causes of the functional deficiency. Blue boxes = cells damaged, or genes and proteins downregulated. Grey boxes = angiotensin receptors AT-1R and related effects due to negative regulation. Orange boxes = cells, genes or proteins upregulated; derived injuries. Red boxes = key genes and associated processes that allow the development of COVID-19. Clarification: The whole process is explained in the previous paragraph.^{7,161,165,168,169,192,209–217} Abbreviations: NF-κB, nuclear transcription factor kappa B; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; STAT-1, signal transducer and activator of transcription 1; NOS2/iNOS, nitric oxide synthase isoform 2/inducible nitric oxide synthase; ANG I, angiotensin 1; ANG II, angiotensin 2; ANG (1–9), angiotensin 1–9; ANG (1–7), angiotensin 1–7; AT-1R, angiotensin 2 receptor type 1; ACE, angiotensin-converting enzyme isoform 1; ACE2, angiotensin-converting enzyme isoform 2; M1 cells, macrophages type 1; M2 cells, macrophages type 2; Th1 cells, lymphocytes T helper type 1; Th2 cells, lymphocytes T helper type 2; lymphocytes T CD4⁺, lymphocytes T expressing cluster of differentiation 4; B-cells, lymphocytes B; IL-1β, interleukin 1β; IL-1, interleukin 1; IL-6, interleukin 6; IL-13, interleukin 13; TNF-α, tumour necrosis factor-α; IFN-γ, interferon-gamma; TMPRSS2, transmembrane serine protease 2; SARS-CoV-2, severe acute respiratory syndrome by coronavirus 2.

others, even if its protein product acts on other organs).¹⁷³ In this way, the functional deficiency of *NOS2* or *AOC1* can promote the development of symptoms in any part of the body, in the case of COVID-19, when their respective enzymes iNOS and DAO fail in the small intestine. Enzymatic inhibition by substances involved in their metabolic pathways, such as the biogenic amines indicated in ►Tables 1 and 2, partly supports the hypothesis, although it is more sensible to think that the saturation of the system is produced by the interactive participation of diverse environmental factors.¹⁷⁴ In addition, we must not forget what has been said about the “disorder by” of homeopathic medicine, which explain the development of symptoms in those parts of the body where the causal factors impact and generate imbalances.¹⁰⁶ However, there will be a tendency to develop impairments in the most prominent tissue because of the cause–effect relationship and the meaning of the protein function in such organ. Thus, for example, the disability of DAO is related to decomposing protein poisoning after bacterial decarboxylation or excessive consumption of foods rich in biogenic amines due to its involvement in their metabolism within the enterocytes and in the portal circulation.^{52,58} Then, DAO deficiency is a pathological condition that is more probable to develop linked to nutrition, although a disposition to suffer symptoms in other locations with enzymatic expression should exist because inhibition will also develop elsewhere once the master organ succumbs and its buffering capacity is lost. This suggests that the pre-existence of the functional disability favours the development of coronavirus infection^{16,17} and it is in this approach to diseases, as a consequence of the previous loss of homeostasis, where the underlying medical philosophy of this study is supported. In the case of *NOS2*, iNOS disfunction does not show the side effects of an excessive amount of its substrate like the previous one, but there will also be an overexpression of polyamines and an upregulation of arginase pathway that depletes arginine.¹⁷⁵ Its replenishment at the expense of other amino acids will lead again to arginase activity because iNOS suppression will still go on and this catabolic trend in protein turnover will lie behind the immunodeficiency that precedes viral invasion.^{120,176}

The genomic-scale model continues with the relationship of COVID-19 symptoms with iNO and DAO. ►Fig. 1 summarizes the wide range of morbid manifestations reported in scientific publications, highlighting fever, fatigue and dry cough.^{5,177–187} Diarrhoea is the most common digestive disturbance^{188,189} and among those who evolve to a severe respiratory clinical picture, there is a quarter part that develops acute kidney injury.^{190,191}

According to what has been commented in Section 2, there are three main reasons to justify the prominent expression of iNOS in the bowel: regulation of intestinal wall permeability, control of microbial flora, and participation in protein metabolism of enterocytes (arginine pathway).¹⁹² Genetic and environmental factors (see ►Table 1) show *NOS2* inhibition through downregulation of NADPH oxidase, reactive oxygen species (ROS), nuclear transcription factor-kappa B (NF-κB), and signal transducer and activator

of transcription-1 (STAT-1). The result is the disturbance of the aforementioned functions, affecting gap junctions, altering the nourishment of gut cells, and favouring translocation which increases the risk of sepsis.¹⁹³ Something similar can happen in the respiratory system, because *NOS2* is found in epithelial cells¹⁹⁴ and the highest concentration of nitric oxide in the exhaled breathe comes from the inducible isoform.¹⁷² This means that the constitutive nitric oxide synthases, that is the neuronal (nNOS) and the endothelial (eNOS), make a little contribution despite they are also present in the airways.¹⁹⁴ So, limited bronchodilation in this case is significantly more influenced by a reduction in the formation of nitrosothiols (nitric oxide + -SH group) derived from iNOS¹⁹⁵ than from nNOS activity as part of the inhibitory nonadrenergic noncholinergic system.¹⁹⁶ iNO also produces peroxynitrite when it reacts with superoxide anion (O_2^-), being an important ROS against pathogens.¹⁹⁵

However, the inflammatory condition proceeds mainly from the positive regulation of arginase and we can conclude that it is linked to iNOS in both the intestine and the lung. This pathway is responsible not only for the immunodeficiency already mentioned, but also for fever¹⁹⁷ and fatigue.¹⁹⁸ Although inflammation of the respiratory system should have an analogous manifestation in the intestinal tract, even more if the hypothesis is to consider it as the main gateway for SARS-CoV-2, some interesting aspects of arginine metabolism should be analysed to present the enterocytes as a silenced front door. When the replenishment of the amino acid occurs at the expense of others, glutamate is the most affected with a consumption ratio of three molecules for each arginine produced.¹²⁰ This increase in protein turnover with a predominance of catabolism ends up altering glutamatergic pathway, which is the main excitatory nervous signalling formed by the synergistic activity of co-expressed acetylcholine and glutamate.¹⁹⁹ Thus, slowed intestinal transit is more likely to occur than diarrhoea.²⁰⁰ This effect can be reinforced by the observed negative correlation between constitutive and inducible NOS.^{133,134,195} While this must have a minor consequence in the lung as has been explained, its impact is relevant in the digestive and central nervous systems. Upregulation of nNOS when iNOS is blocked also consumes arginine,²⁰¹ opposes resistance to urgent intestinal excretion,²⁰² and contributes to the development of seizures.²⁰³ Convulsions may also be associated with downregulation of GABA, which comes from glutamate,²⁰⁴ augments its degradation through activation of GABA transaminase by nNOS,²⁰⁵ and suppresses its hippocampal activity linked to the GABA_A receptor when melatonin binds to the Mel_{1B} receptor.²⁰⁶ In addition, the sleep hormone inhibits *NOS2*.²⁰⁷ Two other highly discussed neurological disorders are loss of taste and smell, which can be caused by limited expression of acetylcholine.²⁰⁸

The imbalance between iNO and arginase alters the expression of immune cells and damages vascular cells, with their injury being the basis of all the symptoms. This has a special impact on the brain, heart and kidney due to their sensitivities related to the occurrence of circulatory events. M1 macrophages, which express iNOS for nitric oxide production against pathogens,¹⁶¹ suffer downregulation and reduce the response of lymphocytes Th1 cells and vascular

Table 3 Tissues with an outstanding expression of RNA and protein for *ACE*, *ACE2*, *TMPRSS2*, *NOS2*, and *AOC1* genes

ACE	ACE2	TMPRSS2	NOS2	AOC1
Small intestine	Small intestine	Small intestine	Small intestine	Small intestine
Large intestine	Large intestine	Large intestine	Large intestine	Large intestine
Kidney	Kidney	Kidney	Kidney	Kidney
Lung	Gallbladder	Stomach	Cerebral cortex	Placenta
Male tissues ^a	Testis	Pancreas	Lower airways	Appendix
Female tissues ^b	Seminal vesicle	Epididymis	Liver	Lower airways ^c
	Lung ^c	Seminal vesicle	Muscle tissues	
		Prostate	Appendix	
		Appendix		
		Lung ^c		

Note: Common organs where values are highest have been highlighted in bold.

^aMale tissues are testis, epididymis, seminal vesicle and prostate.

^bFemale tissues are the fallopian tube and the endometrium. Consensus data come from The Human Protein Atlas version 19.⁶

^cLung has been added despite it has not a prominent expression according to the Human Protein Atlas version 19,⁶ but a recent study has elucidated the presence of ACE2 in respiratory cells (Ziegler et al¹⁷⁰). For TMPRSS2, no score has been assigned at the protein level in the Human Protein Atlas version 19.⁶ AOC1 has a low RNA expression in the lungs and a mild protein expression in the bronchi, but it conditions the expression of HNMT (main histaminase in the airways¹⁷¹) as explained in section 2.

cells via nitric oxide. These last cells have angiotensin II receptor type 1 (AT-1R) and produce angiotensin II that binds to the former for NADPH oxidase/NF- κ B/STAT-1 activation, even in M1 macrophages.^{209–212} The process implicates chemokines and cytokines, among which the tumour necrosis- α (TNF- α) stands out because it allows the production of IFN- γ to protect the body against viruses.²¹³ Furthermore, the minor production of TNF- α linked to NOS2 downregulation also reduces ACE activity.⁷ Then, the inhibition of all the above leads to the transformation of angiotensin I and II into angiotensin (1–9) and angiotensin (1–7), respectively, by ACE2, which competes with ACE substrate/end-product and inhibits NADPH oxidase/NF- κ B activation to reinforce iNOS blockade.⁷ Exogenous administration of angiotensin (1–7) or ACE2 enhancers will favour the biological effect. Although angiotensin (1–7) is anti-inflammatory,⁷ upregulation of arginase in vascular cells leads to oxidative stress and inflammation.²¹⁴ This is potentiated by granulocytes, mainly neutrophils, which express arginase and cause tissue damage through excessive degranulation because the endothelial process of adhesion and migration is in part limited by iNO.¹⁹² Neutrophils can also produce endogenous pyrogens (IL-1, IL-6),²¹⁵ stimulating the liver for the release of acute phase proteins and contributing to the development of systemic inflammation, fever and sepsis.²¹⁶ Finally, arginase is expressed too in M2 macrophages,¹⁶¹ provoking transmembrane serine protease 2 (TMPRSS2) upregulation through IL-13 production¹⁶⁸ by themselves, lymphocytes Th2 cells and lymphocytes B (Th2 cells are activated by M2 macrophages and B-cells by the former).¹⁶⁹ The increment of ACE2 and TMPRSS2 allows SARS-CoV-2 infection in epithelial cells of the gut and airways,¹⁶⁵ considering the possibility that the virus reaches the respiratory system through the bloodstream once the intestinal barrier is overcome. The same environmental factors that inhibit iNOS in enterocytes

can do the same over respiratory cells once they pass the digestive tract, weakening even more the body and favouring the spread of the disease by aerosol droplets. It is also convenient to study the contagious potential through the faeces. The protective role of NOS2 gene against SARS-CoV-2 has been suggested in a recent study.²¹⁷ ►Fig. 2 schematically summarizes the main steps of this suggested infection process.

Regarding DAO, the reduction of its intestinal activity allows histamine to augment its concentration with vasoactive effects that lead to an increase in vascular permeability, hypotension and the development of inflammation.^{19,218} The resulting fever and fatigue are potentiated by other biogenic amines such as putrescine, spermidine and spermine. These have the ability to block sodium and calcium channels in nerve, musculoskeletal and cardiac cells, which intensifies the sensation of collapse.^{219–221} Aberrant histamine signalling on the H1R receptor is the most important. Its activation in immune and vascular cells supports the febrile and inflammatory process, since dendritic cells type 1 (DC1), M1 macrophages, lymphocytes Th1, and muscle and endothelial cells of blood vessels express this receptor.¹⁶² The chain response of these cells shown in ►Fig. 3 includes the recruitment and migration of neutrophils and the production of cytokines, among which there are endogenous pyrogens such as interleukin 1 (IL-1), interleukin 6 (IL-6) and TNF- α from granulocytes and macrophages.^{215,222} The liver also contributes to the process by producing acute phase proteins through the same H1R receptor.²²³

One of the effects of the “cytokine storm” is the release of IFN- γ from IL-12/TNF- α -activated immune cells.^{213,216} This one, along with IFN- α and interferon- β (IFN- β) synthesized by infected cells,²¹⁶ induces the overproduction of nitric oxide to promote systemic inflammation, fever and

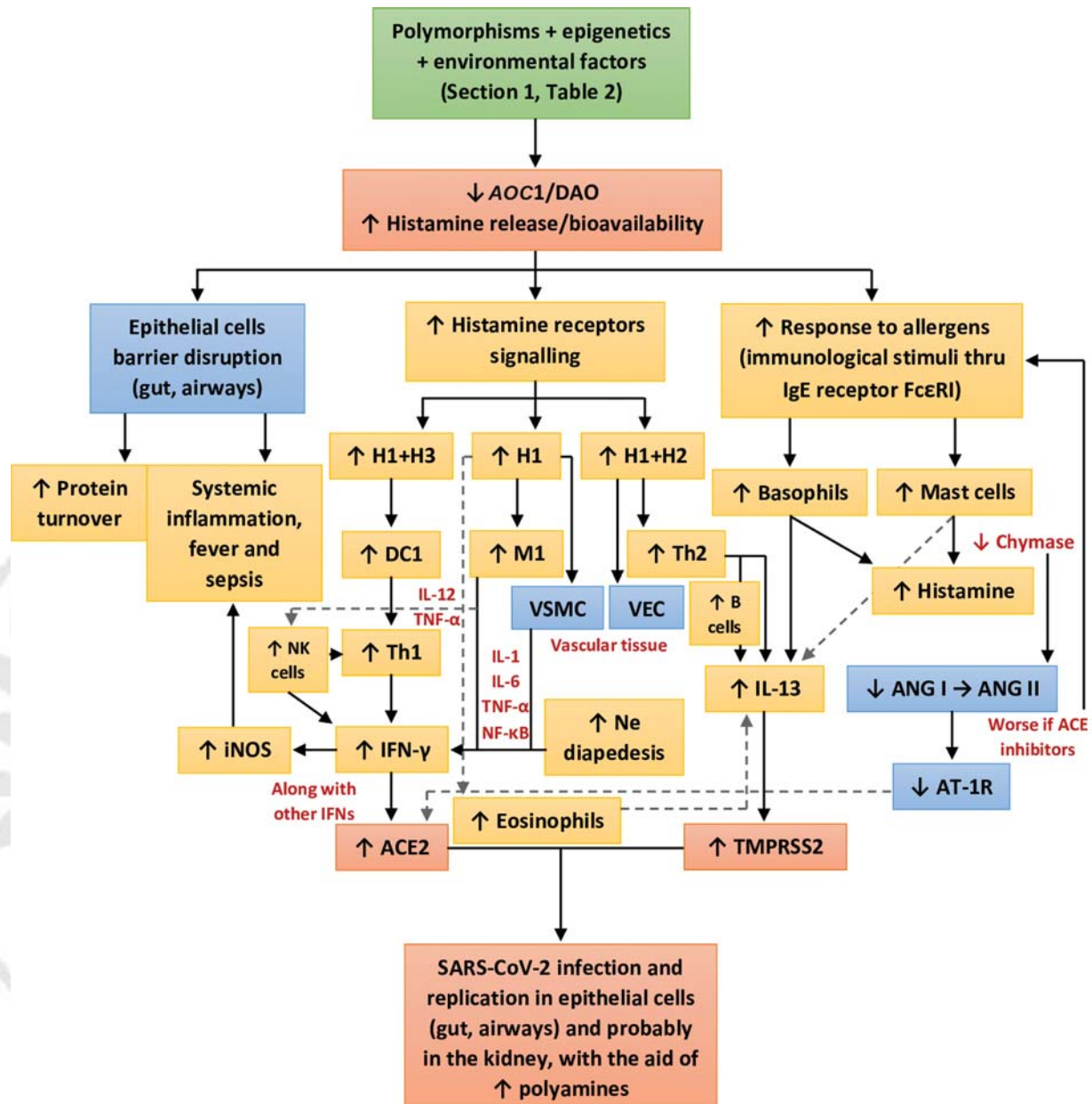


Fig. 3 Enhancement of ACE2 and TMPRSS2 for cell infection by SARS-CoV-2 beginning with the inhibition of AOC1/DAO after exposition to certain environmental factors and with the help of gene polymorphisms and epigenetics. Green box = unique in this colour to symbolize the causes of the functional deficiency. Blue boxes = cells damaged, or pathways downregulated. Orange boxes = cells, genes or proteins upregulated; derived injuries. Red boxes = key genes and associated processes that allows the development of COVID-19. Clarifications: The whole process is explained in the three previous paragraphs.^{19,52,58,124–126,130,162,168–171,213,215,216,218–233} M1 macrophages and neutrophils produce IL-1, IL-6 and TNF- α .^{213,215,216} M1 macrophages also synthesize IL-12, which together with TNF- α activates NK cells.¹⁶² NF- κ B from vascular and immune cells participates in the induction of IFN- γ .^{209–212} Abbreviations: NF- κ B, nuclear transcription factor kappa B; AOC1/DAO, amine oxidase copper containing type 1/diamine oxidase; IgE, immunoglobulin E; Fc ϵ RI, high-affinity receptor for the Fc region of IgE; H1, H2, H3, histamine receptors without the “R” due to reduced space; DC1, dendritic cells type 1; M1 cells, macrophages type 1; Th1 cells, lymphocytes T helper type 1; Th2 cells, lymphocytes T helper type 2; Ne, neutrophils; NK, natural killer; B-cells, lymphocytes B; VSMC, vascular smooth muscle cells; VEC, vascular endothelial cells; IL-1, interleukin 1; IL-6, interleukin 6; IL-12, interleukin 12; IL-13, interleukin 13; TNF- α , tumour necrosis factor- α ; IFN- γ , interferon-gamma; IFNs, interferons, referring to the rest of the family; iNOS, inducible nitric oxide; ANG I, angiotensin 1; ANG II, angiotensin 2; AT-1R, angiotensin 2 receptor type 1; ACE, angiotensin-converting enzyme isoform 1; ACE2, angiotensin-converting enzyme isoform 2; TMPRSS2, transmembrane serine protease 2; SARS-CoV-2, severe acute respiratory syndrome by coronavirus 2.

sepsis.^{224,225} Thus, we see that here the roads of the NOS2 and AOC1 genes separate, since stimulation of ACE2 by IFN- γ in cells of asthmatic patients¹⁷⁰ is in line with DAO deficiency. This pathological condition leads to the development of symptoms similar to those of COVID-19^{52,58}

(including biogenic amines-mediated cell proliferation and necrosis^{124–126}). Precisely, patients with allergic symptoms belonging to histamine intolerance tend to suffer the consequences of an increase in the activity of eosinophils, basophils and mast cells, which produce IL-

13^{169,226} and we have already seen that this cytokine is an enhancer of TMPRSS2.¹⁶⁸ In this case, the typology of cells expressing IL-13 increases, since Th2 and B lymphocytes activated by H1R and H2R receptors are also present here.²²⁷ Furthermore, these two immune cells are involved in the pathophysiology of respiratory processes such as asthma,^{162,226} in which DAO disability situations are promoted by the functional incompetence of the enzyme HNMT^{228,229} (the main histaminase in the respiratory system¹⁷¹).

An interesting fact regarding immunoglobulin E (IgE)-mediated histamine release in mast cells is that the process requires downregulation of chymase.^{230,231} This enzyme has the ability to convert angiotensin I to angiotensin II without the need for ACE.²³⁰ The consequence is that if it is inhibited, the AT-1R receptor will also be underexpressed and angiotensin I can be processed by ACE2. The situation can be aggravated if ACE inhibitors are used, since they cause the degranulation of mast cells²³² and chain processes that increase the activity of TMPRSS2 and ACE2 are stimulated. ► **Fig. 3** outlines this and all the fundamental steps that would favour SARS-CoV-2 infection from AOC1/DAO inhibition. Like NOS2, triggering environmental factors can act directly on the respiratory system, but may also reach the airways via the bloodstream once they pass through the intestine. Furthermore, the increase in the bioavailability of biogenic amines after failing DAO in the enterohepatic circulation may promote viral replication in respiratory cells as just explained. We cannot forget that dysbiosis is a bowel imbalance often associated with histamine-mediated inflammation and this produces zonulin upregulation that allows pathogens to enter across the gut wall.^{130,233}

Section 4

Homeopathic Approach to COVID-19 Treatment Using Drugs that Could Stimulate the NOS2 and AOC1 Genes

Since its conception, homeopathy has been considered a therapy that stimulates the body to solve the symptoms of disease.²³⁴ The consequential cellular reaction to undertake a function that allows recovering health or enhancing physiology is evidenced in scientific publications about human medicine, veterinary medicine and botany.^{235–237} The controversy over its efficacy lies in the fact that ultradilutions defy chemistry and pharmacology because their effect does not depend on Avogadro's number (nonexistent over 12CH²⁵) nor of the dose.²³⁸ Then, a possible mechanism of action focuses on genetic material, since experimentation in this field shows that homeopathic medicines produce gene expression.^{239,240} Furthermore, the existence of nanoparticles in the ultradilutions²⁴¹ allows to establish a physical connection between drugs and cellular response. However, there are nanoparticles within the quantum dots size range²⁴² and the identification of electromagnetic waves in DNA ultradilutions^{243–245} and homeopathic preparations²⁴⁶ points to an energetic effect that goes beyond matter.

While waiting for the unknowns to be clarified, the hypothesis can be raised that if homeopathy produces a biological effect through the expression of DNA, there may

be a key gene for each medicine that, in inhibition or under-expression, justifies the symptoms of the corresponding pathogenesis. To reach this conclusion, traditional Chinese medicine has been considered. Its concept of energy deficiency in relation to a specific meridian and its associated physical organ translates into a functional deficiency that gives rise to all of the patient's symptoms.^{21,23} To this we must add that there is a correlation between the pathophysiology from the eastern point of view and the toxicology of the natural substances used in the preparation of homeopathic ultradilutions, which allows each drug to be linked to a specific organ by virtue of its functional characteristics defined by its meridian and correlated to occidental medicine.^{23,24} Therefore, knowing the correspondence between remedies and acupuncture channels, the data can be expanded for a more accurate homeopathic diagnosis. This is essential and particularly useful when patients (animals and plants) cannot answer the anamnesis questions that allow their symptoms to be compared by similarity with those of the appropriate remedy for their cases (Law of Similars²⁴⁷). The result of the fusion between traditional Chinese medicine and homeopathy is an increase in therapeutic efficacy in the daily veterinary clinic (data not shown).

Silicea terra and *Arsenicum album* are broad-spectrum homeopathic medicines used in infectious and immune-mediated diseases.²⁴⁸ Studies have been published suggesting the use of homeopathy to treat COVID-19.²⁴⁹ Interestingly, the repertorisation of the common symptoms of the disease with the Radar software results in the presence of *Silicea* and *Arsenicum* in the first positions.²⁵⁰ In another study, the second is also one of the most prescribed.²⁵¹ Their respective pathogenesis shows a close link with the small intestine, where the NOS2 and AOC1 genes are enhanced (► **Table 3**). This article aims to serve as a theoretical basis for the experimental demonstration of homeopathy. The hypothesis is that the specific action of each medicine should be the stimulation of a key gene that allows the function of its encoded protein, causing the remission of the patient's symptoms by chain reaction. It is an ambitious goal, but with the conviction of its existence due to the aforementioned improvement in therapeutic efficacy in animals when this reasoning is applied to homeopathic diagnosis and prescription.

Over the course of a year, the author has preliminarily linked different remedies with intestinal proteins that stand out in the small intestine, including enzymes. In this unpublished article, a correlation has been seen between *Silicea terra* and iNOS, *Arsenicum album* and DAO, *Argentum nitricum* and the sodium-glucose transport protein type 1 (SGLT1), *Veratrum album* and the serotonin transporter (SERT), and *Lycopodium clavatum* and serotonin (5-HT). The symptoms of these drugs can be explained from the inhibition, blockade or functional deficiency of said protein products, and the genes that encode them could be the specific place of action of each homeopathic remedy to regulate them (there are various studies that support these statements^{239,240}). As it has already been mentioned, it must be verified. Here, we exposed only the relationships found between the most prominent symptoms

Table 4 Correlation between representative symptoms of *Silicea terra* and scientific studies that allow the pathogenesis to be interpreted as a functional deficiency of NOS2 (gene)/iNOS (protein)

Symptomatic characteristics of <i>Silicea terra</i> (Vijnovsky) ²⁴⁸	Interpretation based on studies supporting underlying NOS2/iNOS deficiency to explain the symptoms
<i>Mentality:</i> (1) Lack of self-confidence, deeply insecure, coward. When the mind needs <i>Silicea</i>, it is in a state of weakness, bewilderment, fear, submission. (2) Patients may also show lack of memory, confusion and difficulty understanding and concentrating. (3) Other patterns are anxiety in anticipation of future events, obsession with sharp objects or perfectionism performing anything.	(1) iNOS knockout mice exhibit freezing behavior when exposed to danger and cannot react boldly.^{133,134} Upregulation of nNOS and downregulation of the endocannabinoid system in the cerebral cortex is part of the process.^{133 (2)} The downward activity of ACh also happens when neuronal nitric oxide is upregulated.^{232,253} This affects learning and memory, being something observed too in experimental Alzheimer's models where iNOS plays a protective role in glial cells against neuro-inflammation and neuro-degeneration.^{254–256 (3)} NOS2 knockout mice show abnormal activity in cortico-striato-thalamo-cortical circuitry in terms of obsessive-compulsive disorders.²⁵⁷ The excessive stimulation of the glutamatergic pathway (glutamate + acetylcholine) may partly explain the subsequent downregulation of ACh as a compensatory response.²⁵³
<i>Physical constitution:</i> (4) Poor nutrition, not due to a lack of food in quantity and quality, but because there is an imperfect assimilation. The patient has a thin and weak appearance.	(4) Inducible nitric oxide controls the permeability of the intestinal wall during digestion by interacting with the bacterial flora.¹⁹² Upregulation of the arginase pathway increases protein turnover in terms of catabolism to replenish arginine from other amino acids (glutamine, glutamate, alanine, aspartate, proline and citrulline).¹²⁰ Most of them are essential for the structural integrity and functionality of the gut.²⁵⁸
<i>General indications:</i> (5) Immune-mediated processes, such as purulent infections (abscesses, fistulas, foreign bodies in the skin, non-closing wounds). (6) Effects of suppressed perspiration. (7) Consequences of vaccination, especially smallpox.	(5) Arginase overexpression produces immunodeficiency.¹⁷⁶ Neutrophils are the immune cells most enriched in this enzyme,⁶ increasing their migration to infectious foci because inhibited iNOS cannot limit adhesion to the vascular wall and diapedesis.^{259–261} Nitric oxide is necessary to kill bacteria²⁶² and phagocytosis is reduced because the activity of M1 macrophages is dependent on NOS2,¹⁶¹ so neutrophils die and form pus along with bacterial debris.^{263,264} Stimulation of ACh, when the degradation of glutamate to replenish arginine stops (ratio, 3:1¹²⁰), allows suppression, the expulsion of foreign bodies and the secretion of sweat. (6) This is because the excitatory synergistic activity of glutamate and acetylcholine (glutamatergic pathway) is essential in the contraction of muscle tissue and perspiration.²⁶⁵ In addition, nNOS increases when neuropathic pain develops due to trauma,²⁵² leading to a reduction in ACh signalling which delays the ejection of sharp objects from wounds. A similar negative correlation between nNOS and ACh occurs in diseases that alter neurotransmission through the neuromuscular junction.²⁵³ iNOS is also important in wound healing; so, the stimulation of VEGF and eNOS for neovascularization influences drainage.^{266 (7)} Inducible nitric oxide has a negative correlation with viral infection, vaccinia among others,²¹³ and plays a critical role in the tolerance of smallpox vaccine.²⁶⁷
<i>General indications:</i> (8) Neurological disorders (epilepsy, somnambulism).	(8) The aforementioned consumption of glutamate (by overstimulated arginase and neuronal nitric oxide), the positive regulation of nNOS and the activation of the hippocampus receptor Mel_{1B} by melatonin, all in the brain and related to the inhibition of NOS2,^{205–207} negatively regulates GABA and produces an increase in spontaneous locomotor activity, such as seizures and sleep walking.^{204,268}
<i>General indications:</i> (9) Neoplasms, cancer.	(9) Polyamines are involved in cell proliferation and malignancies.^{125,269}
<i>Main symptomatic modalities:</i> (10) Worse from cold and humidity (always frozen), better from dry heat. (11) Sensory and sensitive hypersensitivity (allodynia, intolerance to touch and pressure), paraesthesia. (12) Milk aversion and intolerance, even more so if it is raw (including maternal), with propensity to vomiting and diarrhoea after dysbiosis and fermentation.	(10) iNOS is a vasodilator and participates in brown adipose tissue for thermogenesis,²⁷⁰ so its inhibition favours the sensation of cold. To this we must add that polyamines have a hypothermic effect on the hypothalamus.²⁷¹ All this explains the improvement with the heat. Humidity is an aggravating factor at extreme temperatures, this record being in relation to the toxicity of rotten meat (<i>Pyrogenium</i> homeopathic remedy, from an animal source rich in biogenic amines).^{248 (11)} Regarding the alterations in the perception of stimuli, hyperreactivity to pain is linked to

(Continued)

Table 4 (Continued)

Symptomatic characteristics of <i>Silicea terra</i> (Vijnovsky) ²⁴⁸	Interpretation based on studies supporting underlying NOS2/iNOS deficiency to explain the symptoms
	overstimulation of nNOS (especially in trauma), ^{252,272} whereas paraesthesia is a consequence of reduced ACh signalling. ^{199,252,253} (12) Finally, digestive disorders by milk are the consequence of the downward defense activity of NOS2 in the gut, ¹¹² the reduction in the intestinal transit derived from ↑nNOS/↓ACh, ^{200,202} and dysbiosis resulting from the interaction of nutrients and microorganisms in the milk with enterocytes and intestinal flora. ^{103,273–275} Milk is rich in arginine ^{276,277} and supplementation with this amino acid in an iNOS-suppressed condition does not improve functional deficiency, ²⁷⁸ so arginase pathway will still be upregulated with the effects already seen. Moreover, δ-Proteobacteria, which process sulphur and produce H ₂ S with its characteristic foul odour of rotten eggs, increase with the fat of animal milk. ²⁷⁵

Abbreviations: ACh, acetylcholine; eNOS, endothelial nitric oxide synthase; nNOS, neuronal nitric oxide synthase; VEGF, vascular endothelial growth factor.
Note: Numbers have been assigned to the symptoms for better linkage with corresponding reference studies.

of *Silicea* and iNOS, as well as *Arsenicum* and DAO. It should be understood that pathogeneses present their numerous symptoms and symptomatic modalities with a hierarchy, but without a logical connection between them. Not all the morbid manifestations exist in patients, and sometimes the same drug can improve them with diseases symptomatically different. Therefore, it is most likely that the conformation of clinical pictures similar to the pathogenesis of a remedy depends on the environmental factors that cause each disease, adding the genetic predisposition or weakness to explain the individual way of getting sick.

The dataset in ►Table 4 attempts to show that the pathogenesis of *Silicea terra* can be explained as the result of an iNO inhibition that leads to a positive regulation of the arginase pathway, including polyamines, and a compensatory overexpression of neuronal nitric oxide. Both excesses allow a negative regulation of the glutamatergic pathway (glutamate + acetylcholine) and derivatives such as GABA. Note that many details and symptoms by organs and systems have been omitted, except for necessary references, due to the large amount of information contained in the pathogenesis. The selected symptoms are considered sufficient and representative to establish the hypothetical drug–gene–protein relationship. Numbers have been assigned to the symptoms for better linkage with corresponding reference studies.

The dataset in ►Table 5 tries to explain that the pathogenesis of *Arsenicum album* can be the result of an inhibition of DAO that leads to a secondary functional disability of the other histaminase enzyme HNMT, and a positive regulation of biogenic amines (histamine, polyamines) with various pathophysiological effects. The table has similar presentation characteristics as the previous one.

Discussion

This analytical study presents a pathophysiological model for the infectious disease COVID-19, with the small intestine as the main gateway to the body for its causative agent SARS-CoV-2. The hypothesis is based on the richness of the intestinal tissue with respect to five genes whose interaction under certain conditions makes infection possible, with two other important points of possible replication (large intestine and kidney). These conditioning circumstances are genetic and environmental factors that cause a negative regulation of NOS2/iNOS or AOC1/DAO, so that ACE is also inhibited and all leads to a positive regulation of ACE2 and TMPRSS2. Thus, two different ways of developing the infection are proposed depending on whether the inhibition is of the NOS2 gene or the AOC1 gene.

Immune and vascular cells that support immune-incompetence and systemic inflammation are affected in the process. This is interesting because in traditional Chinese medicine, the small intestine connects with the heart and together form a Yin–Yang pair that is part of the Fire element, which comprises body functions related to vessels and blood circulation.¹⁴⁵ The article respects the transmission of the virus through the airways, but along the text it is explained that the respiratory epithelium may be compromised due to the cardiovascular effects of cytokine storm after the intestinal imbalance, the

Table 5 Correlation between representative symptoms of *Arsenicum album* and scientific studies that allow the pathogenesis to be interpreted as a functional deficiency of AOC1 (gene)/DAO (protein)

Symptomatic characteristics of <i>Arsenicum album</i> (Vijnovsky) ²⁴⁸	Interpretation based on studies supporting underlying AOC1/DAO deficiency to explain the symptoms
Mentality: (1) Marked anxiety and restlessness that implies a continuous movement. (2) Fear of everything, panic disorder. (3) Obsessions and compulsions, perfectionism. (4) Depression with thoughts of suicide.	(1–4) The classic histamine receptors are involved in nervous responses such as anxiety (H1R, H2R), panic (H3R), obsession-compulsion (H3R) and depression (H1R, H2R, H3R).¹³⁷ (1) Anxious restlessness is the most characteristic of <i>Arsenicum</i> and is due to the fact that histaminergic neurons extend to all areas of the brain from the hypothalamic TMN,¹³⁷ and stimulate the release of excitatory neurotransmitters (serotonin, norepinephrine, dopamine, glutamate)^{279,280} and hormones (CRH, ACTH).^{281,282} This supposes the activation of the HPA axis and of aminergic nuclei involved in stress responses and reward/reinforcement mechanisms.^{283,284} To this we must add that polyamines excite neurons through glutamate receptor ion channels (NMDA, AMPA, Kainate)²⁸⁵ and block inward rectifier potassium channels (Kir) to make repolarization difficult.²⁸⁶ These effects can occur through biogenic amines from digestion when their concentration is not controlled by diamine oxidase, since they can reach the central nervous system thanks to their abilities to increase vascular and cellular permeability.^{138–142}
General indications: (5) Consequences of consuming meat in poor condition, ptomaine poisoning (today known as biogenic amines intoxication). (6) Excoriating and burning mucous secretions with a putrid odour. (7) Physical weakness and loss of strength that can be extreme (collapse). (8) Thinning till cachexia.	(5) The DAO enzyme is in charge of metabolizing biogenic amines from digestion,⁵⁷ especially histamine in the extracellular space.¹⁵ If it is inhibited or saturated, symptoms of poisoning develop.^{52,58} The HNMT enzyme, which is the intracellular histaminase, cannot compensate for the deficiency of the former and shows functional incompetence.^{228,229} (6) The proinflammatory properties of histamine allow to experience the burning sensation in the mucous membranes and the organoleptic characteristics of putrescine and cadaverine justify the emanation of unpleasant odours.^{19,34} (7) The feeling of fatigue, which can be extreme, is a joint effect of histamine and polyamines, contrasting with their previously mentioned abilities to excite the patient. Putrescine, spermidine and spermine decrease mobility and cause a reduction in muscle strength and tone from nerve centres,²¹⁹ musculoskeletal cells and cardiac cells (blocking sodium and calcium channels).^{220,221} Justifying the sensation of collapse initiated by their hypotensive effect in synergy with histamine.¹⁹ This downward activity is supported by a decrease in the release of TRH and the fall of TSH plasma levels through H2R receptors, contributing to loss of heat and energy.²⁸⁷ (8) Weight reduction is a basic consequence of lower structural integrity and functionality of the intestinal mucosa under conditions of low DAO levels.^{107,108} To this must be added the increase in energy expenditure mediated by histamine²⁸⁸ and the decrease of appetite through the H1R receptor.¹³⁷
General indications: Immune-mediated processes: (9) Sepsis. (10) Abscesses. (11) Allergies. (12) Effects of vaccines. (13) Cancer. (14) Leishmaniasis.	(9–11) The upward signalling of histamine on immune cells and its sustained response in answer to allergens when its degradation is reduced is reflected in ► Fig. 3 and justifies the development of infections and hypersensitivity reactions. (12) The effect of vaccines is associated with histamine/Ig E-mediated anaphylaxis.²⁸⁹ (13) Cancer is the result of the involvement of histamine and polyamines in cell proliferation and malignancies.^{125,126,269} (14) Regarding leishmaniasis, it seems that histamine favours the survival of the Leishmania parasite²⁹⁰ and the H1 receptor antagonists demonstrate their efficacy against <i>Leishmania infantum</i>.²⁹¹ Facts that are probably related to the parasite protein Ig E-dependent histamine-releasing factor.²⁹² On the other hand, the oxidation of diamines and polyamines by a copper amine oxidase of plant origin has opposite effects on promastigotes depending on the derived chemicals. While the aldehydes of putrescine and cadaverine are growth factors, the same type of spermidine and spermine compounds have inhibitory properties.²⁹³ These findings suggest that excessive stimulation of the DAO enzyme will not help.
General indications: Hydric and haemodynamic imbalances: (15) Thirsty in acute cases and reduced water intake in chronic conditions. (16) Haemorrhages. (17) Burns. (18) Simple and pernicious anaemia.	(15) The mechanisms of water intake involve histamine receptors and AVP. The latter is released in the SON through histaminergic neurons and H1R to produce thirst, while activation of H3R or inhibition of H1R and H2R strongly depress the dehydration-induced release of vasopressin.¹³⁷ An improved or maintained activity of histamine increases oedema and encourages the continuous loss of blood circulation fluid.²⁹⁴ (16) If bleeding induced by trauma or experimental procedure leads to a hypovolemic shock, histamine will exert a countermeasure response through H1R and with the involvement of cholinergic system to increase MAP, (Continued)

Table 5 (Continued)

Symptomatic characteristics of <i>Arsenicum album</i> (Vijnovsky) ²⁴⁸	Interpretation based on studies supporting underlying AOC1/DAO deficiency to explain the symptoms
<i>General indications:</i> (19) Neurological disorders (seizures; tremors).	pulse and heart rate.^{295,296} In these cases, diamine oxidase constitutes a serum biomarker of haemorrhagic shock, increasing its concentration in plasma because the blood perfusion of the intestinal mucosa is reduced in that condition. Damage and dysfunction of the intestinal barrier develops, and DAO decreases in the gut due to ischaemia.¹⁵⁵ (17) Similar results have been found in relation to burns, reflecting the importance and influence of DAO and the intestine in the circulatory system.²⁹⁷ (18) H4R contributes to the arrest of haematopoiesis in the bone marrow, causing anaemia.²⁹⁸ The pathogenesis of <i>Arsenicum</i> indicates that it can be of the simple or pernicious type, which affects the metabolism of vitamins B9 and B12, respectively. The relationship with biogenic amines is that both vitamins increase the hepatic biosynthesis of polyamines through the methionine pathway, while together they reduce the activity of PAO and diamine oxidase in the liver.²⁹⁹ To the ability to reduce PAO and DAO functionality, we must add that some foods fortified in both vitamins (B9: leafy vegetables, legumes, kidney, liver; B12: fish, meat, offal, eggs, dairy products³⁰⁰) have precisely high concentrations of histamine or the ability to release it.⁵⁸ Thus, patients with histamine intolerance will tend to show poor assimilation of such foods with vitamins, leading to anaemia through H4R. (19) Biogenic amines are pro-convulsive because polyamines increase neuronal arousal by stimulating glutamate receptor ion channels (NMDA, AMPA, Kainate)²⁸⁵ and blocking the inward rectifier potassium channels (Kir) to hinder re-polarization.²⁸⁶ Polyamines can also cause tremors³⁰¹ and induce histamine release through NMDA receptors,³⁰² which have a histamine-binding site.²⁸⁰ Diamine oxidase is involved in a metabolic route to process putrescine to form GABA,^{303,304} even in the brain³⁰⁵; so, the improvement of the glutamatergic pathway leads to seizures and epilepsy.³⁰⁶ Histamine is also involved in spasms and convulsions through the H3R receptor.¹³⁷
<i>Main symptomatic modalities:</i> (20) Worse at night, especially in the range between 1 and 3 AM, but can also experience that feeling between 1 and 3 PM (21) Periodicity in the appearance of symptoms (every day, week, month or year). (22) Worse from cold and humidity (always frozen), better from dry heat. (23) Worse from temperature changes. (24) Burning pains.	(20) Symptomatic aggravation schedules are the most prominent modality of <i>Arsenicum</i>. In traditional Chinese medicine, the maximum activity time of the small intestine is from 1 to 3 PM and that of the liver is from 1 to 3 AM³⁰⁷; so, the predominantly nocturnal worsening indicates that liver function suffers due to intestinal imbalance. This makes sense because of the anatomical relationship between both organs and the inflammatory effects of histamine on the liver through the H1R receptor.²²³ This same receptor, along with NMDA, serves histamine to over-stimulate hypothalamic SCN and cause circadian rhythm and sleep disturbances. (21) SCN is a master circadian clock and the aforementioned disorders constitute signs of hepatic encephalopathy, reinforcing the intestine–liver relationship.¹³⁷ (22) Sensitivity to low temperatures is related to the hypothermic effect of biogenic amines on the hypothalamus^{271,308} and the inhibition of thyroid hormones by histamine.²⁸⁷ In addition, the hypotension caused by these substances¹⁹ promotes hypoperfusion of tissues due to impairments on local blood flow and blood pressure,³⁰⁹ which is why the patient usually has cold hands and feet. The kidney is also affected in this sense,³¹⁰ being an organ with a great influence on body temperature. Aggravation by humidity is a registered effect in relation to the toxicity of rotten meat (<i>Pyrogenium</i> homeopathic remedy, from an animal source rich in biogenic amines).²⁴⁸ All this explains the improvement with the heat. However, histamine shows a clear ability to produce hyperthermia, involving H1R, H2R, H3R, preoptic area/anterior hypothalamus and brown adipose tissue.^{311,312} (23) This contrast of responses in relation to cold and heat connects with the fact that extreme temperatures favour the release of histamine,⁹⁹ making the patient sensitive to thermal oscillations. (24) The burning sensation of pain can be explained through nondegraded histamine of food origin,⁵⁸ or immunological and non-immunological stimuli-mediated histamine degranulation by mastoid cells^{99,100} on their location next to type C nerve fibres.¹⁴¹

Abbreviations: AVP, angiotensin-vasopressin; HPA, hypothalamic–pituitary–adrenal; MAP, mean arterial pressure; PAO, polyamine oxidase; SCN, suprachiasmatic nucleus; SON, supraoptic nucleus; TMN, tuberomammillary nucleus; TSH, thyroid-stimulating hormone.

Note: Numbers have been assigned to the symptoms for better linkage with corresponding reference studies.

exposure to inhibitors of iNO and DAO, and the increased protein turnover in a catabolic sense to rebalance the enterocytes. This last fact is especially important because these intestinal cells burn glutamine as main fuel and the consumption of the amino acid increases during sepsis, but is less in the intestine to supply the liver and immune cells.³¹³ In any case, the reserves are depleted, and the activity of the enterocytes and the immune system is limited.³¹⁴ To this we must add that glutamine is essential for transglutaminase enzymes to maintain the structure and integrity of epithelia.³¹⁵ Therefore, the lower the bioavailability of the amino acid, the greater the sensitivity to infections. This article also exposes the importance of the functions of iNOS and DAO in the small intestine and how they influence the rest of the organism to maintain homeostasis, in addition to being decisive enzymes to control viral replication through polyamines. However, *NOS2* and *AOC1* present a fundamental difference in their respective pathophysiological pathways for the upregulation of *ACE2* and *TMPRSS2*, being the family of IFNs (especially IFN- γ) that make the difference based on the recent study by Ziegler et al.¹⁷⁰

The approach to the functional deficiency of *NOS2* and *AOC1* genes and their protein products has been made from the oncoming between experimental classical science, oriental medicine and homeopathy, since all perspectives have in common that the development of disease symptoms can occur from a basic weakness. Modern science describes this phenomenon through the GENREs studies, traditional Chinese medicine does it through the energy insufficiency associated with the functions of an organ or part of the organism, and homeopathy relates the process to a single medicine capable of regulating the entire body in a specific way that this article tries to begin to elucidate.

The proposed homeopathic treatment should be understood as one more tool in the fight against the disease as it is equally important to control the triggering factors in a society of excessive consumption in general. Criticism of homeopathy on its efficacy is not based on science because it has amply demonstrated that high dilution drugs have a biological effect, as noted in this article. If the rejection focuses on arguments such as that the patient is not frequently observed to change and the remedies act as a placebo, it should be borne in mind that the same result is observed with traditional drugs and this does not make them less useful. The reality is that when an inappropriate medicine of any specialty is prescribed, its null or debatable action must be discussed based on the wrong choice of the treatment and not on whether it works per se when it has been seen that it does. On the other hand, the argument about Avogadro's number is obsolete because it is governed by the molecule as a functional unit of measurement and experiments with nanoparticles show that they stimulate the expression of genes, which are ultimately those that encode the proteins that make possible the reproduction of physiological and pathological responses in living organisms. In this sense, the silica nanoparticles, analogous to those present in the homeopathic remedy *Silicea terra* (from silicon dioxide²⁴⁸), provoke the expression of iNO.^{316,317} Corbalan et al's experiment³¹⁷ shows results that deserve to be analysed. All the nanoparticles used (10, 100, 150, and

500 nm) produce harmful effects that increase with the dose, but the most severe are caused by the smallest. This is interesting because it is presumable that as the dose is lowered, only a response to the 10-nm particle will be seen. This expected effect has been observed in a study with *Terminalia arjuna* (cardioprotective), whose dose with therapeutic efficacy decreased from 1 to 2 g per day to 0.083 g as the size of the active particles was reduced from 50 μ m to 23 nm.³¹⁸ In different studies on the presence of nanoparticles in homeopathic dilutions, sizes vary from 10 or 15 nm to the quantum dot,^{241,242,319,320} so it would be necessary to consider whether the smaller size confirms a classic homeopathic precept: the higher the dilution, the greater the strength of action and less risk of adverse effects.

Regarding this article, the correlation between the toxicological symptoms of the pathogenesis of *Silicea terra* and *Arsenicum album* and the scientific publications on iNO and DAO allows to relate the first homeopathic remedy with the functional deficiency of *NOS2*/iNOS and the second drug with the functional deficiency of *AOC1*/DAO. It should be clear that it is a theoretical study, so it requires further investigation and evidence of the hypothesis. However, these reasonings improve the therapeutic efficacy of homeopathy in daily clinical practice with animals.

Conclusions

Two possible pathophysiological pathways based on outstanding intestinal genes, polyamines metabolism, histamine, nitric oxide, and beyond have been exposed. Several studies have been written around the world to request the use of homeopathy against COVID-19. The present article joins them in proposing a theory where the homeopathic remedies *Silicea terra* and *Arsenicum album* could help improving the health of patients. Both drugs appear in the repertorisation of homeopaths worldwide. It is time to include them in experimental procedures to elucidate their specific mechanism of action.

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Conflict of Interest

The author declares that there is no conflict of interest.

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