Are the mRNA vaccines inducing the Sanarelli–Shwartzman phenomenon?

Article · March 2024

CITATIONS
0

READS
162

2 authors:

Robert Michael Davidson
Independent Physician and Medical Researcher
61 PUBLICATIONS **579** CITATIONS
SEE PROFILE

Timothy Richard Winey
Goldsmiths University of London
180 PUBLICATIONS **14** CITATIONS
SEE PROFILE

GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(REVIEW ARTICLE)

Check for updates

Are the mRNA vaccines inducing the Sanarelli-Shwartzman phenomenon?

Robert Michael Davidson [1,*] and Timothy Richard Winey [2]

[1] *P.O. Box 1785, Kilgore, TX 75663-1785, USA.*
[2] *Urbanização Dos Salgados Ap 9, 8200-410 Guia Abf, Portugal.*

GSC Advanced Research and Reviews, 2022, 13(02), 015–050

Publication history: Received on 06 August 2022; revised on 22 September 2022; accepted on 24 September 2022

Article DOI: https://doi.org/10.30574/gscarr.2022.13.2.0238

Abstract

Adverse events of myocarditis, pericarditis, and thrombosis, temporally associated with mRNA vaccination(s) and/or mRNA vaccine boosters, have been reported during post-marketing safety surveillance in the U.S. CDC VAERS database and 2021 CDC guidance to physicians. An interim report unexpectedly revealed inflammatory biomarker elevations in vaccine recipients. During review of considerable published research on the Sanarelli-Shwartzman phenomenon (SSP) and the use of nucleic acids as vaccine adjuvants, a novel, hypothesis is proposed. Even today, after being studied for over a century, the pathophysiology of the SSP is not fully understood. Motivated by a paper from 1950, titled "General Adaptation Syndrome" by Hans Selye, and recent published research by Korean investigators, a novel, non-conventional hypothesis was generated. Gluten and lectin sensitivity are cited as examples of sensitizing events of the SSP, for which we propose ensemble hydrophobic chiroptical catalysis may have therapeutic benefit. Under the ensemble HCC hypothesis, we propose that inflammatory stress and scurvy promote loss of chirality control, anomeric fidelity, phenotypic stability, and immune function, both humoral and cell-mediated, with the dialyzable transfer factor, L-ascorbic acid, and spin water playing central roles. It is proposed that therapeutic synergy of L-ascorbic acid, bioflavonoids, and corticosteroids in countering the SARS-CoV-2 pathogen arises from memory of chirality which originated during their biosynthesis. It is proposed that ensemble HCC is powered by radiant and or zero-point energy (quantum vacuum fluctuations) which may support a paradigm shift to supramolecular biology. The distinction between supramolecular biology and supramolecular xenobiology is highlighted.

Keywords: Sanarelli-Shwartzman phenomenon; mRNA vaccines; Anomeric fidelity; Genomic stability; Torsion fields; Spin water

1. Introduction

The Sanarelli-Shwartzman Phenomenon (SSP), often referred to as the generalized Shwartzman Reaction (GSR) or Shwartzman Reaction has been observed and studied for over a century [1, 2], yet many questions as to its detailed pathophysiology remain unanswered. Both generalized and localized types have been described, as well as a third "univisceral" type [3-6]. Biological immune cell responses, inflammatory cytokine responses, loss of hemostasis, and multi-organ dysfunction are commonly reported during the course of both (a) the SSP and (b) SARS-CoV-2 infection, in humans. The clinical responses to infection, i.e. sepsis, bear a striking resemblance to several of the adverse events being reported in temporal association to one or more of the mRNA vaccines. An Abstract by Gundry in 2021 [7, 8] was recently published in *Circulation*, titled "mRNA COVID Vaccines Dramatically Increase Endothelial Inflammatory Markers and ACS Risk as Measured by the PULS Cardiac Test: a Warning" [7-9]. Readers are encouraged to avail themselves of related review articles [10, 11] and conference proceedings [12-15] by Davidson and colleagues. Relevant background can be gained from published conference proceedings in 2015, titled "Biophysical Aspects of the Sanarelli-Shwartzman Phenomenon" presented in Atlanta, GA [13]. More recently, published conference proceedings titled

* Corresponding author: Robert M Davidson; E-mail: ngtchq@protonmail.com
P.O. Box 1785, Kilgore, TX 75663-1785, USA.

"Hydrophobic Catalysis by L-Ascorbic Acid: A supramolecular Strategy to counter the SARS-CoV2 ADP Ribose Glycohydrolase", was presented at the Southwest Regional Meeting of the American Chemical Society on November 1, 2021 in Austin, TX [15], for which a linked supplemental data file (PPTX) is available at *ResearchGate*.

An excerpted paragraph from [10] is provided below, so as to inform readers as to pre-clinical, clinical, and historical background of the SSP, a thrombohemorhagic phenomenon (THP) whose pathophysiology appears to be shared by Dengue, Ebola, and SARS-CoV-2, a pathophysiology clearly warranting further research.

> More than a century ago, in 1858, the Russian investigator Botkin first described what later became known as "erythrocyte agglutination thrombi" [94]. In 1894, Sanarelli first observed a condition which later became known as the generalized Sanarelli-Shwartzman phenomenon (SSP-G) [95], after further clarification by Schwartzman in 1928 [3, 96]. There is ample evidence in the literature that this is an appropriate model for serial exogenous surfactant administration, as in scheduled vaccination programs, a model that may constitute a "preparatory" or "sensitizing" or "priming" event. A final "provocation" or "challenge" or "shocking" event may induce a chain of reactions or a branching (avalanche-like cascade of events [97–102], equated with the Sanarelli-Shwartzman Phenomenon, whether localized or generalized [3,97,98,103,104]. ---Excerpted from Davidson & Seneff 2012 [10].

2. A paradigm shift to supramolecular biology is called for

Arguments being presented supporting the need for a paradigm shift to supramolecular biology are as clinically relevant today as they were when initially proposed in the 60's by Hans Selye. The current persistent global SARS-CoV-2 pandemic provides further support for a foundational change in our thinking [16-19]. A detailed proposal for supramolecular biology was introduced by Davidson & Winey in 2021 [11, 15].

2.1. Pattern recognition

There is a pattern, over the last 70 years, in which L-ascorbic acid (L-AA) and various chiral "hydrophobes" have demonstrated synergy in biological activity. For example, various combinations of L-AA with bioflavonoids and corticosteroids have been shown to synergistically potentiate each other's biological activity, e.g. their anti-inflammatory, antioxidant, and immunomodulatory properties. Most remarkably, the combination of L-AA with corticosteroids was shown to inhibit the SSP [20, 21]. This combination has also been effective in reducing inflammation in patients with rheumatoid arthritis [22-24]. Synergistic antiviral and immunomodulatory activity of L--AA and quercetin against SARS-CoV-2 has been reported [25].

There are literature reports of various combinations of L-AA, corticosteroids, and most recently bioflavonoids, in which anti-inflammatory synergy was demonstrated in treatment of SARS-related sepsis. A synergistic combination, i.e. an "ensemble" of hydrocortisone, L-ascorbic acid, and thiamine, referred to as the "HAT protocol" is now widely used clinically in the treatment of critically-ill patients with COVID-19 induced sepsis [26, 27]. The effect of combinations, i.e. synergistic *ensembles* of L-ascorbic acid with molecules which are chiral or pro-chiral and relatively hydrophobic may, because of their aggregating and self-organizing composite supramolecular chirality, ultimately be proven [28, 29] to provide the physical basis for supramolecular hydrophobic chiral synergy in countering the oxidative and inflammatory stress associated with the SSP during sepsis (explanation to follow).

Ensemble hydrophobic chiroptical catalysis (denoted "ensemble HCC") might provide the biophysical basis for the SSP. Ensemble HCC might also counter microbial and viral pathogens, e.g. the SARS-CoV-2 pathogen. In the Results & Discussion section to follow, we will introduce a novel hypothesis to explain, not only the pathophysiology of the SSP, but might also provide the basis for a supramolecular paradigm for prevention and treatment of *all* diseases. For example, we propose herein that the anxiolytic and antidepressant properties of L-AA represent ensemble HCC and memory of chirality between L-AA and endogenous neurosteroids which are thought to allosterically modulate the neurosteroid-GABA axis [30, 31]. We propose herein that (a) primordial stereospecific steroidogenesis was catalyzed non-enzymatically by ascorbolysis [32-34], and (b) the chirality imparted to the steroids which arose during their biosynthesis, is remembered by L-AA. The ensemble HCC hypothesis is entirely consistent with the view expressed by Hans Selye's work in the 50's and 60's, upon which he reaches the conclusion that most, if not all human diseases are supramolecular in origin, pluri-causal, highly stereotyped, generalizable, and typically non-specific in their etiology [35, 36].

2.2. Striking similarities between the SSP, SARS-CoV-2 pathogenesis, and mRNA inoculations

To appreciate the supramolecular aspects of the SSP, the process described as the "universal non-specific mesenchymal reaction" (UNMR), initially referred to as the "general adaptation syndrome" [35] should be kept in mind. Both the SSP

and UNMR are supramolecular in origin, and discussed in a book by Hans Selye titled "In Vivo – the Case for Supramolecular Biology" [16. 37, 38]. A large number of embedded citations are found in the book titled "Biological Response Modifiers New Approaches to Disease Intervention" edited by P. Torrance in 2012 [39] provide an excellent overview of the human immune system, and a rich source of published research, useful background for readers of all clinical and scientific disciplines, as we collectively consider the best societal response to the ongoing SARS-CoV-2 pandemic.

2.3. In consideration of the U.S. CDC VAERS database and 2021 guidance to physicians

Certain aspects of the adverse event profile associated with the mRNA vaccines bear a striking resemblance to those which characterize the SSP, which is often referred to as the Generalized Shwartzman Reaction, or just Shwartzman reaction, for brevity. Prior studies by Selye, Hauss, and others, over the last century, had frequently noted characteristic temporal and spatial histological changes during *in vivo* Inflammatory, immunologic, and thrombohemorrhagic responses. Sensitizing and/or provocative characteristics, were observed when two successive parenteral injections separated by a variable time interval, were injected. Highly reproducible biological responses were elicited when serial inoculation with various exogenous substances were administered, including materials such as nucleic acids, polysaccharides, proteins, and proteoglycans. Most importantly, the combination of corticosteroids and L-AA has long been known to inhibit the SSP [20]. More recently, L-AA has been shown to enhanced tissue-type, plasminogen activator-mediated fibrinolysis [21]. Clearly, maintaining hemostasis in humans involves a very delicately-balanced dynamical equipoise, for which risks of therapeutic off-target effects present a reality which compels s towards adopting a supramolecular biological paradigm, perhaps embodied in the ensemble HCC theoretical framework presented herein. The time course of inhibition of fibrinolytic activity by hydrocortisone shows a very interesting temporal relation to sensitizing and provocation injections of the SSP [28, 29]. Further, the anti-protease/anti-proteinase activity of L-AA is well-established. We propose that therapeutic synergy in the combination of L-AA with corticosteroids is readily explicable under the ensemble HCC hypothesis. Today, clinical use of the "HAT protocol [26, 27] in patients severely ill with COVID-19 related sepsis, is a case in point, in support of the ensemble HCC hypothesis. We predict that many such therapeutic and preventive synergies will follow.

2.4. The SSP and L-ascorbic acid have central roles in the human humoral and cell-mediated immune response

Remarkably, L-ascorbic acid (L-AA), whose levels are known to be high in human lymphoid tissue, has been identified as a dialyzable "transfer factor" [39, 40] and biological response modifier with both antiviral and immunomodulatory properties. Studies carefully controlled for pH-, solvent-, and redox-dependent chemical speciation and reactivity of L-ascorbic acid, are urgently needed to screen L-AA and its 2-O-substituted amphiphilic derivatives for both primary prevention and mitigation and rescue from microvascular inflammation. The "HAT protocol" (hydrocortisone, ascorbic acid, and thiamine) for treatment of critically-ill patients with sepsis and multi-organ dysfunction is now being widely-used clinically [25-27]. In 2021, L-AA and the L-AA free radical were proposed to play essential roles in both nucleic acid and protein chemistry, including pre-transcriptional and post-translational modifications (PTMs) of proteins in response to inflammatory stress [11, 15, 41, 42] such as that which occurs during the SSP.

2.5. The temporal components of the SSP in the human innate and cell-mediated immune response may represent "memory of chirality" during chemical evolution

Numerous similarities in pathophysiology of SARS-CoV-2 infection and that of inoculation with nucleic acids, e.g. that found in the mRNA vaccines, and gene therapy, *generally*, have been reported [39, 43-46]. It is well-documented [39] that various nucleic acid injection have either stimulated or provoked the SSP. An initial proposal is made, herein, that the temporal relationship of successive inoculations of the SSP may represent a "memory of chirality" that requires a finite amount of time in which to "prepare", after initial extrinsic ensemble chiroptical parenteral seeding of the endothelium. Such a putative chiral "seeding" mechanism may induce stochastic bias that sensitizes and subsequently provokes the catabolic phase of the SSP. Of note, there are now physical spectroscopic measures of composite or ensemble molecular and macromolecular chirality [34, 47-55].

2.6. Off-target effects and collateral damage

With microvascular endothelial dysfunction observed in association with the SARS-CoV-2 viral pathogen (and its variant strains) and numerous reports to the VAERS database of serious adverse events [56-59], including autoimmune [60-72], thrombotic, ischemic, and hemorrhagic events, temporally associated with mRNA vaccine administration, with concomitant inflammatory biomarker elevations, possible off-target effects of the COVID-19 vaccination strategy ought to be considered. It is conceivable that the safety bar is set too low for the mRNA vaccines and boosters presently being employed globally. It is far from clear that gene therapies, *generall*y, either with or without informed consent, are ready

for "prime time". Recent compelling epidemiological data [73-76] support the view that the bar is set too low for mRNA vaccines, in terms of safety, both short and long term. It might be asked, what level of off-target effects should be tolerated? [77-83]. Of the reports of thrombohemorrhagic serious adverse events, both idiopathic thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura (TTP) have been reported [84-89]. A novel procoagulant flow cytometry assay has been recently developed by Lee et al (2022)[90] for clinical diagnosis of VITT (vaccine-induced immune thrombotic thrombocytopenia). VITT is reportedly "a severe prothrombotic complication of adenoviral vaccines". Pathological formation of anti-PF4 antibodies is thought to result in *platelet activation* "via the FcγRIIa receptor to drive thrombosis and thrombocytopenia". This new platelet function assay provides a sensitive and specific assay that "has been adopted as part of a national diagnostic algorithm to identify vaccinated patients with platelet-activating antibodies" [90].

At minimum, with currently available data, this spatial and temporal juxtaposition of mRNA inoculations associated with serious adverse events, point to a need for reconsideration, and possible revision of the current vaccine strategy. In clinical decision-making, the Precautionary Principle is highly relevant and applicable to circumstances such as these [91-93]. Serious questions as to vaccine efficacy and safety, both short- and long-term, have been raised. Based on a large body of compelling published literature, a reasonable basis in science exists upon which to suggest that the mRNA vaccines and boosters are sensitizing and provoking the Sanarelli-Shwartzman Phenomenon. A novel complementary or alternative approach to mitigation and rescue from mRNA adverse events and SARS-CoV-2 viral pathogens is proposed. The temporal component of the SSP may represent variation in nonspecific extrinsic ensemble chiroptical seeding, a stochastic biasing which effectively sensitizes and provokes the SSP, referred to in 1950 by Selye as the general adaptation syndrome [35], and an effect that has probably existed since the emergence of Life on Earth. If the general adaptation syndrome represents an early step in the initial common pathway to inflammation and disease [10, 12], it might be reversible by judicious administration of nonspecific intrinsic chiroptical ensembles of orthomolecular natural products present during the origin of Life.

2.7. Torsion fields and possibly related ortho and para nuclear spin states of water

One of the goals of our research is to develop a sustainable, cost-effective means of restoring biodiversity to what may be perceived as a "dying" planet [94, 95, 18, 19], including humans which inhabit it. We propose that the ensemble hydrophobic chiroptical catalysis theoretical framework (presented herein) may, upon validation, offer a means of accomplishing the "greening" of the environment, both external and internal, in which we live. The supramolecular biological paradigm proposed herein is hoped to strengthen our innate immune system (both humoral and cell-mediated), a necessary step in preserving and maintaining human genomic stability, genomic resilience, and anomeric fidelity, in the face of ever increasing environmental toxicants, which is a price we pay to live in an industrialized society. Certainly not all technological advances, e.g. 5G and mRNA inoculations, are free of toxicological risk.

In about the same time frame that Davidson and colleagues began to develop the early embodiments of the NGTC/ascorbolysis/UNMR hypothesis, Winey was independently studying the material science effects of EM torsion fields on water [96]. Because these physical entities are not well-known to the scientific community, outside of biophysicists, some definitions are in order. Torsion fields are measureable both directly and indirectly, by their effects. Quantum vacuum fluctuations have already been shown to experimentally give rise to homochirality using 2-D equilateral triangles undergoing seeming 'random' motion [97].

So-called 'Torsion Fields' as discovered, described and measured by the Russian astrophysicist Nikolai Kozyrev [98], are a source of ongoing controversy. Winey has experimentally shown alterations to hydrophobicity in wide-ranging experiments ranging from altered lava lamp convection patterns, to increased colloidal stability. Myriad other experiments are suspected to also be influenced by torsion fields whose direct measurement has admittedly proven more elusive. These experiments range from altered fuel combustion to altered IR absorption in water, accelerated plant growth, slowed plant putrefaction, accelerated starch iodine reactions, altered cross-linking in hydrogels, etc. Importantly, Winey's most recent experiments provide experimental evidence that torsion field effects are *transferable*. Controversies surrounding the topic of "torsion" fields notwithstanding, readers should please take note that the translational potential of Winey's findings to solar light-harvesting technologies presently being developed is considerable, both in terms of combating global warming, and clinical light harvesting under the ensemble HCC theoretical framework.

Clinically, in terms of public health, the implications of Winey's experimental findings relative to understanding the SSP and countering viral pathogens, and sepsis, perhaps employing the ensemble HCC theoretical framework as a model from which to work, are considerable. A paradigm shift to supramolecular biology, of the type that was likely responsible for the initial and ongoing emergence of Life, may be necessary to restore balance (homeostasis) to our internal

biological microenvironments. Winey has also shown radio-protective effects of torsion fields on microwave heated water when fed to plants as compared to controls. The biological harm of non-native EMF's is well documented (see Alan Frey) [99, 100]. https://www.cellphonetaskforce.org/the-work-of-allan-h-frey/ In light of Frey's work [99, 100] on relatively weak microwave radiation, the proposed introduction of 5G is arguably a far 'Braver Newer' world than even mRNA gene therapies [101]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8580522/

Based on results from small scale pilot studies, the prospects are good for regenerative medicine, potentially countering premature aging, and potential strengthening the human innate immune response to viral pathogens such as that responsible for the current persistent global pandemic, and any future pandemics which might otherwise arise [102, 18, 19]

Given its ubiquity, we submit that homochirality in biology must be the product of fundamental, primal physical forces/laws. The sheer structural and temporal stability of DNA across all living things shows that the building blocks of life must be part of the fabric of physical forces/laws. If Feng et al are correct, we submit that anything disrupting the delicate hydrophobic balance responsible for the very structure and function of DNA [41], should arguably be viewed as beyond reckless, particularly since the vast bulk of DNA is often arrogantly rejected as 'junk.' Changes in the ratio of ortho to para water may be a quantum entropic effect not unlike the spontaneous chirality emerging from the 2-D triangles. Thus, ortho para ratios may be a property of living systems throwing off entropy by more efficiently dissipating heat and preserving homochirality, the loss of which, some have linked to aging and disease. If water can artificially be made more supermolecularly homochiral, then this could theoretically represent an energy savings to organisms and promote resistance to disease and aging. Indeed, the SSP should be testable by feeding structured water alone or in combination with other compounds to inoculated rats or other plant/animal models of aging and disease.

3. Results and Discussion

3.1. Primary result: novel hypothesis as to the origin of the SSP

Briefly stated, it is hypothesized that the time interval between sensitizing and provocation injections of the SSP may be causally-associated with the introduction of extrinsic substances whose composite intrinsic optical chirality (chiroptical) property may provide the physical basis, i.e. ensemble or composite chirality, that initially sensitizes and subsequently provokes the SSP. This hypothesis may provide a statistical (stochastic), dissipative (non-adiabatic) nonspecific, generalizable, explanation for the synergistic antiviral and immunomodulatory properties of L-ascorbic acid and corticosteroids in the treatment of sepsis [26, 27]. It may also explain why L-ascorbic acid and a bioflavonoid (quercetin) have demonstrated antiviral and immunomodulatory activity against SARS-CoV-2 [25] . Hydrophobic catalysis by L-ascorbic acid during the "unfolded RNA response" was recently proposed [11, 15, 41, 42]. Thus, the description of the current hypothesis is well-described by ensemble, hydrophobic chiroptical catalysis (denoted herein "ensemble HCC") by L-ascorbic acid, the L-ascorbic acid free radical, and 2-O-substituted derivatives of L-AA amphiphiles ("L-AAAs") upon photo-oxidative super-activation, within a moderately acidic, mildly oxidative, relatively hydrophobic microenvironment, typical of that found in inflammatory states [11, 15]. Such a process would potentially provide reversibility and dynamics to quantum phase coherent, regiospecific and stereospecific chemical reactivity to the "fluid" genome, proteome, lipidome, and glycobiome comprising the universal nonspecific mesenchymal reaction (UNMR) and the General Adaptation Syndrome described by Selye in 1950 [35]. Special emphasis should be placed on the words "universal", "nonspecific", "general", and "adaptation". The SSP might have preceded the origin of Life on Earth. If validated, such a mechanism might provide a supramolecular, orthomolecular basis upon which to develop preventive and therapeutic use of non-specific ensemble chiroptical "seeding" of the microenvironment to affect mitigation and rescue from the catabolic (thrombosis, necrosis, and bleeding) stage of the SSP, perhaps even rescue from SARS-CoV-2 and mRNA vaccine-associated adverse events [11, 15, 41, 42].

3.2. Basis of conclusion that both the SARS-CoV-2 morbidity and mortality and mRNA vaccine-associated adverse events are highly-stereotyped, pluri-causal, supramolecular sequelae of the SSP.

Having provided baseline background found in the above citations, we will give a succinct overview and synopsis of what we belief represents the underlying biophysical basis for the adverse events associated with the parenteral administration of the mRNA vaccines against the SARS-CoV-2 viral pathogen and its variants. Gundry's report [7, 8] in Circulation of inflammatory biomarker elevations in temporal association with the administration of one or more of the mRNA vaccines, including especially the reports of acute coronary syndrome (ACS) and myocardial infarctions makes us strongly suspect a microvascular endothelial dysfunction with impaired microvascular perfusion of the heart. Thus, a microvascular inflammatory process may represent a central underlying basis for the mRNA vaccine-associated adverse events [103-108], similar to the SSP, GSR, and DIC (disseminated intravascular coagulation) syndrome. The U.S.

CDC in their guidance to physicians and VAERS database includes frequent mentions of myocarditis, pericarditis, and thrombotic events, occurring in a reported incidence which is grossly disproportionate to adverse event profiles reported for prior vaccines during post-marketing safety surveillance, consisting of spontaneously generated reports from patients, physicians, and voluntarily provided by vaccine manufacturers.

3.3. Ensemble (composite) molecular chirality may prove to be an important biomarker for the SSP, with predictive preventive and therapeutic translational value.

Phenotypic and antigenic determinants of microbial symbionts and pathogens may potentially be characterized by their composite or ensemble molecular chirality, which is likely to be fractal [14, 102].

Winey has documented fractal-like branching of well-defined vortices in mixtures of whole cow's milk and vinegar after experimental milk samples were exposed to torsion fields [109]. https://www.researchgate.net/publication/353183316_Branching_Vortices_of_Raw_Milk_and_Vinegar_with_red_food_coloring_for_contrast

Under the recently introduced NGTC/ascorbolysis/UNMR theoretical framework [11, 15], gene expression, editing, recycling, and error correction, might be regulated and mediated by L-ascorbic acid, the L-ascorbic acid free radical, and ortho and para nuclear spin states of water (spin water) [110-112] , within a moderately acidic, mildly oxidative, relatively hydrophobic microenvironment [11, 15]. L-ascorbic acid levels are known to be high in lymphoid tissue [113-120]. The so-called "dialyzable transfer factor" was identified as L-ascorbic acid [39]. Here is an important null hypothesis that, to the best of our knowledge has not been disproven: 2-O-substituted derivatives of L-AA have been identified intracellularly [121-127]. Collagen synthesis is dependent upon L-AA [128, 129]. So-called "mother's milk" (colostrum) is known to be high in L-AA levels [130]. Bacterial chitinases are known to be "inverting" enzymes which invert the stereochemistry at anomeric centers within glycoproteins [131]. Glycolipid stereospecificity is likely to result in characteristic composite (ensemble) molecular chirality of lipopolysaccharide (LPS) and bacterial endotoxins. Whereas, most mammalian transglycosidases and glycohydrolases are thought to proceed with retention of stereochemistry at the anomeric centers of glycoproteins, e.g. the stereochemistry of the anomeric carbon atoms of proteoglycans and glycosaminoglycans [132. 133]. The stereochemistry of NAD+ glycohydrolases e.g. pig brain and calf spleen NAD+ glycohydrolases has been widely studied, and are known to be *retaining* glycohydrolases [134-137]. Bovine CD38 is an ecto-enzyme with both NAD+ glycohydrolase and ADPR cyclase activity which provides *retention* of C-1 anomeric configuration, presumably following an SN1 dissociative mechanism with an oxo-carbenium ion intermediate [137] during both ADP ribosylation and cyclization of NAD+ to form cyclic ADPR.

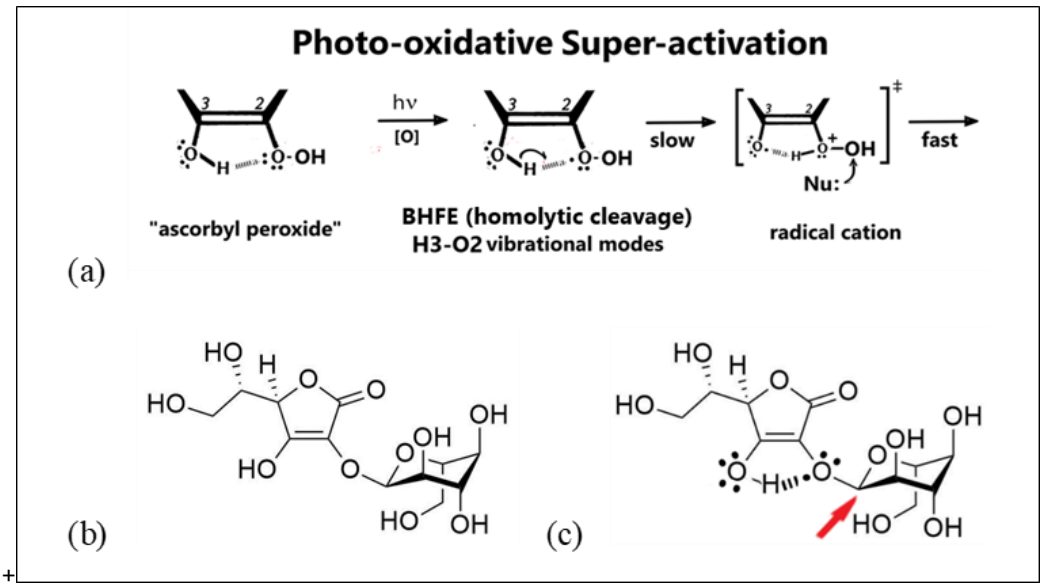

Figure 1 Ensemble HCC theoretical framework provides a chemically plausible biophysical basis for supramolecular chiral helicity and anomeric fidelity of collagen. (a) Proposed "Ascorbyl Peroxide" hydroxylation Factor, for provision of non-enzymatic mono-oxygenase function within inflammatory tissue microenvironments; (b) molecular structure of L-AA-2-O-α-D-glucoside; (c) proposed molecular structure of pre-equilibrium intramolecular hydrogen bonded (IMHB)

L-AA-2-O-α-D-glucoside free radical. Red arrow in (c) depicts postulated electrophilic site (the anomeric carbon atom) for regiospecific, stereospecific nucleophilic SN2 attack by endogenous nucleophiles, e.g. collagen micro-fibers.

Under the ensemble HCC hypothesis, we propose that the reported stabilization of collagen by (b) [138, 139, 128, 129, 33, 34] is explicable by enhanced supramolecular chiral helicity of collagen by L-AA, (b), (c), and chirality of the ortho nuclear spin state of water. The intramolecular hydrogen bond (denoted H3-O2 IMHB) in (c) is proposed to form *prior* to photo-oxidative super-activation of (b) and *prior* to rate-limiting homolytic cleavage of the O-H bond at the 3-position of the gamma lactone ring system of (c). The activation energy for the rate-limiting step in NGTC of non-enzymatic glucosylation *in vivo*, is represented by bond homolysis free energy (in contradistinction to bond dissociation free energy) which we denote BHFE. The BHFE values are proposed to predict auto-catalytic reaction kinetics of NGTC by ascorbolysis in vivo, during inflammatory states within inflammatory tissue microenvironments

Water has been shown to form self-assembled supramolecular chiral micron-scale associates with chirality transfer from the nanoscale [140] upon iterative exposure to hydrophilic polymers (nafion). Konovalov had previously proposed that water was capable of forming long-range nano-associates [141-143]. Hypomagnetic field effects and magnetoreception were reviewed by Binhi in 2017 [144, 145]. Interestingly, Koldunov & Voeikov demonstrated chemiluminescent biophoton emission in their study of L-AA and D-ribose in the Maillard reaction [146]. These biophotons are perhaps the same or very similar to the circularly polarized luminescence (CPL) reported in association with chirality transfer from the nano-scale to the micro-scale [34, 47-55]. Remarkably, radical species have been shown to demonstrate chiral helicity and CPL. It is proposed herein that the biophotons observed and detected by Koldunov & Voeikov were likely to have been generated by the presence of the L-AA free radical in their reaction *gemisch* [146].

Further, it is reasonable to suggest that the glycated (glycosylated) peptides and proteins are formed in a mechanism similar to the mechanism proposed herein for the reversible nonenzymatic stereospecific, regiospecific, fucosylation of peptides and proteins which are known to play important roles in immune recognition [147-152] and the human immune response [153, 154] (see Figure 8 below) within inflammatory microenvironments such as that found in endoplasmic reticulum (ER) stress. It is proposed herein that the L-AA-2-O-fucoside free radical reversibly delivers fucose moieties to the Golgi apparatus of the ER in response to inflammatory stress. The chirality which characterizes stem cell niches (fractones) of the brain, heart, gut, and reticuloendothelial system (RES) are proposed to arise from the chirality of nanoassociates of the ortho nuclear spin state of spin water [11, 14, 15]. The mechanism of chirality transfer of the prebiotic "ribozymes" is proposed to be the same or similar to the mechanism by which chirality is imparted to nascent proteins at the ER today, during inflammatory and cytoproliferative states [102, 155].

3.4. NGTC/ascorbolysis/UNMR theoretical framework has been extended to include ensemble hydrophobic chiroptical catalysis by L-AA and the L-AA free radical

In the present paper, the evolving non-enzymatic group transfer catalysis (NGTC)/ascorbolysis/universal non-specific mesenchymal reaction (UNMR) theoretical framework [11, 15] has been extended to include provision of a biophysical basis for lifelong maintenance of composite molecular chirality of our biomacromolecules. It is postulated that the "priming" or "sensitizing" phase of the SSP represents a "memory of chirality" which is thought to either stimulate or retard gene expression, phase-coherently, at the levels of miRNA, RNA, and DNA [156]. The necessity and technology now exist to validate or refute the ensemble hydrophobic chiroptical catalysis hypothesis, denoted ensemble HCC hypothesis, introduced initially in general terms, herein. The hypothesis is well-suited to be tested mathematically with stochastic complexity [157], AI [158], and network theory [159]. The hypothesis can be examined for correlation with temporal changes in inflammatory biomarkers, i.e. IFN, TNF, ILs, miRNAs, and TLRs, whose levels are known to vary during the SSP [160, 161]. The so-called "pathogen-associated molecular patterns" (PAMPs) [162-164] employed by TLRs to discriminate "frend from foe" are proposed to provide antigenic determinants in the form of chiral anomeric configurations of glycosidic linkages to both oxygen and nitrogen atoms on the surface of microbes, e.g. bacterial, fungal, and viral pathogens. Regiospecific, stereospecific PTMs, e.g. fucosylation, is thought to play an important role in immune recognition [165-169].

3.5. Urgent need for additional case-control studies of temporal changes in inflammatory biomarker assays during the SSP, i.e. during SARS-CoV-2 infection, sepsis, and serial nucleic acid (e.g. mRNA) inoculations.

In light of the "signal" detected and reported in the Gundry Abstracts [7, 8], perhaps primed by prior dietary gluten and lectin sensitization [170-173], and provoked by subsequent polynucleotide (nucleic acid) inoculation [39], it will be very important to look at the time course of various biomarker elevations, e.g. IL-16, Fas, and HGF levels, during the SSP [174-176]. Moreover, miRNA-146a levels should be studied during the SSP [170]. Micro-RNA levels are thought to be post-transcriptional, translational regulators of gene expression [156]. MiRNA-146a has been associated with

Alzheimer's disease *and with IL-16 elevation* [177-181]. Interestingly, vitamin and mineral micronutrients have been proposed by Beckett [156] to regulate miRNA levels.

Importantly, several of the inflammatory biomarkers, found to be elevated by Gundry, e.g. IL-16, Fas, and HGF, bear a striking similarity to biomarkers found over the last 70 years to be elevated at various stages of the SSP, e.g. IFN, TNF, ILs, miRNAs, and TLRs [39, 160, 161]. There may be potential pitfalls and precautions that vaccine designers (manufacturers) would do well to consider. Drug and vaccine safety, both short-term and long-term should be of concern. The temporal relationships between mRNA administration and the biomarker responses need further study, urgently. The technology exists to focus on the human heart as but one of several target organs. Specifically, functional in vivo 31P-NMR (phosphorus nuclear magnetic resonance spectroscopy) might be employed [182] sequentially in case-controlled studies, initially in small animal models of the SSP, concomitant with serial PULS biomarker and hemorheological parameter measurements. Intravital microscopy of in vivo capillary blood flow, and perhaps concomitant, nuclear medicine perfusion imaging studies (co-registered SPECT and PET studies) might also be considered, although there are obvious technical and logistical issues to be worked out, when studying patients during the SSP, e.g. during sepsis associated SARS-CoV-2 infection. A functional NMR spectroscopic measurement of fractional anisotropy (FA) obtained with concomitant diffusion tensor imaging (DTI-MRI) studies of the heart, *and brain*, might be considered [183-185]. A loss of FA of water protons preceeding the catabolic phase of the SSP, would suggest a biophysical, supramolecular, epigenetic etiology to the SSP. Case-control functional imaging and spectroscopic studies should be correlated with temporal changes in inflammatory biomarker levels. We propose herein that the elevation in HGF identified by Gundry may be related to memory of the chirality found in human heparan sulfate proteoglycans whose composite molecular chirality and L-AA levels are proposed to play important roles in the SSP during chemical evolution [186, 187].

3.6. Proposed biophysical basis for the SSP and UNMR: transformative clinical potential

L-ascorbic acid is thought to be one of the earliest molecules to emerge during the initial chemical evolution of Life on Earth. As such, it might be inferred that L-AA plays a central role in human immune health, including specifically, a central role in the SSP and UNMR. Under the NGTC/ascorbolysis/UNMR theoretical framework, introduced in 2021 [11, 15], multiple quantum phase-coherent radical chain reactions are enabled by "ascorbolysis", a vinylogous, hyperconjugated, redox active variant of acidolysis. Intramolecular-1,4-hydrogen atom transfer (denoted "intra-1,4-HAT") has been proposed to catalyze the initiation, propagation, and termination steps of the radical chain reactions, all of which are proposed to comprise the UNMR. The reported adverse event profile associated with the mRNA vaccines has many, if not all, of the characteristics of the SSP which occurs when a "preparatory", i.e., injection of bacterial filtrates, is followed after a proper time interval by intravenous "provocation" with the same or some similar material [36, 37, 188-190].

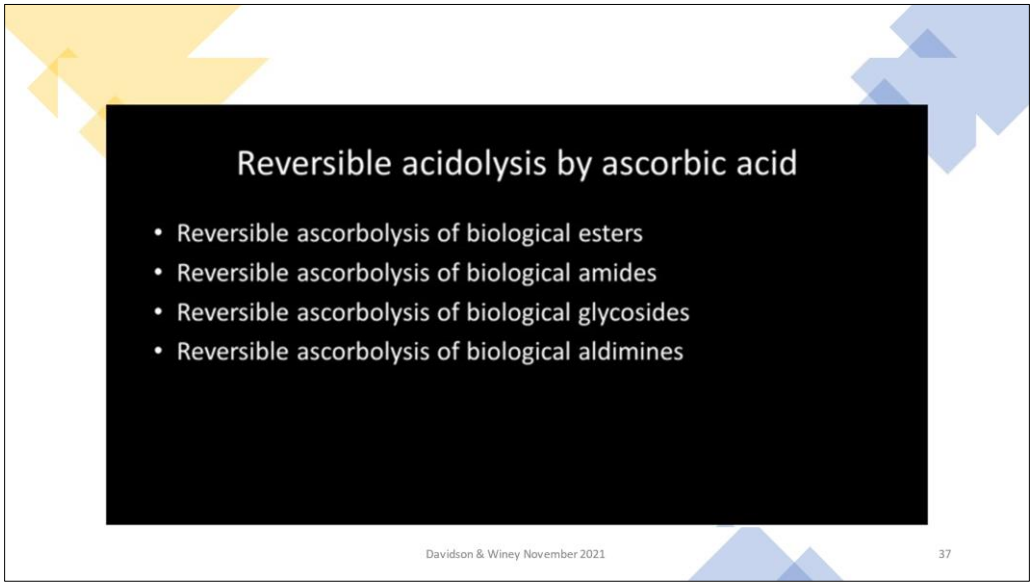

Figure 2 Industrial chemical acidolysis provides precedents for the ascorbolysis hypothesis. Reversible ascorbolysis may prove to be generalizable to all endogenous biological electrophiles, effectively providing non-enzymatic chirality control of a endogenous chiral electrophilic reserve capacity, the loss of which leads to aging and death [194, 11, 15, 18, 19]

A microvascular endothelial cascade of events is thought to initially involve the universal non-specific mesenchymal reaction (UNMR), a highly-stereotyped, pluricausal supramolecular, anabolic, self-assembling, auto-catalytic process attempting to rescue the extracellular matrix and endothelial glycocalyx layer (EGL). Upon exhaustion of endogenous coagulation factors, a catabolic process ensues, characterized by thrombosis, necrosis, and bleeding [36, 37, 190-193].

The Mirriam-Webster definition of "acidolysis" is useful, for chemists and non-chemists, alike. *Acidolysis* is defined as "any chemical reaction analogous to hydrolysis in which an acid plays a role similar to that of water." (Mirriam-Webster). Importantly, acidolysis is reversible, pH-dependent, and solvent-dependent. Considerable industrial chemical precedent exists for the reaction. Ascorbolysis can be thought of as a redox active vinylogous variant of acidolysis. Endogenous electrophiles are potential "substrates" for ascorbolysis, e.g. fucosylated proteins, GDP-fucose, GTP, ATP, cholesterol sulfate, sphingosine-1-phosphate, S-adenosyl-methionine, S-nitrosated proteins, acetyl-S-coenzyme A, phosphorylated proteins, phospholipids, L-carnitine, cAMP, cGMP, cADPR, miRNAs, RNA, DNA, proteins, peptides, glycosaminoglycans, proteoglycans, etc. Consider the effect of endogenous hydrophobic chiral ensembles, e.g. corticosteroids, bioflavonoids, repurposed SSRIs, HCQ, ivermectin, etc. to reversible ascorbolysis of endogenous electrophiles. Consider possible reversible ascorbolysis during complex coacervates [194-198] formed during the emergence of Life on Earth, within an aqueous microenvironment, driven by energy and chirality of external environmental torsion fields, essential ultra-trace minerals, and "spin water", i.e. ortho and para nuclear spin states of water, in an open, dissipative, non-adiabatic ecosystem, far from thermodynamic equilibrium. Reversible generalizable ascorbolysis might be a safer, sustainable means of maintaining dynamical, metastable equipoise of biosemiotics coherence, than employing double-edged swords, i.e. "magic bullets" of *extrinsically* chiral, e.g. PARP inhibitors, PARG inhibitors, *extrinsic* nucleoside analogues. Consider the effect of ultra-weak magnetic fields on reaction yields of NGTC by the ensemble HCC hypothesis [199-201, 142, 144, 145].

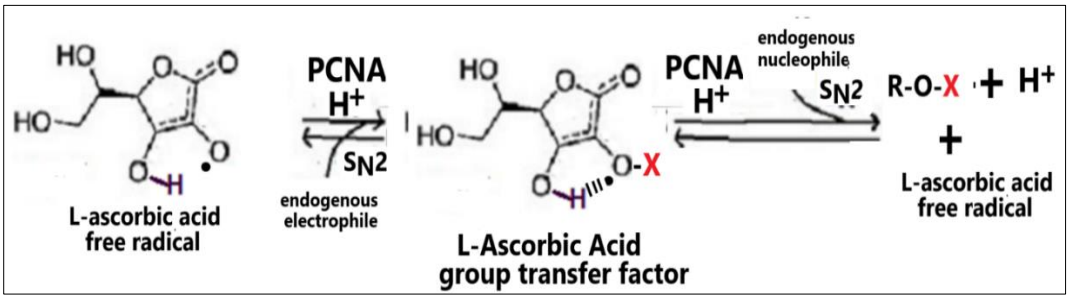

Figure 3 Postulated generalizable, reversible, auto-catalytic radical chain propagation reactions under the ascorbolysis hypothesis, potentially providing the biophysical basis for biosemiotics phase-coherence during the anabolic ("healing") phase of the SSP, elicited non-specifically, by highly-stereotyped, pluri-causal events, e.g. sensitizing or priming events during "General Adaptation Syndrome" and UNMR. Postulated reversibility and auto-catalysis of these radical chain reactions is thought to provide for lifelong maintenance of the molecular chirality of our biomolecules, under the ensemble hydrophobic chiroptical catalysis embodiment of the evolving (work in progress) NGTC/ascorbolysis/UNMR theoretical framework

Under the NGTC/ascorbolysis/UNMR theoretical framework, the concept of an endogenous electrophilic "reserve" capacity is suggested. ATP, PAPS, acetyl-S-Coenzyme A, S-adenosyl methionine, NAD+, NADP+, cAMP, and cGMP are examples of endogenous biomolecules which are chiral and possess electrophilic sites within their structures, making them susceptible to SN2 nucleophilic attack by the L-AA free radical, which has tentatively been assigned to possess nucleophilic radical philicity [11, 15, 202, 203].

2-O-substituted derivatives of L-AA have been proposed [11, 15] to represent a novel class of electrophiles which undergo photo-oxidative super-activation, thereby imparting even greater electrophilicity to their character, making them chemically more reactive. Application of an electrophilicity index [204] and DFT computational chemical studies of both the closed and open-shell 2-O-substituted derivatives of L-AA would potentially be very helpful, prospectively, in predicting there *in vivo* biological reactivity. This putative class of super-activated, 2-O-substituted, radical derivatives of L-AA have been tentatively assigned electrophilic radical philicity [11, 15, 202, 19]. The L-AA free radical is proposed to be an excellent "leaving group" in SN2 reactions with endogenous biological nucleophiles, for which PTMs of proteins are examples. Of note, inflammation is thought to promote PTMs of proteins, polysaccharides, glycoproteins, glycolipids, and polysaccharides [165-169] . PTMs of this type are proposed to be readily accomplished via the anabolic direction of reversible ascorbolysis, i.e. NGTC during the UNMR.

All blood cell lines have been implicated variously in the SSP, including red blood cells, white blood cells, and platelets. Of particular note, are the multiple reports that second messenger levels, i.e. cAMP in platelets, and cGMP levels in monocytes, are induced by L-AA [40, 205-207], *but not by its salts?* Compelling arguments were presented by Davidson & Winey [11, 15] as to the likely rationale for inconsistent results in large randomized clinical trials (RCTs) of vitamin C. It was pointed out that the pH-dependent solvent-dependent, and redox-dependent chemical speciation of L-AA must be carefully controlled to avoid inconsistent, conflicting results. Much of the vast published literature on vitamin C needs to be reevaluated for failure to control for the chemical speciation of L-AA, which is highly likely to influence its in vivo chemical reactivity, biodistribution, and pharmacokinetics. With the aforementioned precautions clearly in mind, the following postulated non-enzymatic reaction mechanisms, (1) and (2) below, are introduced. They are proposed to represent sequential radical chain propagation steps by which cGMP may be reversibly generated nonenzymatically in monocytes (1) and cAMP may be generated nonenzymatically in platelets (2), respectively.

L-AA free radical + GTP → L-AA-2-O-GMP radical + PPi → cGMP + L-AA free radical ……(1)

L-AA free radical + ATP → L-AA-2-O-AMP radical + PPi → cAMP + L-AA free radical ……(2)

Also, under the ascorbolysis hypothesis, the non-enzymatic chemical reactivity of the L-AA free radical, a radical whose radical philicity has been tentatively assigned to be nucleophilic [11, 15, 202, 203, 18, 19], might also afford a non-enzymatic route to reversible depurination and trans-purination reactions of the second messengers, cAMP and cGMP depicted in (3), (4), and (5):

L-AA free radical + cGMP → L-AA-2-O-α-D-ribose-5'-3' cPhosphate radical + guanine …… (3)

L-AA free radical + cAMP → L-AA-2-O-α-D-ribose-5'-3' cPhosphate radical + adenine …… (4)

cAMP + L-AA free radical + guanine → L-AA-2-O-α-D-ribose-5'-3' cPhosphate radical -→ cGMP + L-AA free radical + adenine ……..(5)

In such putative reaction mechanisms, tentative assignments of nucleophilic radical philicity to the L-AA free radical, and electrophilic radical philicity to the 2-O-substituted L-AA radical derivatives, are assumed [11, 15, 202, 203] . Reactions (1) and (2) also assume that the most electrophilic site for SN2 nucleophilic attack by the L-AA free radical, is at the phosphorus atom at the alpha position of the ubiquitous endogenous electrophiles, GTP and ATP, respectively. Such putative reactions are proposed to occur within inflammatory microenvironments, in vivo, which are typically moderately acidic, mildly oxidative, and relatively hydrophobic [11, 15]. The initiation and termination radical chain steps are proposed to occur via a unimolecular dismutation reaction of the L-AA free radical [11, 15]. See Figure 10 below. Of particular note, both cGMP and cAMP possess chiral centers at the phosphorus atom, i.e. the exocyclic oxygen atoms bound to phosphorus are spatially non-equivalent. This point may be relevant to the ensemble HCC hypothesis introduced in this paper. A tacit assumption is made that *in the beginning*, on the primordial/prebiotic planet Earth, small and fast molecules took precedence over big and slow molecules, because our biomacromolecules had not yet evolved, chemically.

Natural killer T-cells, T-lymphocytes, monocytes, and macrophages, have been implicated in lethal cases of the Shwartzman reaction [208]. Vascular endothelial and renal tubular cells have also been implicated in the GSR [160]. Both hematological and immunological components of the SSP are involved, with the onset of hematological events perhaps *preceding* the onset of immunological events [209]. More recently, platelet activation, neutrophil "traps" denoted "NETs", complement activation, and tissue factor have been implicated in SARS-CoV-2 induced immunothrombosis in humans [210]. Inflammatory and hemorheological biomarkers, e.g. Cytokine and chemokine biomarkers, including IFN, TNF, ILs, miRNAs, and TLRs, have been identified during various stages of the SSP. The erythrocyte sedimentation rate (ESR), a hemorheological biomarker of inflammation, is often elevated [211-214, 28, 29, 39, 160, 161]. Tissue Factor (TF) of the extrinsic coagulation pathway and Tissue Factor Pathway Inhibitor (TFPI) are thought to become dysregulated, resulting in loss of hemostasis during the GSR [190, 192, 215, 216] . Fibrin microthrombi [28] are thought to "shower" the systemic microvasculature, e.g. during the Waterhouse-Friderich syndrome (see Figure 6 below), a univisceral variant of the DIC (disseminated intravascular coagulation) syndrome, for which fibrin split products (FSPs) and D-dimer levels are used as clinical biomarkers, e.g. during acute pulmonary embolism (PE) and/or deep vein thrombosis (DVT).

3.7. Protecting the ECM and restoring the EGL: postulated anabolic phase of the SSP

Interestingly, Chinese herbal medicine practitioners have long been aware of antiviral properties of certain plant-derived acid mucopolysaccharides [217, 218]. Hauss's pioneering studies of radiolabeled Sulfate uptake in sGAGs of the ECM during the SSP, provide strong support for the assertion (herein) that the initial phase of the SSP is anabolic [188, 189]. Importantly, ascorbolysis has been postulated [11, 15] to be reversible. Support for this proposal is found in the case report of prompt reversal of virus-induced ARDS by high dose IVC [219, 220]. It is tempting to speculate that in this setting, IVC provided prompt reversal of endothelial dysfunction, restoring membrane function and surface tension in human lung endothelium, providing life-saving restoration of pulmonary gas exchange and extubation.

Survivors of COVID-19 infection are often discharged home from the hospital on "blood thinners" so as to lessen the risk of serious adverse thrombotic events, during their recovery, e.g. low molecular weight heparin (LMWH). Heparin is a sulfated polysaccharide which inhibits the Shwartzman reaction in rabbits [221. 222]. Heparain is a sulfated mucopolysaccharide [223]. Heparin and heparan sulfate structures are examples of molecules whose ensemble, i.e. composite, molecular chirality is very high [224, 225, 186, 187]. Under the ensemble HCC hypothesis, heparin is likely to be one of many biomolecules whose composite chirality is "remembered" by L-AA and the L-AA free radical, which are postulated (herein) to have been involved in their biosynthesis, early in chemical evolution of Life. Clearly, heparin and L-AA are closely related to the SSP. Non-enzymatic sulfurylation of heparin is likely to require participation of a "universal" non-enzymatic sulfurylation factor [13, 14] .

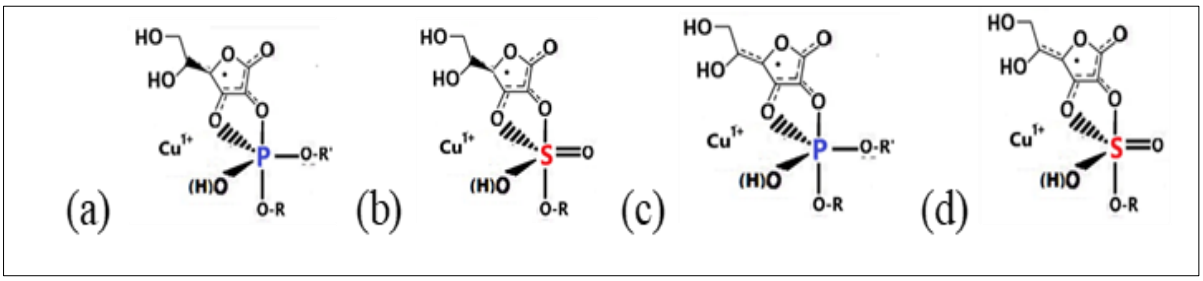

Figure 4 Postulated universal phosphorylation and sulfurylation factors (reactive transients) during early prebiotic chemical evolution. (a) and (b) represent putative L-AA-2-O-phosphate radical and L-AA-2-O-sulfate radical, respectively; (c) and (d) represent putative 2-O-phosphate butenolide radical and 2-O-sulfate butenolide radical, respectively. Butenolide (4,5 unsaturated) ϒ-lactone derivatives of L-AA were identified by JC Deutsch (1994) to be a major early oxidation product of L-AA in presence of Cu2+ within a moderately acidic (pH ca. 4-6) aqueous solution [226, 227] by GC/MS methodology. See [11, 15] for details

Note the chiral center at the sulfur atoms of both figure 4b and 4d (above) which are proposed herein to catalyze reversible stereospecific post-translational sulfurylation, e.g. sulfurylation of HSPGs, CSPGs, polysaccharides, corticosteroids, etc. Similarly, the chiral center at the phosphorus atoms of figure 4a and 4c (above) have been proposed [11, 15] to catalyze non-enzymatic stereospecific post-translational phosphorylation of proteins, in addition to catalyzing reversible non-enzymaticnucleotide triphosphate, i.e. non-enzymatic oxidative phosphorylation, and polynucleotide synthesis. [11, 15] for details. According to pioneering studies of Hauss, acid mucopolysaccharides, i.e. sulfated acid mucopolysaccharides are synthesized in the ECM during the SSP [188, 189] within inflammatory microenvironments, which are typically moderately acidic, mildly oxidative, and relatively hydrophobic.

Much of the composite homo-chirality of our biomolecules during the prebiotic chemical evolution of Life, is proposed to arise non-enzymatically, in the presence of magnetic and or torsion fields acting upon ortho nuclear spin states of water (some physicists have postulated that all magnetic fields possess a small torsion component), spin-coupled to the L-AA free radical. For example, he "elusive", often contemplated, "ascorbyl peroxide", under the evolving ascorbolysis hypothesis, might account for the homo-chirality of our non-enzymatically hydroxylated biomolecules, both large and small (e.g. collagen, D3, dopamine, pituitary neuropeptides, HIF-1-α, DNA) during inflammatory states, via reversible, non-enzymatic mono-oxygenase-like and dioxygenase-like function.

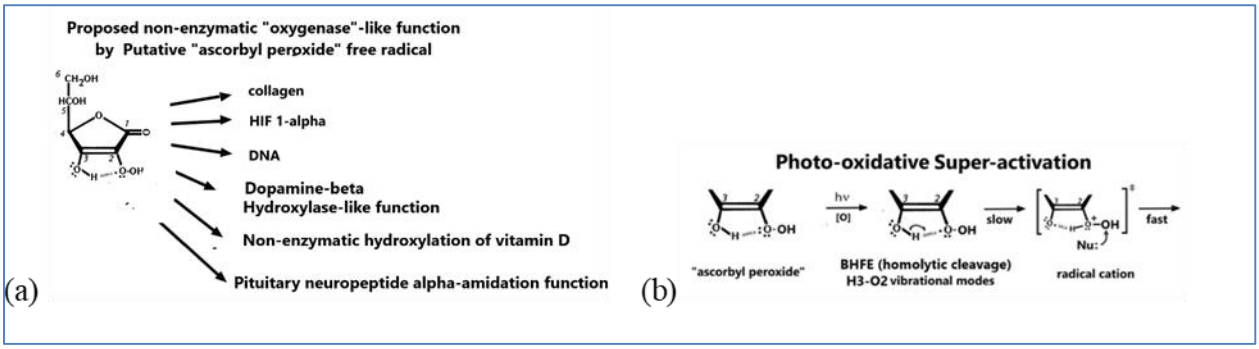

Figure 5 Putative non-enzymatic "mono-oxygenase-like" function under the ascorbolysis and ensemble HCC theoretical framework: (a) proposed structure of putative "ascorbyl peroxide" free radical and (b) putative reversible non-enzymatic, auto-catalytic, radical chain reactions with endogenous biological nucleophiles (denoted "Nu :") afforded by the ascorbolysis hypothesis. See [11, 15] for details

Much of the chirality of heparin, heparan sulfate proteoglycans (HSPGs), and chondroitin sulfate proteoglycans (CSPGs) may reasonably be inferred to have arisen prior to the sulfurylation step(s) which are generally acknowledged to represent post-translational modifications (PTMs) of the protein [228, 229] and/or polysaccharide "substrate". L-AA levels are known to be high in proximity to the Golgi apparatus of the endoplasmic reticulum [128, 230-233, 156]. The ascorbolysis hypothesis provides a chemically-feasible means by which anomeric specificity arises within our biomacromolecules. Anomeric specificity leads to antigenic and morphological determinants of our endogenous macromolecules. Characteristic chiral helical morphologies (chiral helicity) of many of our endogenous proteins, polysaccharides,, glycolipids, and nucleic acids are postulated to arise from helicity of spin water [234-237], whose chirality is fractal, related to the "fractal dimension", specifically the chirality of ortho and para nuclear spin states of spin water [14, 102, 234] .

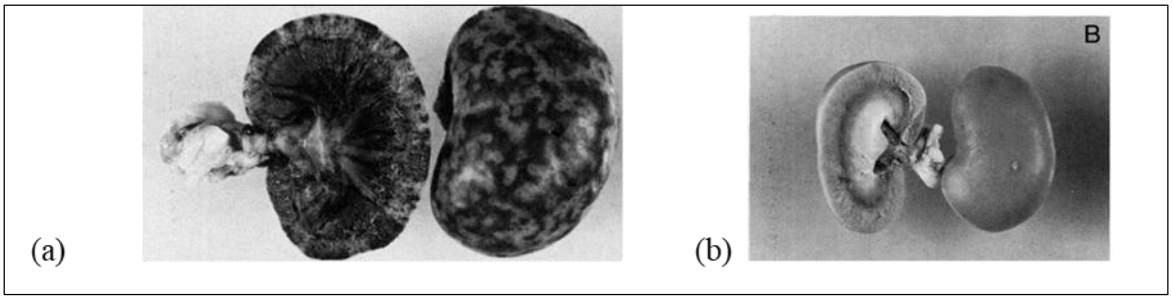

Figure 6 Waterhouse-Friderich syndrome is an example of the univisceral type of SSP: (a) The gross appearance of hemorrhagic necrosis of the kidney (generalized Shwartzman reaction) from a rabbit administered antirabbit EPI Fab, 10 mg/kg, before and 2 hours after the injection of endotoxin. (b) The normal gross appearance of the kidney from a rabbit injected with nonimmune IgG, 10 mg/ kg, before the injection of endotoxin. Images (with captions) from Sandset (1991) [190] are reproduced here with permission of the publisher.

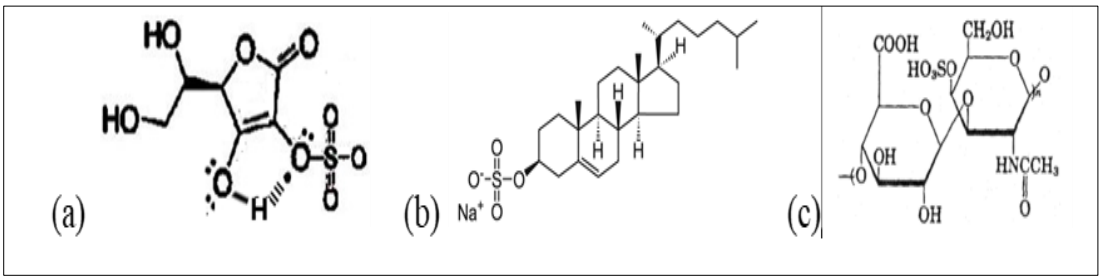

Figure 7 Proposed need for a non-enzymatic, universal sulfurylation factor. (a) proposed structure of the L-AA-2-O-sulfate radical; (b) the known structure of the ubiquitous sterol sulfate "cholesterol sulfate", shown to be sulfurylated nonenzymatically by L-AA-2-O-sulfate by Verlangieri & Mumma (1973) [238]; and (c) the known structure of chondroitin sulfate, which was shown to be sulfurylated non-enzymatically by L-AA-2-O-sulfate by Hatanaka & Egami

(1976) [239]. Readers should note that molecular chirality of (a), (b), and (c) is a structural characteristic which might be enhanced by hydrophobic chiral "seeding" under the ensemble HCC hypothesis introduced herein

Of note, sulfurylated corticosteroids and proteoglycans, e.g. HSPGs and CSPGs, are likely to require a stereospecific, regiospecific, and chemio-specific "universal" non-enzymatic sulfurylation factor such as the L-AA-2S derivative initially synthesized by Ralph Mumma (1968) [240] and subsequently studied *in vivo* by Verlangieri & Mumma (1973) [238] and Hatanaka & Egami (1976) [239]. These studies [238] and [239], effectively provide an initial proof of concept for the NGTC/ascorbolysis/UNMR theoretical framework [11, 15]. In light of [11] and Beckett (2014) [156] , it is reasonable to infer that the "dialyzable transfer factor" [39], i.e. L-AA and serotonin, regulates (a) human hemostasis, (b) gene expression, and (c) immune function during the SSP and UNMR. Proper burn and wound healing and prevention of scurvy in humans is today known to have an absolute requirement for L-AA, typically acquired from dietary plant, vegetable, and fruit sources [241] . Recovery from sepsis and SARS-CoV-2 infections, requires adequate levels of L-AA. Of course, prevention is typically far less expensive and less risky than resorting to therapeutics [242-245].

The main protease ("Mpro") of the SARS-CoV-2 pathogen is an attractive target for drug design, if off-target effects can be minimized. We suggest various ensembles of naturally-occurring compounds may provide clinically-useful therapeutics in countering the viral pathogen by means of ensemble HCC [25, 246]. We propose that the antiviral and immunomodulatory synergy between L-AA and quercetin may be readily explicable under the ensemble HCC theoretical framework presented herein. It is conceivable that methylation, glycosylation, sulfurylation, and recycling of quercetin, and correction of the STAT3 phosphorylation defect, may be catalyzed non-enzymatically by ascorbolysis, within inflammatory tissue microenvironments. Under this proposal, L-AA would essentially *potentiate* the antiviral and immunomodulatory activity of quercetin, on several biosemiotics levels, concomitantly [25, 246, 11, 15, 18, 19].

Interestingly, a recent case report documented recovery from virus-induced acute respiratory distress syndrome ("ARDS") with adjunctive administration of high-dose intravenous L-ascorbic acid (IVC) (Fowler 2017) [219], suggesting that pulmonary membrane permeabilization was reversed and surface tension was normalized by high dose IVC treatment. This effect is likely to be synergistic with corticosteroid and/or serotonin reuptake inhibitors administration, under the ensemble hydrophobic chiroptical catalysis ("ensemble HCC") hypothesis. It has been reported that dexamethasone ("DEX") can be life-saving to mountain climbers attempting to climb some of the world's tallest mountains [247].

Importantly, L-ascorbic acid has long been known to inhibit aryl sulfatases, matrix metallo proteinases [214, 248-250], and proteases, both seriene- and cysteine-proteases (Caspaces) [242]. This makes sense, intuitively, because Hauss's earlier work clearly demonstrated that the initial phase of the SSP is anabolic, e.g. favoring the incorporation of sulfate into glycosaminoglycans of the extracellular matrix (ECM) [188, 189]. In 2015 conference proceedings, a need for a "universal sulfurylation factor" was proposed, in order to cope with moderately acidic pH and oxidative conditions which characterize inflammatory microenvironments (see [13, 14]). The reversible anabolic/catabolic property of "ascorbolysis" [11. 15], and Figure 3 (above) and Figure 15 (below) has been proposed to represent one of several non-enzymatic supramolecular mechanisms by which L-AA counters viral pathogens, during NGTC and the UNMR. It may be postulated that when TFPI is consumed during the consumptive coagulopathy of the microvasculature represented by the SSP, that the delicately balanced hemostatic "equipoise" will be "tipped" from thrombosis to bleeding, <u>*but for*</u> adequate blood levels of L-AA. Reversible post-translational and pre-transcriptional modification of proteins, catalyzed non-enzymatically by L-AA, the L-AA free radical, and their 2-O-substituted derivatives, essential for genomic stability, is thought to be 'powered by radiant and or zero-point energy' (quantum vacuum fluctuations).

3.8. Preventing the postulated catabolic hydrolytic phase of the SSP: proposed therapeutic role for the ensemble HCC hypothesis *upon validation*.

Ultimately, during the catabolic phase of the SSP, e.g. SARS-CoV-2 related sepsis, quantum biosemiotics phase coherence is thought to fail on multiple scales of time and space, resulting in genomic instability, loss of redox homeostasis, hijacked energy metabolism during infection [11, 15, 39, 251, 252], loss of glycosidic anomeric fidelity (e.g. loss of antigenic determinants), immune dysfunction, and a consumptive coagulopathy of the microvasculature [10, 12-14] . Such a postulated scenario, i.e. the catabolic, hydrolytic phase of the SSP, would likely occur more readily in patients suffering from subclinical or clinically-marginal scurvy [11, 13-15, 241] . Moreover, the combination of NAD+ depletion and L-ascorbic acid deficiency is likely to predispose to impaired innate immune response [251, 252] . Baseline pre-infectious levels of NAD+ and L-AA, along with various other micro-nutrient levels, might result in some observed clinical variability of the temporal component of priming and provocation inoculations of the SSP. Subclinical or marginal scurvy is rarely diagnosed, yet readily treatable [241].

Sadly, the global pandemic persists, now in the form of new variants, e.g. “Delta” and "Omichron". Government policies don't appear to be succeeding. in many respects, we appear to be repeating *and “doubling-down”* on recent mistakes. Long held conventional "wisdom" (dogma), both clinical and scientific, need to be revisited. The recent WARNING by Gundry in 2021 Abstracts was published in *Circulation* [7, 8]. His data and warning appear to parallel and explain the numerous reports of myocarditis, pericarditis, and thrombotic events, which have been reported by the U.S. CDC in their guidance to physicians and the U.S. CDC VAERS database, notwithstanding the generally acknowledged gross under-reporting of vaccine-associated adverse events to the VAERS database. Recent studies from Israel have also reported an association of mRNA vaccination to myocarditis, amongst serious adverse events [103-106] . Further reports in the recent published literature [56, 107, 108] provide clinical case reports, including cardiac magnetic resonance (CMR) data, provide strong clinical support for the biomarker data in the Gundry Abstracts [7, 8]. Any risk/benefit analysis of parenteral exogenous nucleic acid inoculations, e.g. gene therapy [77-83], should acknowledge that the “risk” has a name, i.e. the SSP, for which there is a considerable body of published data over the last century. To best understand, predict, and mitigate risk, a better understanding of the pathophysiology and biophysics of the SSP is called for.

Optimistically, the ensemble HCC hypothesis introduced herein, upon validation, offers the possibility of minimizing off-target effects which appear to impede and impair current mRNA vaccines and antiviral therapies. In countering the SARS-CoV-2 viral pathogen, for example, ensemble HCC by L-AA and ensembles of chiral hydrophobes (e.g. corticosteroids, bioflavonoids, repurposed SSRIs, HCQ, ivermectin, etc.) offer the promise of countering the pathogen by supramolecular biological means, wherein inhibition of viral entry, replication, and packing and assembly, take place concomitantly, phase-coherently, on all biosemiotics levels. Such a novel approach to countering human disease represents a potentially sustainable, complementary, and/or alternative approach to the current mRNA vaccine strategy. Beyond its potential as a new class of antiviral therapeutics, is the possibility of cost-effective primary prevention, which would be win-win-win in terms of efficacy, safety, and cost. Governments and healthcare providers would, if the ensemble HCC hypothesis is validated, not have to live in fear of the “next” viral pandemic or variant strain to arise. The intrinsic supramolecular chirality of our biomacromolecules, whose morphology and function evolved chemically over 4 billion years, would act in concert with the tempo and rhythms set by magnetic and torsion fields , spin water, and the L-AA free radical, lessening destructive interference and restoring diversity to the ecosystem, both internal and external.

Clinically, endothelial dysfunction [220], generally, and he Sanarelli-Shwartzman Phenomenon (SSP), specifically, is neither rare nor unpredictable [10, 12]. Thus, the inflammatory microvascular and thrombotic events being reported in temporal association with the mRNA inoculations should not be portrayed as either rare or unpredictable *"Black Swan"* events. To wit, the SSP has been observed and studied for over a century. Sepsis, cancer, and myocardial ischemia, e.g. "acute coronary syndromes (ACS), have probably been present and afflicting humans since antiquity, e.g. *Purpura Fulminans* and sepsis [13, 209] . Several of the published papers in [39] are directly on point to the question raised rhetorically, in the title of this paper. It has been observed for nearly a century that nucleic acids often strongly stimulate and/or suppress the human immune system, but in many instances does so non-specifically. The general adaptation syndrome studied in great detail by Hans Selye [36, 37, 191] and others is perhaps the opposite of the fanciful “magic bullet” therapies proposed by Paul Ehrlich. Directly relevant to the adverse event profile reported for the mRNA vaccines is the section in [39] which focuses on toxicity of certain parenterally-administered polynucleotides and polynucleotide complexes (see [39] at pages 111, 113).

> One of the deterrents to the use of the adjuvant effect of nucleic acids has been their *occasional toxicity* perhaps operative during delayed-type hypersensitivity responses. ---Excerpted from Torrence (2012) [39]. Underline and italics have been added for emphasis.

4. Ensemble HCC - a supramolecular biological strategy to combat viral pathogens

Readers should please note that the “HAT” protocol, consisting of hydrocortisone, L-ascorbic acid, and thiamine, has become standard practice in the treatment of critically-ill patients with sepsis [26, 27]. It remains to be seen whether a combination of empiric NAD+ repletion and L-ascorbic acid supplementation may have synergistic therapeutic and/or preventative benefit, clinically. Empiric NAD+ repletion [251, 252], L-ascorbic acid (L-AA) supplementation, and bioflavonoid (e.g. quercetin) administration might be considered as primary prevention. Of note, the combination of quercetin and L-AA has been recently shown to possess both antiviral and immunomodulatory properties, perhaps acting at the level of interferon (IFN) [25]. In 2019, it was reported that IFN-α, induced by either IL-12 or LPS, was a crucial event in sensitization for the GSR [161]. The underlying physical rationale for the observed synergy may represent hydrophobic catalysis by L-ascorbic acid [11, 15, 41, 42]. Interestingly, *serum surface tension* was reported by Enoki Yoshisuke to be transiently elevated after provocation injection for the Shwartzman reaction. See [10] at page 1403.

Importantly, prospective population-scale case-control studies, perhaps employing the PULS Cardiac Test longitudinally (with patients as their own control) are urgently needed to ascertain possible synergistic primary prevention and reversal (rescue) from oxidative stress and the catabolic phase of the SSP, comparing empiric combinations of NAD+ repletion. Bioflavonoids (quercetin), curcumin, anthocyanins, and L-ascorbic acid amphiphiles (L-AAAs) supplementation (see [11] and [15]).

The SSP, often referred to as the Schwartzman reaction, is neither especially rare nor particularly unexpected. The SSP is not fully understood [20, 209]. It may represent an essential component of evolutionary homeostasis and genomic stability of the human species. Similarly, so-called "dialyzable transfer factor(s)" [39, 40, 207], e.g. L-ascorbic acid, serotonin, and perhaps, depending on pH, redox state, nuclear spin state of water, chirality, and hydrophobicity of the microenvironment, 2-O-substituted derivatives of L-ascorbic acid, have likely played a central role, f*rom the beginning*. A useful societal goal might be to employ all technologies at our disposal to reverse-engineer the "initial common pathway" to Life with AI and network theory techniques [11, 15, 159]. The human immune response may be stimulated or suppressed [39]. Enoki (see [10] at page 1403) and others [39] have shown that nucleic acids are not the only means of eliciting generalizable biophysical responses [10, 12, 36, 37, 39], *in vivo*. Indeed, certain proteins, polysaccharides, phospholipids, and peptidoglycans have demonstrated this capacity [10, 12, 36, 37, 39]. As was suggested by Selye in 1950 [35], a combination of several non-specific stimuli might represent biophysical "seeding" of the microenvironment, as a potentially preventive and/or therapeutic prelude, effectively "boosting" both humoral and cell-mediated immune responses, for better or worse. Optimistically, therapeutic "synergies" might be identified. This approach would be a departure from the so-called "magic bullet" concept originally described by Paul Ehrlich [253-256]. If the current ongoing, persistent viral pandemic has taught us anything, it is that more research in this area is called for.

4.1. Proposed means for delivery of L-fucose to the Golgi apparatus by putative "ascorbyl fucoside free radical" (L-AA-2-O-α-L-fucoside free radical).

Fucosyl transfers to endogenous biological nucleophiles has gained recognition as playing an important role in immune recognition during the human immune response [153, 154, 171]. Post-translational modification (PTMs) of proteins is thought to take place at or near the Golgi apparatus of the endoplasmic reticulum [172, 173]. L-AA is thought to mitigate oxidative endoplasmic reticulum (ER) stress [156, 230-232, 257] . This role probably arose prebiotically, at or near primitive "ribozymes". It has been suggested that the L-AA free radical may represent one of the earliest "enzymes" during the origin of Life [11, 15]. Non-enzymaticfucosylation is proposed herein to proceed regiospecifically, stereospecifically, and chemiospecifically within a moderately acidic, mildly oxidative, relatively hydrophobic microenvironment under the ensemble HCC hypothesis.

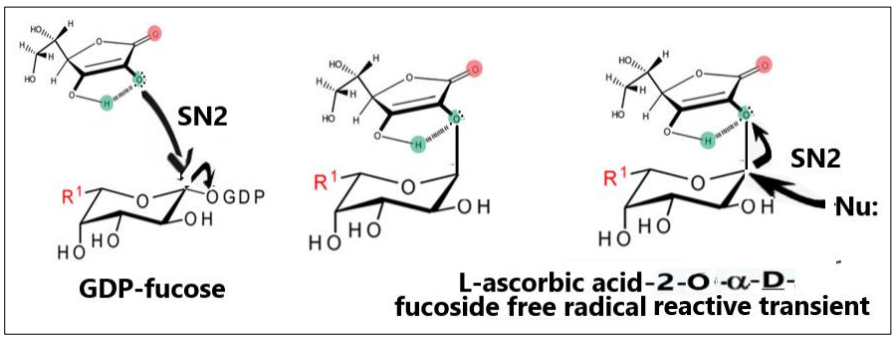

Figure 8 Proposed stereospecific non-enzymatic ascorbolysis of GDP fucose via SN2 nucleophilic attack by the L-AA free radical upon the C-1 carbon atom, with GDP as leaving group, generating a putative L-AA-2-O-α-D-fucoside free radical reactive transient for subsequent fucosylation of biological nucleophiles, e.g. proteins. Of note, the mechanism provides for retention of anomeric configurations, generally, providing for anomeric fidelity during inflammatory states. The process is postulated to be reversible. Proper innate immune function is proposed to critically depend on maintenance of anomeric fidelity, hence preservation of antigenic determinants, during, for example, discrimination by TLRs of PAMPs. The scheme is generalizable to many, if not all, endogenous biological electrophiles. *Umpolung* (entropic charge reorganization) catalysis and proton coupled nucleophilic attack(s) are mechanistic tenets [258-260]. The scheme is proposed to consist of two successive SN2 radical chain propagation reactions, wherein sequential, back-to-back inversions of stereochemistry at C-1 yield net retention of anomeric configuration. Overall, the scheme provides non-enzymatic maintenance of anomeric fidelity during inflammatory states, e.g. during the human immune response

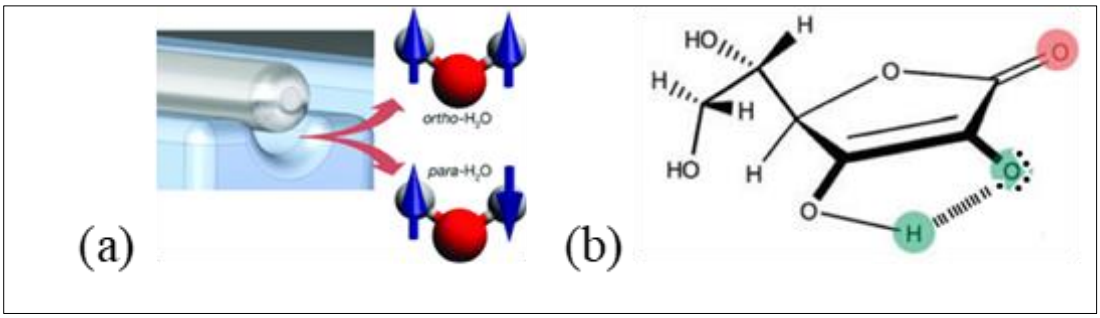

Figure 9 The major "players" in the NGTC/ascorbolysis/UNMR/ensemble HCC theoretical framework: (a) Graphical depiction of the ortho and para, nuclear spin states of water from [110] (Horke 2014) reproduced here with permission of the publisher; (b) graphical depiction of the L-ascorbic acid free radical, for which Davidson coined the term "nano-scalpel" to convey the instrument used by a fanciful great surgeon, slicing, splicing, sewing, and annealing on the molecular nano-scale. The structure is adapted from a structure found in a quantum theory of atoms in molecules (QTAIM) study (Ebrahini et al 2016) [261] of hydrogen bond cooperativity by L-ascorbic acid with permission of the publisher

The L-ascorbic acid free radical has been tentatively assigned nucleophilic radical philicity in SN2 reactions during two successive radical chain propagation steps, described as ascorbolysis [11, 15]. See Figure 3 (above). Of particular note is the recent finding that organic radicals induce self-assembly, supramolecular chirality, and circularly polarized luminescent (CPL) magnetic emitters [262, 263, 146].

During chemical evolution of Life, it may be suggested that the mechanism by which the earliest homo-chiral peptides and proteins appeared, prior to the advent/emergence of "enzymes" at the primitive primordial "ribozyme" is similar in many respects to the mechanism which have been proposed in 2021 [11, 15] to underlie ascorbolysis. The postulated reversible ascorbolysis of amide bonds may well have prebiotic precedence. We suggest that prebiotic protein folding events at primordial "ribozymes" might easily have been facilitated by ensemble HCC . Experiments might be designed to look for enantiomeric purity of such "early" steps in chemical evolution. Today, the elongation factor at the ER may well have evolved, chemically, as a "mimic" of nonenzymatic radical chain propagation steps postulated in the ascorbolysis hypothesis during inflammatory and cytoproliferative states. Under the ensemble HCC hypothesis, intrinsic chirality of our biomolecules, both large and small, is proposed to enable proper protein folding and routing of misfolded newly synthesized proteins within the endoplasmic reticulum and Golgi apparatus, the equivalent of primitive, prebiotic, primordial "ribozymes" [155], wherein chiral hydrophobes act as molecular "chaperones", and L-AA and L-AA free radicals provide a reversible, supramolecular "surgeon's nano-scalpel", by way of analogy. Upon validation, the ascorbolysis and ensemble HCC hypotheses should facilitate use of stochastic complexity theory, AI, and network theory to reverse-engineer the "initial common pathway" to Life on Earth [10-15, 157-159].

There is a critically-significant distinction (dichotomy) between the fanciful "magic bullet(s)" proposed by Ehrlich [253-256] and the orthomolecular "surgeon's nanoscalpel" proposed by Davidson and Winey in 2021 [11, 15]. The "nanoscalpel" has been proposed to be reversible, pH-dependent, solvent-dependent, and quantum phase coherent across all biosemiotics levels, in vivo, thereby minimizing epigenetic "collateral damage" to the living host [25, 10, 12]. Similarly, there is likely to be a fundamental distinction between orthomolecular supramolecular biology during human chemical evolution and supramolecular xenobiology, which may *or may not* be prospectively conducive to genomic stability, evolutionary resilience [264-267], and biosemiotics coherence. "At present, no specific antiviral therapy or vaccine has been proven to be effective for treating or preventing of HCoV infections [267]." [266-268].

On an optimistic note, it may be possible under the NGTC/ascorbolysis/UNMR theoretical framework to develop a supramolecular biological strategy with which to target the site-specific cleavage of SARS-CoV-2 RNA and its associated proteins [11, 15]. Regiospecific, stereoselective, cleavage of viral RNA, viral DNA, and viral proteins is postulated to flow logically, as biophysical, supramolecular consequences of the ensemble HCC hypothesis.

The putative rate-limiting intermediates and transition states are typically chiral making the ensemble hydrophobic chiroptical catalysis (denoted herein "ensemble HCC") hypothesis, a logical extension of the NGTC/ascorbolysis/UNMR theoretical framework [11, 15]. Supramolecular chiral helicity of "spin water," L-AA, and the L-AA free radical is proposed to play central roles. Magnetically altered reaction yields and low magnetic field effects are expected based in part on recent pioneering study of Evans in 2016 [199]. The interaction(s) of flavin mononucleotides and L-AA are thought (by us) to typify the type of chemistry catalyzed nonenzymatically under the ensemble HCC theoretical

framework. Magneto-receptors and low magnetic field effects are generally thought to enable birds (and bats) to fly at night. As 5G technology "ramps up" there is considerable uncertainty as to how chiral torsion EM field effects will impact commercial navigation, as well as that of birds, bats, and insects, that provide pollination of plants, and provide a substantial proportion of the food supply. If ensemble HCC provides the biophysical basis for bio-diversity, as well as genomic stability and genomic resilience of the human species, 5G deployment may need serious reconsideration. Cross-talk between solar light-harvesting technologies and 5G technology may need prospective consideration. The light-harvesting aspects of the ensemble HCC hypothesis may be essential for Life (see Figure 10c).

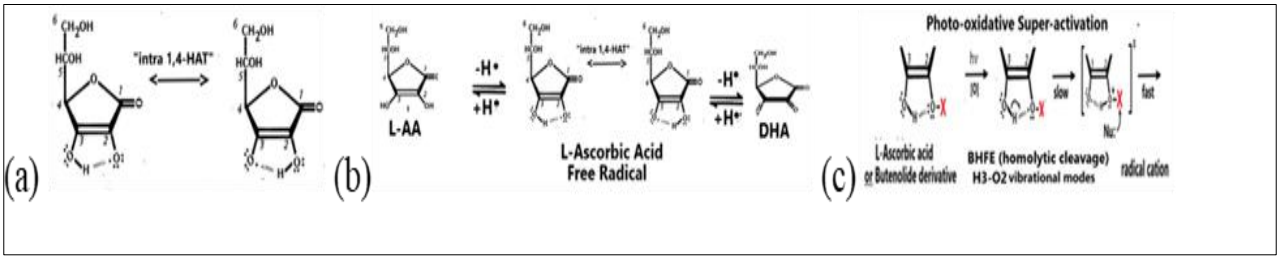

Figure 10 Chemical mechanistic depiction of the postulated ascorbolysis hypothesis [11, 15]. (a) intramolecular-1,4-hydrogen atom transfer ("intra-1,4-HAT") is proposed to stabilize the L-AA free radical and lower activation energies for the initiation, propagation, and termination steps of branching cascades of self-assembling, phase-coherent, auto-catalytic, radical chain reactions comprising the UNMR; (b) postulated first-order, unimolecular "dismutation" mechanism via intra-1,4-HAT providing initiation and termination steps to the radical chain reactions catalyzed nonenzymatically by ascorbolysis and ensemble HCC; and (c) mechanistic depiction of postulated photo-oxidative super-activation of L-ascorbic acid and its 2-O-substituted derivatives during the UNMR, e.g. during reversible post-translational modifications of proteins [168]

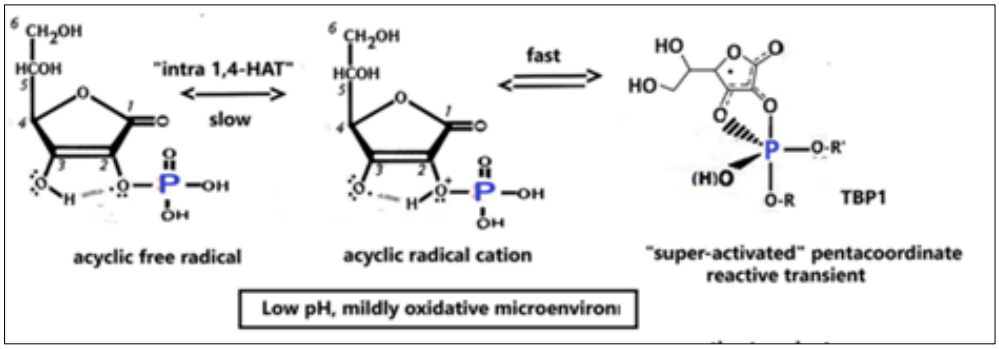

Figure 11 Pre-equilibrium intramolecular H-bonding precedes oxidative photo-activation, followed by (a) *rate-limiting homolytic cleavage of the O-H bond at the 3-position* accompanied by intramolecular 1,4 hydrogen atom transfer with formation of a radical-cation during charge reorganization ("umpolung" catalysis [258-260] and orbital steering towards the "sigma hole", quantum tunneling; and (b) subsequent fast cyclization to form a cyclic pentacoordinate phosphorus free radical. The trigonal bipyramidal cyclic pentacoordinate free radical reactive transient is then able to pseudorotate (pairwise fluxional isomerization of trigonal bipyramidal intermediates) following Westheimer's rules [269, 270], with "flattening" of the free energy landscape. In the low pH, mildly oxidative, relatively hydrophobic aqueous microenvironment. The super-activated cyclic pentacoordinate phosphorus reactive transient is able to stereo-specifically, regio-specifically, and chemio-specifically phosphorylate endogenous nucleophiles, including RNA, DNA, and proteins, behaving much like a primordial molecular motor, e.g. a non-enzymatic RNA polymerase, or nuclease in the reverse direction

The activation energy for the proposed rate-limiting O-H bond homolytic cleavage step in ascorbolysis is thought to be subject to (a) pre-equilibrium intramolecular hydrogen bonding, (b) inductive effects of the functional group being transferred, (c) vibrational modes of the O-H bond at the 3-position, (d) nuclear quantum "tunneling" along the path of the H3-O2 intramolecular hydrogen bond, and (c) the presence of a σ-hole (singly occupied sp3 orbital) at the O-2 position (upon photo-oxidative super-activation. Nuclear quantum tunneling during proton coupled electron transfer (PCET) by L-AA is supported by the measurement of unusually large kinetic isotope effects, experimentally, when studied in *relatively hydrophobic* dioxane/water mixtures of L-AA [271-273].

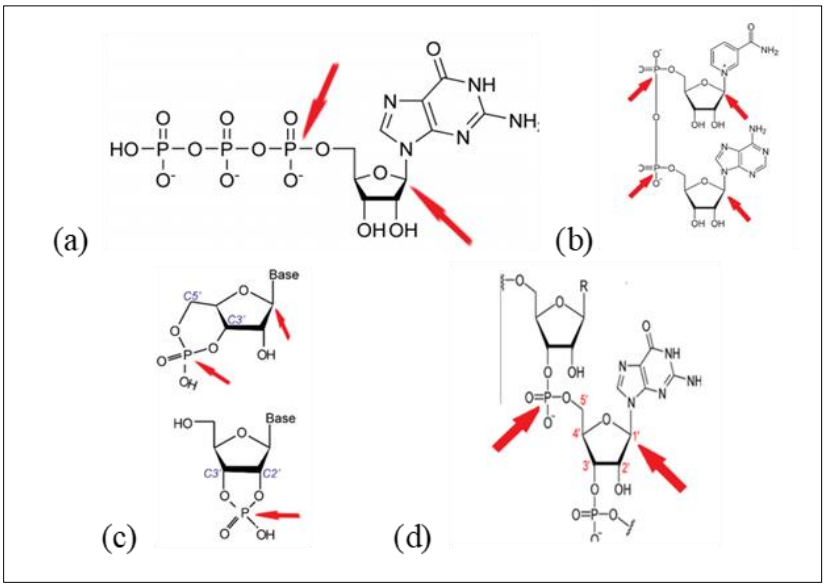

Figure 12 Electrophilic sites (denoted by red arrows) within endogenous electrophiles, e.g. dNTPs, NTPs, ATP, GTP, S-adenosyl methionine, acetyl-S-coenzyme A, NAD+, NADP+, cAMP, cGMP, miRNA, RNA, and DNA. (a) the α-phosphorus atom of ATP and GTP (probably complexed to a divalent cation such as Mg2+ and/or Mn2+) are potential sites for reversible non-enzymatic, auto-catalytic SN2 attack by the L-AA free radical with pyrophosphate (PPi) acting as leaving group, under conditions promoting proton-coupled nucleophilic attack (PCNA) followed by radical chain polymerization to form either RNA polymers, DNA polymers, or cyclization to form 5'-3'-cyclic nucleotides; (b) several electrophilic sites within NAD+ and NADP+ provide sites for putative SN2 attack by the L-AA free radical (successive "back-to-back" inversions of stereochemistry at the C-1 anomeric position, provide stereospecific non-enzymatic retention of stereochemistry of mono-ADP ribosylation (MARylation) and polyADP ribosylation (PARylation) of endogenous nucleophiles); (c) the endogenous cyclic nucleotides, e.g. cAMP and cGMP, upon SN2 reaction with the L-AA free radical provide reactive "transients" which may effectively regulate energy metabolism, redox homeostasis (B3 metabolome), the fluid genome, and immune function in humans; and (d) electrophilic sites within miRNA and RNA are potential sites for reversible SN2 attack by the L-AA free radical with subsequent regulation, editing, recycling, error-correction, and polynucleotide polymerization, of the dynamical "fluid genome".

Ensemble HCC (described herein) is a central tenet of the NGTC/ascorbolysis/UNMR theoretical framework. Such a mechanism, if validated experimentally, should be amenable to application of stochastic complexity theory [157], AI, and network theory, perhaps providing a route to reverse-engineering the "initial common pathway" to Life on Earth

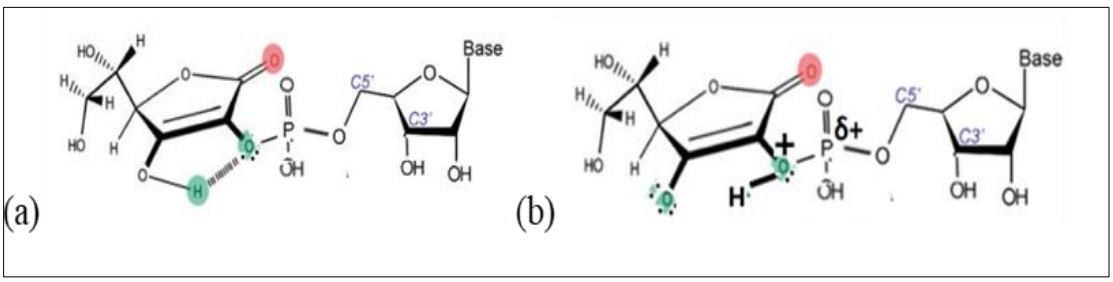

Figure 13 Postulated radical chain propagation steps in prebiotic RNA polymerization and cyclic 5'-3' nucleotide synthesis. (a) depiction of reactive transient in first of two successive radical chain propagation steps; (b) depiction of reactive transient in second of two successive radical chain propagation steps

Under the NGTC/ascorbolysis/UNMR/ensemble HCC theoretical framework, a possible scheme for the nonenzymatic prebiotic synthesis of RNA. DNA, cAMP, cGMP, and cNMPs is contemplated. Reactions (6) and (7) below are postulated to result in prebiotic non-enzymatic RNA synthesis. Reactions (11) and (12) below are proposed to provide alternative routes to RNA polymerization. The relative proportion of RNA polymerization via (6) and (7) versus RNA polymerization via (11) and (12) is proposed to be governed by apicophilicity of TBP ligands, *Berry* pseudorotation of TBP intermediates, and substrate availability (see Figure 12(a),(c) and Figure 13(a),(b) above). Reactions (8) and (9)

below are postulated to result in DNA synthesis. Reaction (10) below is postulated to result in either RNA polymerization or 5',3'-cyclicNMP formation, perhaps depending on "substrate" availability. The hydrophobic effect, π-π base stacking interactions, hydrogen bond interactions, divalent metal ions (denoted M2+ below), and Westheimer's guidelines [269, 270] are postulated to control reversible, auto-catalytic, non-enzymatic polynucleotide and cyclic nucleotide formation. Reactions (6)-(13) below are postulated to take place within a moderately acidic, mildly oxidative, relatively hydrophobic microenvironment, in the presence of spin water and powered by radiant and or zero-point energy (quantum vacuum fluctuations).

L-AA free radical + NTP + M2+ → L-AA-2-O-5'-NMP radical + PPi + M2+ …….. (6)

L-AA-2-O-5'-NMP radical + M2+ + 3'-NMP → RNA polymers + L-AA free radical + M2+…….. (7)

L-AA free radical + dNTP + M2+ → L-AA-2-O-5'-dNMP radical + PPi + M2+ …….. (8)

L-AA-2-O-5'-dNMP radical + M2+ + 3'-dNMP → DNA polymers + L-AA free radical + M2+…….. (9)

L-AA free radical + NTP + M2+ → L-AA-2-O-5'-NMP radical + PPi + M2+ → 5',3'-cNMP + L-AA free radical…….. (10)

L-AA free radical + 2',3'-cNMP + M2+ → L-AA-2-O-3'-NMP radical + M2+ …….. (11)

L-AA-2-O-3'-NMP radical + 5'-NMP + M2+ → RNA polymers + L-AA free radical + M2+…….. (12)

L-AA-2-O-3'-NMP radical → 5',3'-cNMP + L-AA free radical + M2+ …….. (13)

RNA and DNA polymerizations (7) and (9), respectively, and cNMP formation (reactions 10 and 13) are alcoholysis reactions wherein alcoholysis is favored over hydrolysis within relatively hydrophobic microenvironments. See Figure 3 (above) for the general case. Similarities between putative prebiotic nonenzymatic reactions (6),(7) and (10)-(13) above, and enzymatic reactions thought to occur at the ER and Golgi apparatus are suggested. It is inferred that small and fast, non-enzymatic chemical evolution of small molecules preceded comparably big and slow enzymatic chemical evolution of our biomacromolecules [274, 275]. Further, it is not unreasonable to surmise that the large molecules of today, might in certain respects, be constrained by the small molecule evolutionary "events", such as the emergence of homo-chirality, which preceded them, on the evolutionary timescale.

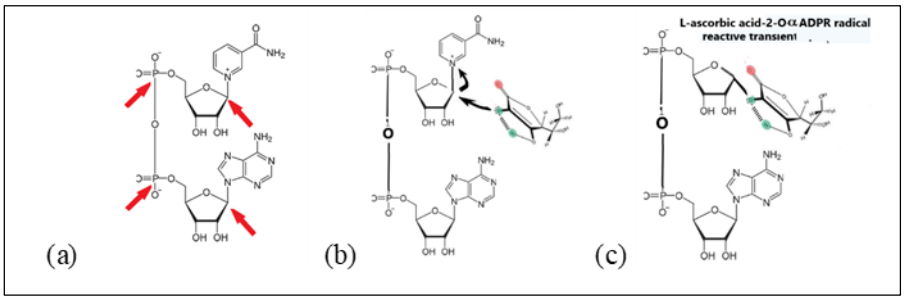

Figure 14 Sequential back-to-back inversions of stereochemistry at C-1 of NAD+ yields retention of stereochemistry during mono-ADP ribosylation (MARylation) and poly-ADP ribosylation (MARylation) of proteins during inflammatory states. (a) potential electrophilic sites within NAD+ for non-enzymatic reversible cleavage and recycling during energy metabolism and redox homeostasis by the B3 metabolome; [277, 278, 251, 252]; (b) Proposed non-enzymatic radical chain propagation steps under the ascorbolysis hypothesis. SN2 nucleophilic attack by the L-AA free radical upon C-1 carbon atom of NAD+; and (c) putative L-AA-2-O-α-D-ribose radical reactive transient in reactions with endogenous nucleophile targets during reversible, stereospecific *MARylation* and *PARylation* of proteins [271-273, 161, 251, 252]

Human health, generally, might well prove to be based *in total* on supramolecular orthomolecular chemical biology, typified by the "general adaptation syndrome" [35]. Inspired by Selye, a paper by Elia in 2017 [140], and a recent publication from Korea (Mun et al 2020) [47], a logical, science-based hypothesis to explore is whether or not non-specific hydrophobic chiral "seeding" of the microenvironment might catalyze the UNMR, avoid the catabolic phase of the SSP, and provide preventive and/or therapeutic benefit in countering the SARS-CoV-2 pathogen and in mitigating and rescue from adverse events associated with the mRNA vaccines. Biophysical spectroscopic measures of composite

or ensemble chirality may prove useful in evaluating such a non-specific hydrophobic chiral (chiroptical) "seeding" proposal. Such a proposal, if validated, might provide a supramolecular non-enzymatic biological means of (a) restoring chirality control and anomeric fidelity during viral pathogen-related sepsis, (b) provide site-specific cleavage of viral RNA and viral proteins by the L-ascorbic acid free radical upon photo-oxidative super-activation, and (c) provide an ensemble stochastic chiroptical "drive" for radical chain reactions, during the UNMR. Such a novel approach to human health, if validated, may have applicability to many disciplines of medicine, including preventive medicine, infectious disease, hematology/oncology, cardiology, neurology, rheumatology, food science, agronomy, regenerative medicine, anti-ageing, and "greening" of the biosphere, generally, including air, water, food, medicines, and vaccines.

Under the ascorbolysis hypothesis, such electrophilic sites are postulated to undergo reversible, stereospecific SN2 reactions with the L-AA free radical. Such a non-enzymatic "recycling" mechanism provides a facile means of redirecting energy metabolism to RNA polymerization, cyclic nucleotide ("second messenger") formation, ADP-ribosylation, depurination, and trans-purination, as circumstances warrant, e.g. during the SSP, cytoproliferation, infection, and sepsis. Ascorbolysis is proposed to be photo-oxidatively super-activated, spin-correlated with ortho nuclear spin states of water, and powered by radiant and or zero-point energy (quantum vacuum fluctuations), i.e. torsion fields which are chiral and likely fractal.

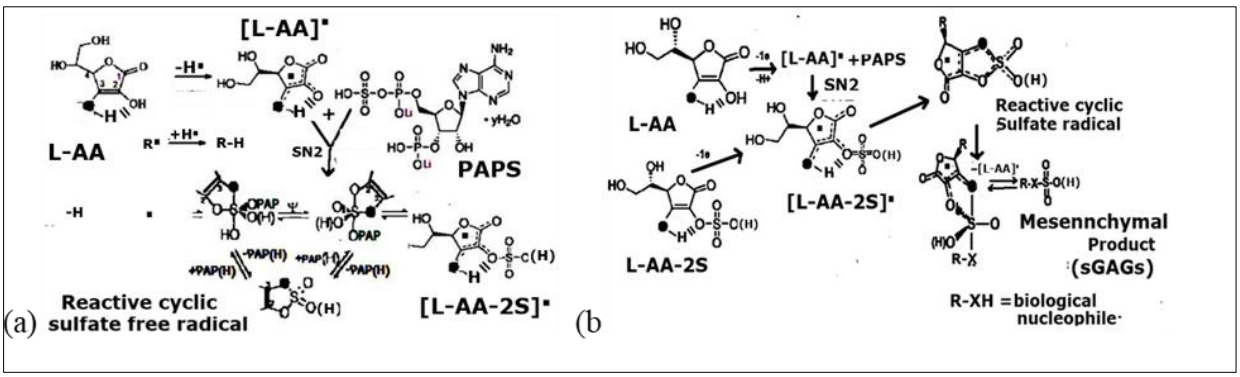

Figure 15 Ascorbolysis of endogenous electrophiles. Preformed PAPS and ATP (not shown) provide "penultimate" electrophilic sulfuryl and phosphoryl (not shown) sources, respectively, within inflammatory microenvironments, e.g. during the anabolic phase of the SSP. Scheme (a) depicts the first of two successive radical chain propagation steps. Scheme (b) depicts the second of two successive radical chain propagation steps. Together (a) and (b) result in the nonenzymatic sulfurylation of endogenous nucleophiles such as glycosaminoglycans, forming the acid mucopolysaccharides, typically referred to as sulfurylated glycosaminoglycans (sGAGs). Heparan sulfate proteoglycan (HSPG) and chondroitin sulfate proteoglycan (CSPG) are ubiquitous sGAGs of the extracellular matrix in (b). The postulated universal sulfurylation factor, L-ascorbic acid-2-O-sulfate free radical is a reactive transient, denoted [L-AA-2S]* in (a)

There is considerable literature precedent for stabilization of sulfate and phosphate ester intermediates and transition states via fluxional isomerization (pairwise exchange of axial and equatorial ligands of trigonal bipyramidal (TBP) intermediates, a process referred to as *Berry* pseudorotation. Figures 15 (a) and (b) are proposed to represent the 2 radical chain propagation steps of nonenzymatic sulfuryl group transfer during the anabolic phase of the SSP.

5-membered ring cyclic phosphate and sulfate esters have been shown to readily undergo ring-opening reactions with alcohols. Rate enhancements for such alcoholysis reactions have been reported which are ca. 5-6 orders of magnitude faster than their acyclic counterparts. Importantly, alcoholysis of such cyclic sulfate and phosphate esters is favored over hydrolysis. This observation may prove highly relevant to nucleic acid chemistry, *in vivo*. Phosphorylation reactions in vitro, and presumably also in vivo, are generally thought to follow an "in-line", associative, SN2-style mechanism. Phosphorylation reactions of pyruvate kinase is an example of in-line mechanism. By extension to nucleic acid polymerization and recycling reactions, SN2 mechanisms are thought to prevail over SN1 mechanisms in phosphoryl group transfers. Of course, NGTC of phosphoryl group transfer by L-AA-2P is postulated to follow an associative SN2 mechanism.

Importantly, NMR and X-ray crystallographic techniques were employed by Cabral & Haake [276] to demonstrate an acid-catalyzed rearrangement of L-AA-3S and L-AA-3P derivatives to L-AA-2S and L-AA-2P derivatives, respectively. The 3-O-acetyl substituted L-AA derivative showed a similar thermodynamic proclivity to rearrange to the 2-position of the lactone ring system. We suggest that such non-enzymatic intramolecular acyl group rearrangements point to the

likelihood of the 2-O-substituted L-AA derivatives providing non-enzymatic *intermolecular* biological group transfers, *in vivo*, as was demonstrated by Verlangieri & Mumma [238] and Hatanaka & Egami [239]. Their pioneering studies effectively provide the foundation upon which the NGTC/ascorbolysis/UNMR theoretical framework rests. It may be surmised that *in the beginning*, ascorbolysis provided for prebiotic reversible nonenzymatic "kinase-like", "sulfotransferase-like", and "SIRTUIN-like" function, prior to the advent of enzymes during chemical evolution of Life.

4.2. Westheimer's guidelines [269, 270] for *Berry* pseudorotation of cyclic pentacoordinate trigonal bipyramidal (TBP) intermediates may provide the thermodynamic rationale for the observed rearrangement. It was proposed in 2021 that the 2-O-sulfate substituted L-AA radical is most likely to represent a universal sulfurylation factor (reactive transient) during inflammatory and cytoproliferative states such as that of the SSP (see [11-15] for greater detail). We suggest that a ^{31}P cardiac nuclear magnetic resonance NMR spectroscopic study and electron spin resonance (ESR) study of L-AA-2P amd the L-AA-2P radical may provide useful preclinical and clinical information, in light of the Gundry abstracts [7, 8]. Under the ensemble HCC theoretical framework, chirality control and maintenance of anomeric fidelity may prove to be essential for human health, wellness, and longevity

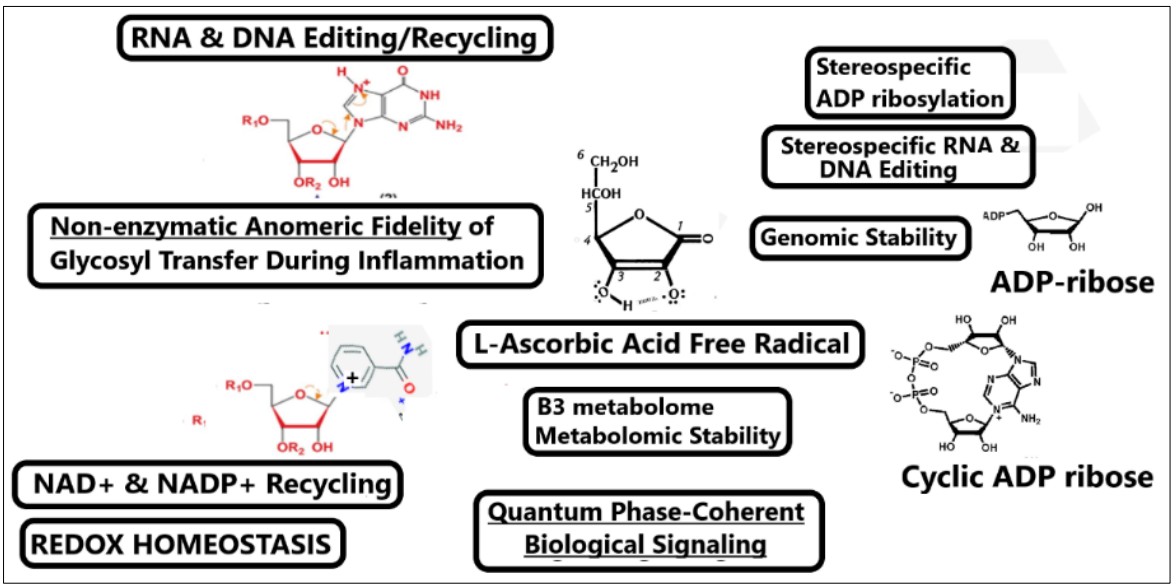

Figure 16 Depiction of biological complexity focusing on early and ongoing chemical evolution. NGTC by small molecules undergoing complex coacervations resulting in genomic, proteomic, and metabolic dynamical metastable equipoise within an aqueous liquid crystalline microenvironment. The putative reversible ascorbolysis of NAD+ is cited as but one of many examples of endogenous biological electrophiles, whose chirality at the anomeric carbon is preserved non-enzymatically during inflammatory states, e.g. during polyADP ribosylation (PARylation) and monoADP ribosylation (MARylation) of proteins [247, 248]. Ascorbolysis has been proposed to nonenzymatically catalyze stereo-, regio-, and chemio-specific reversible biological group transfers. The maintenance of anomeric fidelity under the ensemble HCC theoretical framework has translational primary prevention and therapeutic clinical implications for current ongoing SARS-CoV-2 pandemic. For further explanation, please see [11, 15]

Genomic, proteomic, and metabolomic homeostasis is proposed to have begun and continues at the supramolecular biological level. Several essential small molecule "players" during chemical evolution are depicted in Figure 16 (above). We propose herein that stochastic complexity, AI, and network theory might be well-suited to provide a computational means of validating and applying the ensemble HCC hypothesis introduced herein. This approach might be employed to effectively reverse engineer the presumed "initial common pathway" to Life on Earth [10, 12]. On the timescale of chemical evolution, we might ask whether we are closer to the "beginning" or the "end", i.e. extinction. Recurrent pandemics and apparent loss of biodiversity do not bode well for our species. Barcode-style "magic bullet" approaches currently being taken, may not offer benefits, i.e. fewer off-target effects that a supramolecular biological approach to public health, e.g. genomic stability, might provide. According to Sir David Attenborough, a well-respected natural historian, there is a great need to restore biodiversity to a "dying planet" [94, 95, 18, 19]. The development of solar light-harvesting technologies offers the promise of one day restoring biodiversity on both the ecosystem scale and our internal microenvironment, e.g. by validation and application of ensemble hydrophobic chiroptical catalysis.

While enzymatic glycosylation reactions are generally thought to proceed *via* dissociative SN1 "oxo-carbenium ion" intermediates, NGTC *via* ascorbolysis *and ensemble HCC* is proposed to follow an associative SN2 mechanism with "umpolung" catalysis (entropic charge reorganization), beginning with photo-oxidative super-activation and rate-limiting O-H bond homolysis, intramolecular 1,4 hydrogen atom transfer ("intra-1,4-HAT"), and proton-coupled nucleophilic attack (PCNA) within a moderately acidic, mildly oxidative, relatively hydrophobic aqueous microenvironment, typically found during inflammatory states.

Most importantly, it should be recognized that anomeric fidelity is ensured under the ascorbolysis mechanism. Without a mechanism such as NGTC *via* ascorbolysis, anomeric fidelity could not be assured in a prebiotic world, *prior to the advent of enzymes*. Therefore, the mechanistic distinction between NGTC/ascorbolysis (associative SN2) and enzymatic (dissociative SN1) is pivotal, *in the beginning*, just as it is today. Under the NGTC/ascorbolysis hypothesis, "back-to-back", i.e. serial, inversions of stereochemistry at the anomeric carbon of sugars, provides net retention of stereochemistry, i.e. provides for obligatory anomeric fidelity. Chirality control of our biomolecules is largely tantamount to "health". It has been recently proposed that aging may represent a loss of molecular chirality, i.e. racemization of our biomolecules [194]. The non-equilibrium thermodynamic theory of aging presented by Dyakin et al (2021) [194] is entirely compatible with the ensemble HCC hypothesis introduced herein.

5. Conclusion

We have shared with your readers the perspective of a chemical biologist/biochemist and materials scientist/inventor on the very important Abstract published in Circulation by Gundry. The Gundry Abstract calls out a warning that the current mRNA vaccines are demonstrating more than just an ordinary side-effect profile. While the interim data presented by Dr Gundry is not final, it is still quite troubling, and clearly warrants our attention and consideration of the clinical implications of the current mass vaccination program underway, both nationally and internationally, with the mRNA vaccines, and multiple successive booster inoculations. The short-term adverse event profile being observed for the mRNA vaccines has many, if not all, of the earmarks of the SSP. The SSP is often characterized by the administration of two separate parenteral injections separated by a variable time interval. Initial injection is thought to cause a sensitization, and the second injection is thought to provoke a response, which can be either localized or generalized. The most striking aspects of Gundry's data is the strong evidence of inflammation of the microvasculature of the heart, and various other organs. Endothelial dysfunction characteristic of ACS, sepsis, and cancer is known to be promptly reversed by intravenous administration of high-dose L-ascorbic acid. Similarities between the Sanarelli-Shwartzman phenomenon and reported adverse biological responses to mRNA vaccines were considered. Viewed in total, the above cited published data supports a tentative conclusion, that the answer to the question posed in the title of this article, "Are the mRNA vaccines (and boosters) inducing the Sanarelli-Shwartzman Phenomenon?", may reasonably be answered in the affirmative.

A novel spin-correlated, radical theory of non-enzymatic polynucleotide synthesis, editing, and recycling, initially introduced in 2021, is further elaborated, highlighting its potential role in the human immune response. An initial proposal has been made in this paper for hydrophobic chiral "seeding" of the microenviroment as a means of promoting memory of chirality and hydrophobic catalysis by L-ascorbic acid and chiral hydrophobes, thereby preserving redox homeostasis and biosemiotics coherence. This ensemble hydrophobic chiral seeding proposal, subject to experimental validation, may have prebiotic significance, perhaps leading to an overall "greening" of the ecosystem in which we live, including that of our internal microenvironment. Under this proposal, it is suggested that lectin and gluten sensitivity may represent sensitizing phenomena during the SSP, by means of memory of chirality, for which ensemble hydrophobic chiroptical catalysis may have therapeutic benefit. A role is proposed for ensemble combination therapy with L-ascorbic acid, bioflavonoids, and corticosteroids in countering the SARS-CoV-2 viral pathogen and its variants. It is proposed that ensemble HCC by L-AA, chiral hydrophobes, and spin water may provide a sustainable means of regulating function of the human stem cell niches of the brain, heart, gut, and reticuloendothelial system. Initial proposal for nonenzymatic regiospecific cleavage of viral RNA and viral proteins under the latest iteration/embodiment of the ensemble HCC theoretical framework is introduced.

Compliance with ethical standards

Acknowledgments

The authors gratefully acknowledge the professionalism, quality, and timeliness by which the peer review process and decision to accept for publication were made.

Disclosure of conflict of interest

The authors have no conflicts of interest to disclose.

Legal Disclaimer

The authors declare that the information in this article is not intended as a diagnosis, recommended treatment, prevention, or cure for any human condition or medical procedure that may be referred to in any way. Users and readers must use their own judgment concerning specific applications. The contributing authors disclaim any liability or responsibility to any person or entity for any harm, financial loss, physical injury, or other penalty that may stem from any use or application in any context of information, conclusions, research findings, opinions, errors, or any statements found in the article. The material presented is freely offered to all users who may take an interest in examining it, but how they may choose to apply any part of it, is the sole responsibility of the viewer/user.

References

[1] Sanarelli J. Etudes sur la fievre typhoide experimentale. Ann Inst Pasteur (Paris). 1894;8:193–230.

[2] Hjort PF, Rapaport SI. The Shwartzman reaction: pathogenetic mechanisms and clinical manifestations. Annual Review of Medicine. 1965;16(1):135–68.

[3] Shiga J, Mori W. A Light- and Electron-Microscopic Study of the so-Called Uni-Visceral Shwartzman Reaction. Pathology International. 1980;30(5):705–12.

[4] Mori W. The Shwartzman reaction: a review including clinical manifestations and proposal for a univisceral or single organ third type. Histopathology. 1981;5(2):113–26.

[5] Nakajima Y. Shwartzman Reaction in the Brain Induced by Fractions of Fusobactebium Necrophorum and Escherichia Coli Lipopolysaccharide in Rabbits. Pathology International. 1988;38(5):541–7.

[6] Nakajima Y, Ueda H. Shwartzman reaction in the brain induced by Haemophilus somnus and Escherichia coli lipopolysaccharide in rabbits. Journal of Comparative Pathology. 1989 Apr 1;100(3):231–6.

[7] Gundry SR. MRNA COVID vaccines dramatically increase endothelial inflammatory markers and ACS risk as measured by the PULS cardiac test: A warning. Circulation [Internet]. 2021 [cited 2022 Apr 5]; Available from: https://doi.org/10.1161/circ.144.suppl-1.10712

[8] Gundry SR. Observational Findings of PULS Cardiac Test Findings for Inflammatory Markers in Patients Receiving mRNA Vaccines. Circulation. 2021 Nov 16;144(Suppl_1):A10712-.

[9] Gundry SR. Abstract 412: Dietary Lectins Cause Coronary Artery Disease via an Autoimmune Endothelial Attack Mediated by Interleukin 16. Arteriosclerosis, Thrombosis, and Vascular Biology. 2018 May;38(Suppl_1):A412–A412.

[10] Davidson RM, Seneff S. The Initial Common Pathway of Inflammation, Disease, and Sudden Death. Entropy. 2012 Aug;14(8):1399–442. https://doi.org/10.3390/e14081399

[11] Davidson RM, Winey TR. Vitamin C Mitigating and Rescuing from Synergistic Toxicity: Sodium Fluoride, Silicofluorides, Aluminum Salts, Electromagnetic Pollution, and SARS-CoV-2. Vaccine Theory Prac & Res [Internet]. 2021 Jan. 5 [cited 2022 Nov. 3];1(2):243-82. Available from: https://www.ijvtpr.com/index.php/IJVTPR/article/view/12

[12] Davidson R. The Initial Common Pathway of Inflammation, Disease, and Death [Internet]. Presentation presented at; figshare; 2022 Jan 16 [cited 2022 Nov 2]. Available from: https://figshare.com/articles/presentation/The_Initial_Common_Pathway_of_Inflammation_Disease_and_Death/18515063/1

[13] Davidson R, Lauritzen A, Seneff S, Kette S, Wainwright G, Samsel A, et al. Biophysical Aspects of the Sanarelli-Shwartzman Phenomenon. In 2015.Available from: http://dx.doi.org/10.13140/RG.2.1.4837.0005

[14] Davidson R, Lauritzen A, Seneff S, Kette S, Wainwright G, Samsel A, et al. A Novel Hypothesis as to the Origin of Autism: An Alteration in Biological Water Dynamics Disrupts Proton-Coupled Electron Transfer and the Organizing Function of CNS Fractones. In 2015. Available from: http://dx.doi.org/10.13140/RG.2.1.3133.0647

[15] Winey, Timothy; Davidson, Robert Michael (2021): Hydrophobic Catalysis by L-Ascorbic Acid: A supramolecular Strategy to counter the SARS-CoV2 ADP Ribose Glycohydrolase. figshare. Presentation. https://doi.org/10.6084/m9.figshare.17207309.v1

[16] Feinstein AR. In Vivo: The Case for Supramolecular Biology. Yale J Biol Med. 1967 Dec;40(3):243.

[17] Selye H, Tuchweber B, Gabbiani G. Effect of heparin upon various forms of the thrombohemorrhagic phenomenon (THP). Blood. 1965 Nov;26(5):533-40.

[18] Davidson R, Winey T. Restoring Biodiversity to a Dying Planet April 29 2022 FINAL.docx. 2022 May 11 [cited 2022 Nov 2]; Available from: https://figshare.com/articles/poster/Restoring_Biodiversity_to_a_Dying_Planet_April_29_2022_FINAL_docx/19747711/1

[19] Davidson R, Winey T. Radical Philicity of Intermediates during Ascorbolysis April 29 FINAL.docx. 2022 May 11 [cited 2022 Nov 2]; Available from: https://figshare.com/articles/poster/Radical_Philicity_of_Intermediates_during_Ascorbolysis_April_29_FINAL_docx/19750345/1

[20] De Vita P. [Inhibition of the Schwartzman-Sanarelli phenomenon with associated desoxycorticosterone-vitamin C treatment]. Boll Soc Ital Biol Sper. 1950 Jul;26(7):1197–8.

[21] Kikuchi K, Setoyama K, Takada S, Otsuka S, Nakanishi K, Norimatsu K, et al. E8002 Inhibits Peripheral Nerve Adhesion by Enhancing Fibrinolysis of l-Ascorbic Acid in a Rat Sciatic Nerve Model. International Journal of Molecular Sciences. 2020 Jan;21(11):3972.

[22] Littman DS, Stockdale RH, Williamson GR. Desoxycorticosterone acetate and ascorbic acid in the treatment of rheumatoid arthritis. AMA Arch Intern Med. 1951 May;87(5):707–12.

[23] Rossi CA. [Treatment of rheumatoid arthritis with desoxycorticosterone and ascorbic acid]. Prensa Med Argent. 1951 Jun 1;38(22):1773–4.

[24] McKENDRY JBR, SCHAFFENBURG CA, McCULLAGH EP. COMBINED ADMINISTRATION OF DESOXYCORTICOSTERONE ACETATE AND ASCORBIC ACID: I. Clinical Results in Rheumatoid Arthritis and Laboratory Studies. AMA Archives of Internal Medicine. 1951 Feb 1;87(2):190–8.

[25] Colunga Biancatelli RML, Berrill M, Catravas JD, Marik PE. Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19). Front Immunol. 2020 Jun 19;11:1451.

[26] Marik PE. Vitamin C for the treatment of sepsis: The scientific rationale. Pharmacology & Therapeutics. 2018 Sep 1;189:63–70.

[27] Marik PE. Hydrocortisone, Ascorbic Acid and Thiamine (HAT Therapy) for the Treatment of Sepsis. Focus on Ascorbic Acid. Nutrients. 2018 Nov;10(11):1762.

[28] Szczepanski M, Lucer C. Soluble fibrin monomer complexes and fibrinolytic activity in kidney during the generalized Shwartzman reaction in rabbit. Thrombosis Research. 1975 May 1;6(5):399–408.

[29] Szczepanski M, Lucer C. The influence of large doses of hydrocortisone on the generalized Shwartzman reaction in rabbit. Thrombosis Research. 1976 Jan 1;8(1):71–81.

[30] Nuss P. Anxiety disorders and GABA neurotransmission: a disturbance of modulation. Neuropsychiatry Dis Treat. 2015;11:165–75.

[31] Moritz B, Schwarzbold ML, Guarnieri R, Diaz AP, Rodrigues ALS, Dafre AL. Effects of ascorbic acid on anxiety state and affect in a non-clinical sample. Acta Neurobiol Exp. 2017;77:362–72.

[32] Kitabchi AE. Ascorbic Acid in Steroidogenesis. Nature. 1967 Sep;215(5108):1385–6.

[33] Ono M, Eguchi K, Konoshita M, Furusawa C, Sakamoto J, Yasuda S, et al. A new diterpenoid glucoside and two new diterpenoids from the fruit of Vitex agnus-castus. Chemical and Pharmaceutical Bulletin. 2011;59(3):392–6.

[34] Hassan DS, Santos ZAD los, Brady KG, Murkli S, Isaacs L, Wolf C. Chiroptical sensing of amino acids, amines, amino alcohols, alcohols and terpenes with π-extended acyclic cucurbiturils. Org Biomol Chem. 2021 May 19;19(19):4248–53.

[35] Selye H. Stress and the General Adaptation Syndrome. Br Med J. 1950 Jun 17;1(4667):1383–92.

[36] Selye H. Thrombohemorrhagic phenomena. Springfield, Ill.: CC Thomas; 1966.

[37] Selye H. Introduction: Experimental thrombohemorrhagic phenomena. The American Journal of Cardiology. 1967 Aug 1;20(2):153–60.

[38] Szabo S, Tache Y, Somogyi A. The legacy of Hans Selye and the origins of stress research: A retrospective 75 years after his landmark brief "Letter" to the Editor# of Nature. Stress. 2012 Sep 1;15(5):472–8.

[39] Torrence P. Biological response modifiers: New approaches to disease intervention. Elsevier; 2012.

[40] Sandler JA, Gallin JI, Vaughan M. Effects of serotonin, carbamylcholine, and ascorbic acid on leukocyte cyclic GMP and chemotaxis. J Cell Biol. 1975 Nov;67(2PT.1):480–4.

[41] Feng B, Sosa RP, Mårtensson AKF, Jiang K, Tong A, Dorfman KD, et al. Hydrophobic catalysis and a potential biological role of DNA unstacking induced by environment effects. Proceedings of the National Academy of Sciences. 2019 Aug 27;116(35):17169–74.

[42] Xiao F, Chen Z, Wei Z, Tian L. Hydrophobic Interaction: A Promising Driving Force for the Biomedical Applications of Nucleic Acids. Advanced Science. 2020;7(16):2001048.

[43] Lowery SA, Sariol A, Perlman S. Innate immune and inflammatory responses to SARS-CoV-2: Implications for COVID-19. Cell Host & Microbe. 2021 Jul 14;29(7):1052–62.

[44] Hsu JCC, Laurent-Rolle M, Pawlak JB, Wilen CB, Cresswell P. Translational shutdown and evasion of the innate immune response by SARS-CoV-2 NSP14 protein. Proceedings of the National Academy of Sciences. 2021 Jun 15;118(24):e2101161118.

[45] Zhang Y, Chen S, Jin Y, Ji W, Zhang W, Duan G. An Update on Innate Immune Responses during SARS-CoV-2 Infection. Viruses. 2021 Oct;13(10):2060.

[46] Li W, Maeda N, Beck MA. Vitamin C deficiency increases the lung pathology of influenza Virus–Infected gulo−/− mice. The Journal of nutrition. 2006 Oct 1;136(10):2611-6.

[47] Mun J, Kim M, Yang Y, Badloe T, Ni J, Chen Y, et al. Electromagnetic chirality: from fundamentals to nontraditional chiroptical phenomena. Light Sci Appl. 2020 Sep 2;9(1):139.

[48] Cao Z, Gao H, Qiu M, Jin W, Deng S, Wong KY, et al. Chirality Transfer from Sub-Nanometer Biochemical Molecules to Sub-Micrometer Plasmonic Metastructures: Physiochemical Mechanisms, Biosensing, and Bioimaging Opportunities. Advanced Materials. 2020;32(41):1907151.

[49] Cao Z, Hao A, Xing P. Photoresponsive chiral vesicles as a light harvesting matrix with tunable chiroptical properties. Nanoscale. 2021 Jan 22;13(2):700–7.

[50] Wang Z, Zhang H, Hao A, Zhao Y, Xing P. Modular Molecular Self-Assembly for Diversified Chiroptical Systems. Small. 2020;16(30):2002036.

[51] Huang S, Yu H, Li Q. Supramolecular Chirality Transfer toward Chiral Aggregation: Asymmetric Hierarchical Self-Assembly. Advanced Science. 2021 Apr;8(8):2002132.

[52] Borovkov V. Supramolecular chirality in porphyrin chemistry. Symmetry. 2014 Apr 23;6(2):256-94.

[53] Sang Y, Han J, Zhao T, Duan P, Liu M. Circularly polarized luminescence in nanoassemblies: generation, amplification, and application. Advanced Materials. 2020 Oct;32(41):1900110.

[54] Hashimoto Y, Suzuki T, Hashimoto K. Mechanisms of action of fluvoxamine for COVID-19: a historical review. Mol Psychiatry. 2022 Jan 7;1–10.

[55] Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA. 2020;2292–300.

[56] Das BB, Moskowitz WB, Taylor MB, Palmer A. Myocarditis and Pericarditis Following mRNA COVID-19 Vaccination: What Do We Know So Far? Children. 2021 Jul;8(7):607.

[57] Luk A, Clarke B, Dahdah N, Ducharme A, Krahn A, McCrindle B, Mizzi T, Naus M, Udell JA, Virani S, Zieroth S. Myocarditis and pericarditis after COVID-19 mRNA vaccination: practical considerations for care providers. Canadian Journal of Cardiology. 2021 Oct 1;37(10):1629-34.

[58] Calcaterra G, Mehta JL, de Gregorio C, Butera G, Neroni P, Fanos V, et al. COVID 19 Vaccine for Adolescents. Concern about Myocarditis and Pericarditis. Pediatric Reports. 2021 Sep;13(3):530–3.

[59] Alamer E, Alhazmi A, Qasir NA, Alamer R, Areeshi H, Gohal G, et al. Side Effects of COVID-19 Pfizer-BioNTech mRNA Vaccine in Children Aged 12–18 Years in Saudi Arabia. Vaccines. 2021 Nov;9(11):1297.

[60] Pavenski K. Relapse of Immune Thrombotic Thrombocytopenic Purpura Following Vaccinationwith COVID19 mRNA Vaccine. TH Open. 2021 Jul;05(3):e335–7.

[61] Giuffrida G, Condorelli A, Di Giorgio MA, Markovic U, Sciortino R, Nicolosi D, et al. Immune-mediated thrombotic thrombocytopenic purpura following administration of Pfizer-BioNTech COVID-19 vaccine. Haematologica. 2022 Apr 1;107(4):1008–10.

[62] Ruhe J, Schnetzke U, Kentouche K, Prims F, Baier M, Herfurth K, et al. Acquired thrombotic thrombocytopenic purpura after first vaccination dose of BNT162b2 mRNA COVID-19 vaccine. Ann Hematol. 2022 Mar 1;101(3):717–9.

[63] Julian JA, Mathern DR, Fernando D. Idiopathic Thrombocytopenic Purpura and the Moderna Covid-19 Vaccine. Annals of Emergency Medicine. 2021 Jun 1;77(6):654–6.

[64] Krajewski PK, Szepietowski JC. Immune thrombocytopenic purpura associated with COVID-19 Pfizer-BioNTech BNT16B2b2 mRNA vaccine. J Eur Acad Dermatol Venereol. 2021 Jun 16;10.1111/jdv.17444.

[65] Malayala SV, Papudesi BN, Sharma R, Vusqa UT, Raza A. A Case of Idiopathic Thrombocytopenic Purpura After Booster Dose of BNT162b2 (Pfizer-Biontech) COVID-19 Vaccine. Cureus [Internet]. 2021 Oct 23 [cited 2022 Apr 5];13(10).

[66] Furer V, Zisman D, Kibari A, Rimar D, Paran Y, Elkayam O. Herpes zoster following BNT162b2 mRNA COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series. Rheumatology. 2021 Oct 1;60(SI):SI90–5.

[67] Karabulut K, Andronikashvili A, Kapici AH. Recurrence of Thrombotic Thrombocytopenic Purpura after mRNA-1273 COVID-19 Vaccine Administered Shortly after COVID-19. Case Reports in Hematology. 2021 Sep 13;2021:e4130138.

[68] Waqar SHB, Khan AA, Memon S. Thrombotic thrombocytopenic purpura: a new menace after COVID bnt162b2 vaccine. Int J Hematol. 2021 Nov 1;114(5):626–9.

[69] Bril F, Diffalha SA, Dean M, Fettig DM. Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: Causality or casualty? Journal of Hepatology. 2021 Jul 1;75(1):222–4.

[70] Magliulo D, Narayan S, Ue F, Boulougoura A, Badlissi F. Adult-onset Still's disease after mRNA COVID-19 vaccine. The Lancet Rheumatology. 2021 Oct 1;3(10):e680–2.

[71] Park SY, Lee KH. Adult-onset Still's Disease after BNT162b2 mRNA COVID-19 Vaccine. J Korean Med Sci. 2021 Dec 14;36(50):e344.

[72] Bamidis AD, Koehler P, Cristanziano V di, Rasche K, Demirel B, Bacher P, et al. First manifestation of adult-onset Still's disease after COVID-19. The Lancet Rheumatology. 2021 May 1;3(5):e319–21.

[73] Pantazatos S, Seligmann H. COVID vaccination and age-stratified all-cause mortality risk. Media. ellinkahoaxes. gr. 2021 Oct.

[74] Classen JB. COVID-19 RNA based vaccines and the risk of prion disease. Microbiol Infect Dis. 2021;5(1):1–3.

[75] Perez JC, Lounnas V, Montagnier M. THE OMICRON VARIANT BREAKS THE EVOLUTIONARY LINEAGE OF SARS-COV2 VARIANTS. International Journal of Research Granthaalayah. 2021;

[76] Zerr I. Laboratory Diagnosis of Creutzfeldt–Jakob Disease. New England Journal of Medicine. 2022;386(14):1345–50.

[77] Lawal Ammani M, Oko G. A Review on CRISPR/CAS9 And Its Application in Research, Industry and Health Biotechnology. 2018 Jun 18;

[78] Kim H, Kim JS. A guide to genome engineering with programmable nucleases. Nat Rev Genet. 2014 May;15(5):321–34.

[79] Kim S, Kim D, Cho SW, Kim J, Kim JS. Highly efficient RNA-guided genome editing in human cells via delivery of purified Cas9 ribonucleoproteins. Genome Res. 2014 Jun;24(6):1012–9.

[80] Ain QU, Chung JY, Kim YH. Current and future delivery systems for engineered nucleases: ZFN, TALEN and RGEN. Journal of Controlled Release. 2015 May 10;205:120–7.

[81] Ding Q, Lee YK, Schaefer EAK, Peters DT, Veres A, Kim K, et al. A TALEN Genome-Editing System for Generating Human Stem Cell-Based Disease Models. Cell Stem Cell. 2013 Feb 7;12(2):238–51.

[82] Lin S, Staahl BT, Alla RK, Doudna JA. Enhanced homology-directed human genome engineering by controlled timing of CRISPR/Cas9 delivery. Weigel D, editor. eLife. 2014 Dec 15;3:e04766.

[83] Liu J, Gaj T, Yang Y, Wang N, Shui S, Kim S, et al. Efficient delivery of nuclease proteins for genome editing in human stem cells and primary cells. Nat Protoc. 2015 Nov;10(11):1842–59.

[84] Blauenfeldt RA, Kristensen SR, Ernstsen SL, Kristensen CCH, Simonsen CZ, Hvas AM. Thrombocytopenia with acute ischemic stroke and bleeding in a patient newly vaccinated with an adenoviral vector-based COVID-19 vaccine. Journal of Thrombosis and Haemostasis. 2021;19(7):1771–5.

[85] Yoshida K, Tanaka K, Suto Y, Fukuda H. Repeated Cardioembolic Stroke after COVID-19 mRNA Vaccination: A Case Report. Journal of Stroke and Cerebrovascular Diseases. 2022 Feb 1;31(2):106233.

[86] Hippisley-Cox J, Patone M, Mei XW, Saatci D, Dixon S, Khunti K, et al. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. BMJ. 2021 Aug 27;374:n1931.

[87] Iba T, Levy JH. The roles of platelets in COVID-19-associated coagulopathy and vaccine-induced immune thrombotic thrombocytopenia. Trends in Cardiovascular Medicine. 2022 Jan 1;32(1):1–9.

[88] Kircheis R. Coagulopathies after Vaccination against SARS-CoV-2 May Be Derived from a Combined Effect of SARS-CoV-2 Spike Protein and Adenovirus Vector-Triggered Signaling Pathways. Int J Mol Sci. 2021 Oct 6;22(19):10791.

[89] Slofstra SH, Cate H ten, Spek CA. Low dose endotoxin priming is accountable for coagulation abnormalities and organ damage observed in the Shwartzman reaction. A comparison between a single-dose endotoxemia model and a double-hit endotoxin-induced Shwartzman reaction. Thrombosis Journal. 2006 Aug 24;4(1):13.

[90] Lee CSM, Liang HPH, Connor DE, Dey A, Tohidi-Esfahani I, Campbell H, et al. A novel flow cytometry procoagulant assay for diagnosis of vaccine-induced immune thrombotic thrombocytopenia. Blood Advances. 2022 Mar 31;bloodadvances.2021006698.

[91] Resnik DB. Is the precautionary principle unscientific? Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences. 2003 Jun 1;34(2):329–44.

[92] Resnik DB. The Precautionary Principle and Medical Decision Making. The Journal of Medicine and Philosophy. 2004 Jun 1;29(3):281–99.

[93] Graham JD. Decision-analytic refinements of the precautionary principle. Journal of Risk Research. 2001 Apr 1;4(2):127–41.

[94] Attenborough SD. Adventures of a Young Naturalist: SIR DAVID ATTENBOROUGH'S QUEST EXPEDITIONS. John Murray Press; 2017. 472 p.

[95] Attenborough D. A life on our planet: My witness statement and a vision for the future. Random House; 2020.

[96] Winey T. 2015 Water Conference Presentation.; 2015. doi:10.13140/RG.2.1.4420.0403

[97] Pupols M, Newsroom U. Entropy and Particle Shape Cause Chirality in Dense Systems [Internet]. SciTechDaily. 2012 [cited 2022 Apr 10]. Available from: https://scitechdaily.com/entropy-and-particle-shape-cause-chirality-in-dense-systems/

[98] Yurth DG. Torsion field mechanics: verification of non-local field effects in human biology. JOURNAL OF NEW ENERGY. 2000 Dec 5;5:64-75.

[99] Frey AH. Human auditory system response to modulated electromagnetic energy. Journal of Applied Physiology. 1962 Jul 1;17(4):689–92.

[100] Frey AH. Electromagnetic field interactions with biological systems 1. FASEB j. 1993 Feb;7(2):272–81.

[101] Rubik B, Brown RR. Evidence for a connection between coronavirus disease-19 and exposure to radiofrequency radiation from wireless communications including 5G. J Clin Transl Res. 2021 Sep 29;7(5):666–81.

[102] Lee S, Lim J, Lee JH, Ju H, Heo J, Kim Y, et al. Ascorbic Acid 2-Glucoside Stably Promotes the Primitiveness of Embryonic and Mesenchymal Stem Cells Through Ten–Eleven Translocation-and cAMP-Responsive Element-Binding Protein-1-Dependent Mechanisms. Antioxidants & Redox Signaling. 2020;32(1):35–59.

[103] Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, et al. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. N Engl J Med. 2021 Dec 2;385(23):2132–9.

[104] Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. New England Journal of Medicine. 2021 Sep 16;385(12):1078–90.

[105] Sharabi A, Shiber S, Molad Y. Adult-onset Still's disease following mRNA COVID-19 vaccination. Clin Immunol. 2021 Dec;233:108878.

[106] Shiravi AA, Ardekani A, Sheikhbahaei E, Heshmat-Ghahdarijani K. Cardiovascular Complications of SARS-CoV-2 Vaccines: An Overview. Cardiol Ther. 2022 Mar 1;11(1):13–21.

[107] Das A, Kelly C, Teh I, Nguyen C, Brown LAE, Chowdhary A, et al. Phenotyping hypertrophic cardiomyopathy using cardiac diffusion magnetic resonance imaging: the relationship between microvascular dysfunction and microstructural changes. Eur Heart J Cardiovasc Imaging. 2021 Oct 25;23(3):352–62.

[108] Manolis AS, Manolis TA, Melita H. Cardiovascular Complications of COVID-19 Vaccination: COVID-19 Vaccines. Rhythmos. 2021 Oct 30;16(4):73–8.

[109] Winey T. Branching Vortices of Raw Milk and Vinegar with red food coloring for contrast. 2021.

[110] Horke DA, Chang YP, Długołęcki K, Küpper J. Separating Para and Ortho Water. Angewandte Chemie International Edition. 2014;53(44):11965–8.

[111] Pershin SM, Ismailov ESh, Suleimanova ZG, Abdulmagomedova ZN, Zagirova DZ. Spin-selective interaction of magnetic ortho-H2O isomers with yeast cells. Phys Wave Phen. 2012 Jul 1;20(3):223–30.

[112] Pershin SM, Ismailov ESh, Dibirova MM, Akhmedov ME, Tagirova FV, Shashkov DI, et al. Multiple increase in productivity of the yeast at reducing the fraction of D2O in water. Dokl Biochem Biophys. 2017 Sep 1;476(1):299–302.

[113] Leibovitz B, Siegel BV. Ascorbic Acid and the Immune Response. In: Phillips M, Baetz A, editors. Diet and Resistance to Disease [Internet]. Boston, MA: Springer US; 1981 [cited 2022 Apr 5]. p. 1–25. Available from: https://doi.org/10.1007/978-1-4615-9200-6_1

[114] Franco-Molina MA, Santana-Krímskaya SE, Zarate-Triviño DG, Zapata-Benavides P, Hernández-Martínez SP, Cervantes-Wong F, et al. Bovine Dialyzable Leukocyte Extract IMMUNEPOTENT CRP: Evaluation of Biological Activity of the Modified Product. Applied Sciences. 2021 Jan;11(8):3505.

[115] Franco-Molina M, Mendoza-Gamboa E, Miranda-Hernández D, Zapata-Benavides P, Castillo-León L, Isaza-Brando C, et al. In vitro effects of bovine dialyzable leukocyte extract (bDLE) in cancer cells. Cytotherapy. 2006 Jan 1;8(4):408–14.

[116] Kirkpatrick CH, Smith TK. EFFECTS OF DIALYZABLE TRANSFER FRACTOR ON ACCUMULATION OF CYCLIC NUCLEOTIDES BY LEUKOCYTES. In: Ascher MS, Gottlieb AA, Kirkpatrick CH, editors. Transfer Factor [Internet]. Academic Press; 1976. p. 161–72.

[117] Fudenberg HH. "Transfer Factor": An Update. Proceedings of the Society for Experimental Biology and Medicine. 1985 Mar 1;178(3):327–32.

[118] Wilson GB, Smith CL, Fudenberg HH. Effects of dialyzable leukocyte extracts (DLEs) with transfer factor activity on leukocyte migration in vitro. III. Characterization of the antigen-independent migration inhibition factor in DLEs as a neutrophil immobilizing factor. J Allergy Clin Immunol. 1979 Jul;64(1):56–66.

[119] Wilson GB, Fudenberg HH. Effects of dialyzable leukocyte extracts with transfer factor activity on leukocyte migration in vitro. II. Separation and partial characterization of the components in DLE producing antigen-dependent and antigen-independent effects. The Journal of Laboratory and Clinical Medicine. 1979 May 1;93(5):819–37.

[120] Wilson GB, Fudenberg HH, Horsmanheimo M. Effects of dialyzable leukocyte extracts with transfer factor activity on leukocyte migration in vitro. I. Antigen-dependent inhibition and antigen-independent inhibition and enhancement of migration. The Journal of Laboratory and Clinical Medicine. 1979 May 1;93(5):800–18.

[121] Eguchi M, Fujiwara M, Mizukami Y, Miwa N. Cytoprotection by pro-vitamin C against ischemic injuries in perfused rat heart together with differential activation of MAP kinase family. Journal of Cellular Biochemistry. 2003;89(5):863–7.

[122] Saitoh Y, Miwa N. Cytoprotection of vascular endotheliocytes by phosphorylated ascorbate through suppression of oxidative stress that is generated immediately after post-anoxic reoxygenation or with alkylhydroperoxides. Journal of cellular biochemistry. 2004;93(4):653–63.

[123] Zhou Y, Gan T, Jiang R, Chen H, Ma Z, Lu Y, et al. Whole-cell catalytic synthesis of 2-O-α-glucopyranosyl-l-ascorbic acid by sucrose phosphorylase from Bifidobacterium breve via a batch-feeding strategy. Process Biochemistry. 2022 Jan 1;112:27–34.

[124] Miao F, Su MY, Jiang S, Luo LF, Shi Y, Lei TC. Intramelanocytic Acidification Plays a Role in the Antimelanogenic and Antioxidative Properties of Vitamin C and Its Derivatives. Oxidative Medicine and Cellular Longevity. 2019 May 12;2019:e2084805.

[125] Kandil SM, Soliman II, Diab HM, Bedair NI, Mahrous MH, Abdou EM. Magnesium ascorbyl phosphate vesicular carriers for topical delivery; preparation, in-vitro and ex-vivo evaluation, factorial optimization and clinical assessment in melasma patients. Drug Deliv. 2022 Dec;29(1):534–47.

[126] Fukumoto K, Inoue E, Nagao N, Hiyama E, Miwa N. Age-dependent telomere shortening is slowed down by enrichment of intracellular vitamin C via suppression of oxidative stress. Life Sciences. 1998 Aug 7;63(11):935–48.

[127] Yokoo S, Furumoto K, Hiyama E, Miwa N. Slow-down of age-dependent telomere shortening is executed in human skin keratinocytes by hormesis-like-effects of trace hydrogen peroxide or by anti-oxidative effects of pro-vitamin C in common concurrently with reduction of intracellular oxidative stress. Journal of Cellular Biochemistry. 2004;93(3):588–97.

[128] Pacifici M, Iozzo RV. Remodeling of the rough endoplasmic reticulum during stimulation of procollagen secretion by ascorbic acid in cultured chondrocytes. A biochemical and morphological study. Journal of Biological Chemistry. 1988 Feb 15;263(5):2483–92.

[129] Yi Y, Wu M, Zhou X, Xiong M, Tan Y, Yu H, et al. Ascorbic acid 2-glucoside preconditioning enhances the ability of bone marrow mesenchymal stem cells in promoting wound healing. Stem Cell Research & Therapy. 2022 Mar 21;13(1):119.

[130] Przybylska J, Albera E, Kankofer M. Antioxidants in Bovine Colostrum. Reproduction in Domestic Animals. 2007;42(4):402–9.

[131] Arimori T, Kawamoto N, Shinya S, Okazaki N, Nakazawa M, Miyatake K, et al. Crystal Structures of the Catalytic Domain of a Novel Glycohydrolase Family 23 Chitinase from Ralstonia sp. A-471 Reveals a Unique Arrangement of the Catalytic Residues for Inverting Chitin Hydrolysis. Journal of Biological Chemistry. 2013 Jun 28;288(26):18696–706.

[132] Yamamoto I, Muto N, Nagata E, Nakamura T, Suzuki Y. Formation of a stable l-ascorbic acid α-glucoside by mammalian α-glucosidase-catalyzed transglucosylation. Biochimica et Biophysica Acta (BBA) - General Subjects. 1990 Jul 20;1035(1):44–50.

[133] Lambrecht MJ, Brichacek M, Barkauskaite E, Ariza A, Ahel I, Hergenrother PJ. Synthesis of Dimeric ADP-Ribose and Its Structure with Human Poly(ADP-ribose) Glycohydrolase. J Am Chem Soc. 2015 Mar 18;137(10):3558–64.

[134] Oppenheimer NJ. Structural determination and stereospecificity of the choleragen-catalyzed reaction of NAD+ with guanidines. Journal of Biological Chemistry. 1978;253(14):4907–10.

[135] Oppenheimer NJ, Davidson RM. 15N nuclear magnetic resonance studies of [1-15N]nicotinamide adenine dinucleotides. Organic Magnetic Resonance. 1980;13(1):14–6.

[136] Oppenheimer NJ, Handlon AL. 10 Mechanism of NAD-Dependent Enzymes. In: The enzymes. Elsevier; 1992. p. 453–505.

[137] Egea PF, Muller-Steffner H, Kuhn I, Cakir-Kiefer C, Oppenheimer NJ, Stroud RM, et al. Insights into the Mechanism of Bovine CD38/NAD+Glycohydrolase from the X-Ray Structures of Its Michaelis Complex and Covalently-Trapped Intermediates. PLOS ONE. 2012 Apr 18;7(4):e34918.

[138] Kumano Y, Sakamoto T, Egawa M, Tanaka M, Yamamoto I. Enhancing Effect of 2-O-α-D-Glucopyranosyl-L-ascorbic Acid, a Stable Ascorbic Acid Derivative, on Collagen Synthesis. Biological & Pharmaceutical Bulletin. 1998;21(7):662–6.

[139] Stamford NP. Stability, transdermal penetration, and cutaneous effects of ascorbic acid and its derivatives. Journal of cosmetic dermatology. 2012;11(4):310–7.

[140] Elia V, Yinnon TA, Oliva R, Napoli E, Germano R, Bobba F, Amoresano A. Chiral micron-sized H2O aggregates in water: circular dichroism of supramolecular H2O architectures created by perturbing pure water. Water. 2017;8:1-29.

[141] Ryzhkina IS, Kiseleva YV, Timosheva AP, Safiullin RA, Kadirov MK, Valitova YN, et al. Low-concentration aqueous solutions of an amphiphilic calix [4] resorcinarene derivative: Self-organization, physicochemical properties, and biological activity under common and hypoelectromagnetic conditions. In: Doklady Physical Chemistry. SP MAIK Nauka/Interperiodica; 2012. p. 193–9.

[142] Konovalov AI. The formation of nanosized molecular ensembles in highly dilute aqueous solutions. Her Russ Acad Sci. 2013 Nov 1;83(6):513–9.

[143] Konovalov AI, Ryzhkina IS. Formation of nanoassociates as a key to understanding of physicochemical and biological properties of highly dilute aqueous solutions. Russ Chem Bull. 2014 Jan 1;63(1):1–14.

[144] Binhi VN, Prato FS. Biological effects of the hypomagnetic field: An analytical review of experiments and theories. PLOS ONE. 2017 Jun 27;12(6):e0179340.

[145] Kattnig DR, Evans EW, Déjean V, Dodson CA, Wallace MI, Mackenzie SR, et al. Chemical amplification of magnetic field effects relevant to avian magnetoreception. Nature Chem. 2016 Apr;8(4):384–91.

[146] Koldunov VV, Kononov DS, Voeikov VL. Oscillations of photon emission accompanying the oxidative process in aqueous solutions of glycin with ribose or glucose and effects of transition metals and ascorbic acid. InRivista di Biologia/Biological Forum 2000 (Vol. 93, pp. 143-145).

[147] Schneider M, Al-Shareffi E, Haltiwanger RS. Biological functions of fucose in mammals. Glycobiology. 2017;27(7):601–18.

[148] Becker DJ, Lowe JB. Fucose: biosynthesis and biological function in mammals. Glycobiology. 2003 Jul 1;13(7):41R-53R.

[149] Somers WS, Stahl ML, Sullivan FX. GDP-fucose synthetase from Escherichia coli: structure of a unique member of the short-chain dehydrogenase/reductase family that catalyzes two distinct reactions at the same active site. Structure. 1998 Dec 15;6(12):1601–12.

[150] García-García A, Serna S, Yang Z, Delso I, Taleb V, Hicks T, et al. FUT8-Directed Core Fucosylation of N-glycans Is Regulated by the Glycan Structure and Protein Environment. ACS Catal. 2021 Aug 6;11(15):9052–65.

[151] Lira-Navarrete E, Valero-González J, Villanueva R, Martínez-Júlvez M, Tejero T, Merino P, et al. Structural Insights into the Mechanism of Protein O-Fucosylation. PLOS ONE. 2011 Sep 26;6(9):e25365.

[152] Miyoshi E, Noda K, Yamaguchi Y, Inoue S, Ikeda Y, Wang W, et al. The α1-6-fucosyltransferase gene and its biological significance. Biochimica et Biophysica Acta (BBA) - General Subjects. 1999 Dec 17;1473(1):9–20.

[153] Wang W, Hu T, Frantom PA, Zheng T, Gerwe B, del Amo DS, et al. Chemoenzymatic synthesis of GDP-l-fucose and the Lewis X glycan derivatives. Proceedings of the National Academy of Sciences. 2009 Sep 22;106(38):16096–101.

[154] Becker BF, Jacob M, Leipert S, Salmon AHJ, Chappell D. Degradation of the endothelial glycocalyx in clinical settings: searching for the sheddases. British Journal of Clinical Pharmacology. 2015;80(3):389–402.

[155] Hammond C, Helenius A. Quality control in the secretory pathway: retention of a misfolded viral membrane glycoprotein involves cycling between the ER, intermediate compartment, and Golgi apparatus. J Cell Biol. 1994 Jul;126(1):41–52.

[156] Beckett EL, Yates Z, Veysey M, Duesing K, Lucock M. The role of vitamins and minerals in modulating the expression of microRNA. Nutrition Research Reviews. 2014 Jun;27(1):94–106.

[157] Rissanen J. Stochastic Complexity. Journal of the Royal Statistical Society: Series B (Methodological). 1987;49(3):223–39.

[158] Cichy RM, Roig G, Andonian A, Dwivedi K, Lahner B, Lascelles A, et al. The Algonauts Project: A Platform for Communication between the Sciences of Biological and Artificial Intelligence. arXiv:190505675 [cs, q-bio] [Internet]. 2019 May 14

[159] Almaas E. Biological impacts and context of network theory. Journal of Experimental Biology. 2007 May 1;210(9):1548–58.

[160] Ogasawara K, Takeda K, Hashimoto W, Satoh M, Okuyama R, Yanai N, et al. Involvement of NK1+ T Cells and Their IFN-γ Production in the Generalized Shwartzman Reaction. The Journal of Immunology. 1998 Apr 1;160(7):3522–7.

[161] Grunewald ME, Chen Y, Kuny C, Maejima T, Lease R, Ferraris D, et al. The coronavirus macrodomain is required to prevent PARP-mediated inhibition of virus replication and enhancement of IFN expression. PLOS Pathogens. 2019 May 16;15(5):e1007756.

[162] Cuevas AM, Clark JM, Potter JJ. Increased TLR/MyD88 signaling in patients with obesity: is there a link to COVID-19 disease severity? Int J Obes (Lond). 2021;1152–4.

[163] Albrecht C, Boutrot F, Segonzac C, Schwessinger B, Gimenez-Ibanez S, Chinchilla D, et al. Brassinosteroids inhibit pathogen-associated molecular pattern–triggered immune signaling independent of the receptor kinase BAK1. Proceedings of the National Academy of Sciences. 2012 Jan 3;109(1):303–8.

[164] Chai LYA, Vonk AG, Kullberg BJ, Verweij PE, Verschueren I, van der Meer JWM, et al. Aspergillus fumigatus cell wall components differentially modulate host TLR2 and TLR4 responses. Microbes and Infection. 2011 Feb 1;13(2):151–9.

[165] Mowen KA, David M. Unconventional post-translational modifications in immunological signaling. Nature immunology. 2014;15(6):512–20.

[166] Brentville VA, Vankemmelbeke M, Metheringham RL, Durrant LG. Post-translational modifications such as citrullination are excellent targets for cancer therapy. Seminars in Immunology. 2020 Feb 1;47:101393.

[167] Anderton SM. Post-translational modifications of self antigens: implications for autoimmunity. Current Opinion in Immunology. 2004 Dec 1;16(6):753–8.

[168] Liu B, Gao C. Regulation of MAVS activation through post-translational modifications. Current Opinion in Immunology. 2018 Feb 1;50:75–81.

[169] Engelhard VH, Altrich-Vanlith M, Ostankovitch M, Zarling AL. Post-translational modifications of naturally processed MHC-binding epitopes. Current Opinion in Immunology. 2006 Feb 1;18(1):92–7.

[170] Gundry SR. Abstract 412: Dietary Lectins Cause Coronary Artery Disease via an Autoimmune Endothelial Attack Mediated by Interleukin 16. Arteriosclerosis, Thrombosis, and Vascular Biology. 2018 May;38(Suppl_1):A412–A412.

[171] Köttgen E, Volk B, Kluge F, Gerok W. Gluten, a lectin with oligomannosyl specificity and the causative agent of gluten-sensitive enteropathy. Biochemical and Biophysical Research Communications. 1982 Nov 16;109(1):168–73.

[172] Rouhanifard SH, Lopez Aguilar A, Meng L, Moremen KW, Wu P. Engineered Glycocalyx Regulates Stem Cell Proliferation in Murine Crypt Organoids. Cell Chemical Biology. 2018 Apr 19;25(4):439-446.e5.

[173] Brazil JC, Parkos CA. Finding the sweet spot: glycosylation mediated regulation of intestinal inflammation. Mucosal Immunol. 2022 Feb;15(2):211–22.

[174] Chen H, Bai C, Wang X. The value of the lipopolysaccharide-induced acute lung injury model in respiratory medicine. Expert Review of Respiratory Medicine. 2010 Dec 1;4(6):773–83.

[175] Scheller C, Knöferle J, Ullrich A, Prottengeier J, Racek T, Sopper S, et al. Caspase inhibition in apoptotic T cells triggers necrotic cell death depending on the cell type and the proapoptotic stimulus. Journal of Cellular Biochemistry. 2006;97(6):1350–61.

[176] Kash JC, Walters KA, Davis AS, Sandouk A, Schwartzman LM, Jagger BW, et al. Lethal synergism of 2009 pandemic H1N1 influenza virus and Streptococcus pneumoniae coinfection is associated with loss of murine lung repair responses. mBio. 2011;2(5):e00172-11.

[177] Bowman GL, Dayon L, Kirkland R, Wojcik J, Peyratout G, Severin IC, et al. Blood-brain barrier breakdown, neuroinflammation, and cognitive decline in older adults. Alzheimer's & Dementia. 2018 Dec 1;14(12):1640–50.

[178] Popp J, Oikonomidi A, Tautvydaitė D, Dayon L, Bacher M, Migliavacca E, et al. Markers of neuroinflammation associated with Alzheimer's disease pathology in older adults. Brain, Behavior, and Immunity. 2017 May 1;62:203–11.

[179] Dayon L, Núñez Galindo A, Wojcik J, Cominetti O, Corthésy J, Oikonomidi A, et al. Alzheimer disease pathology and the cerebrospinal fluid proteome. Alzheimer's Research & Therapy. 2018 Jul 18;10(1):66.

[180] Rochfort KD, Collins LE, Murphy RP, Cummins PM. Downregulation of blood-brain barrier phenotype by proinflammatory cytokines involves NADPH oxidase-dependent ROS generation: consequences for interendothelial adherens and tight junctions. PloS one. 2014 Jul 3;9(7):e101815.

[181] Asby D, Boche D, Allan S, Love S, Miners JS. Systemic infection exacerbates cerebrovascular dysfunction in Alzheimer's disease. Brain. 2021 Jun 1;144(6):1869–83.

[182] Buchthal SD, den Hollander JA, Merz CN, Rogers WJ, Pepine CJ, Reichek N, Sharaf BL, Reis S, Kelsey SF, Pohost GM. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. New England Journal of Medicine. 2000 Mar 23;342(12):829-35.

[183] Chapman SB, Aslan S, Spence JS, Hart JJ Jr, Bartz EK, Didehbani N, et al. Neural Mechanisms of Brain Plasticity with Complex Cognitive Training in Healthy Seniors. Cerebral Cortex. 2015 Feb 1;25(2):396–405.

[184] Hsu EW, Buckley DL, Bui JD, Blackband SJ, Forder JR. Two-component diffusion tensor MRI of isolated perfused hearts. Magnetic Resonance in Medicine. 2001;45(6):1039–45.

[185] Echouffo-Tcheugui JB, Conner SC, Himali JJ, Maillard P, DeCarli CS, Beiser AS, et al. Circulating cortisol and cognitive and structural brain measures: The Framingham Heart Study. Neurology. 2018 Nov 20;91(21):e1961–70.

[186] Zsila F. The anticancer agent ellipticine binds to glycosaminoglycans at mildly acidic pH characteristic of the extracellular matrix of tumor tissues. RSC Adv. 2015 Dec 21;6(1):810–4.

[187] Gill DM, Povinelli APR, Zazeri G, Shamir SA, Mahmoud AM, Wilkinson FL, et al. The modulatory role of sulfated and non-sulfated small molecule heparan sulfate-glycomimetics in endothelial dysfunction: absolute structural clarification, molecular docking and simulated dynamics, SAR analyses and ADMET studies. RSC medicinal chemistry. 2021;12(5):779–90.

[188] Hauss WH, Junge-Hülsing G, Holländer HJ. Changes in metabolism of connective tissue associated with ageing and arterio- or atherosclerosis. Journal of Atherosclerosis Research. 1962 Jan 1;2(1):50–61.

[189] Hauss WH, Gerlach U, Junge-Hülsing G, Themann H, Wirth W. Studies on the "Nonspecific Mesenchymal Reaction" and the 1transit Zone" in Myocardial Lesions and Atherosclerosis. Annals of the New York Academy of Sciences. 1969;156(1):207–18.

[190] Sandset PM, Warn-Cramer BJ, Maki SL, Rapaport SI. Immunodepletion of extrinsic pathway inhibitor sensitizes rabbits to endotoxin-induced intravascular coagulation and the generalized Shwartzman reaction. Blood. 1991 Sep 15;78(6):1496–502.

[191] Selye H, Somogyi A, Végh P. Inflammation, topical stress and the concept of pluricausal diseases. Biochem Pharmacol. 1968 Mar;Suppl:107-122.

[192] Graham DI, Behan PO, More IA. Brain damage complicating septic shock: acute haemorrhagic leucoencephalitis as a complication of the generalised Shwartzman reaction. Journal of Neurology, Neurosurgery & Psychiatry. 1979 Jan 1;42(1):19–28.

[193] Wojtala M, Rybaczek D, Wielgus E, Sobalska-Kwapis M, Strapagiel D, Balcerczyk A. The Role of Lysine-Specific Demethylase 1 (LSD1) in Shaping the Endothelial Inflammatory Response. Cell Physiol Biochem. 2021;55:569–89.

[194] Dyakin VV, Dyakina-Fagnano NV, Mcintire LB, Uversky VN. Fundamental Clock of Biological Aging: Convergence of Molecular, Neurodegenerative, Cognitive and Psychiatric Pathways: Non-Equilibrium Thermodynamics Meet Psychology. Int J Mol Sci. 2021 Dec 28;23(1):285.

[195] Oparin AI, Gladilin KL. Evolution of self-assembly of probionts. Biosystems. 1980 Jan 1;12(3):133–45.

[196] Liebl V, Novák VJA, Masinovský Z, Pacltová B, Bejšovcová L. The evolution of prebiological self-organization: Probable colloid-chemical evolution of first prokaryotic cells. Origins Life Evol Biosphere. 1984 Dec 1;14(1):323–34.

[197] Weinbreck F, de Vries R, Schrooyen P, de Kruif CG. Complex Coacervation of Whey Proteins and Gum Arabic. Biomacromolecules. 2003 Mar 1;4(2):293–303.

[198] Otto S. An Approach to the De Novo Synthesis of Life. Acc Chem Res. 2022 Jan 18;55(2):145–55.

[199] Evans EW, Kattnig DR, Henbest KB, Hore PJ, Mackenzie SR, Timmel CR. Sub-millitesla magnetic field effects on the recombination reaction of flavin and ascorbic acid radicals. J Chem Phys. 2016 Aug 28;145(8):085101.

[200] Voeikov VL, Naletov VI. Weak Photon Emission of Non-Linear Chemical Reactions of Amino Acids and Sugars in Aqueous Solutions. In: Chang JJ, Fisch J, Popp FA, editors. Biophotons [Internet]. Dordrecht: Springer Netherlands; 1998 [cited 2022 Apr 6]. p. 93–108. Available from: https://doi.org/10.1007/978-94-017-0928-6_8

[201] Fauzee NJS, Li Q, Wang Y lan, Pan J. Silencing Poly (ADP-Ribose) Glycohydrolase (PARG) Expression Inhibits Growth of Human Colon Cancer Cells In Vitro via PI3K/Akt/NFκ-B Pathway. Pathol Oncol Res. 2012 Apr 1;18(2):191–9.

[202] Parsaee F, Senarathna MC, Kannangara PB, Alexander SN, Arche PDE, Welin ER. Radical philicity and its role in selective organic transformations. Nat Rev Chem. 2021 Jul;5(7):486–99.

[203] O'Malley PJ. Density Functional Calculations Modelling the Spin Density Distribution, Hyperfine Couplings, and Hydrogen Bonding Environment of the Ascorbate (Vitamin C) Free Radical. J Phys Chem B. 2001 Nov;105(45):11290–3.

[204] Chattaraj PK, Maiti B, Sarkar U. Philicity: A Unified Treatment of Chemical Reactivity and Selectivity. J Phys Chem A. 2003 Jun 1;107(25):4973–5.

[205] Atkinson JP, Weiss A, Ito M, Kelly J, Parker CW. Effects of ascorbic acid and sodium ascorbate on cyclic nucleotide metabolism in human lymphocytes. J Cyclic Nucleotide Res. 1979 Jan 1;5(2):107–23.

[206] Pickett WC, Austen KF, Goetzl EJ. Inhibition by non-steroidal anti-inflammatory agents of the ascorbate-induced elevations of platelet cyclic AMP levels. J Cyclic Nucleotide Res. 1979 Jan 1;5(3):197–209.

[207] Sandler JA, Clyman RI, Manganiello VC, Vaughan M. The effect of serotonin (5-hydroxytryptamine) and derivatives on guanosine 3',5'-monophosphate in human monocytes. J Clin Invest. 1975 Feb 1;55(2):431–5.

[208] Heremans H, Dillen C, van Damme J, Billiau A. Essential role for natural killer cells in the lethal lipopolysaccharide-induced Shwartzman-like reaction in mice. European Journal of Immunology. 1994;24(5):1155–60.

[209] Chahin AB, Opal JM, Opal SM. Whatever happened to the Shwartzman phenomenon? Innate Immun. 2018 Nov 1;24(8):466–79.

[210] Skendros P, Mitsios A, Chrysanthopoulou A, Mastellos DC, Metallidis S, Rafailidis P, et al. Complement and tissue factor–enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. The Journal of clinical investigation. 2020;130(11):6151–7.

[211] Müller-Berghaus G, Hocke M. Production of the Generalized Shwartzman Reaction in Rabbits by Ancrod ('Arvin') Infusion and Endotoxin Injection. British Journal of Haematology. 1973;25(1):111–22.

[212] Brozna JP. Shwartzman reaction. Semin Thromb Hemost. 1990 Oct;16(4):326–32.

[213] Argenbright LW, Barton RW. Interactions of leukocyte integrins with intercellular adhesion molecule 1 in the production of inflammatory vascular injury in vivo. The Shwartzman reaction revisited. The Journal of clinical investigation. 1992;89(1):259–72.

[214] Allahtavakoli M, Amin F, Esmaeeli-Nadimi A, Shamsizadeh A, Kazemi-Arababadi M, Kennedy D. Ascorbic Acid Reduces the Adverse Effects of Delayed Administration of Tissue Plasminogen Activator in a Rat Stroke Model. Basic & Clinical Pharmacology & Toxicology. 2015;117(5):335–9.

[215] Mori W. The Shwartzman reaction: a review including clinical manifestations and proposal for a univisceral or single organ third type. Histopathology. 1981;5(2):113–26.

[216] Nakajima Y, Ueda H. Shwartzman reaction in the brain induced by Haemophilus somnus and Escherichia coli lipopolysaccharide in rabbits. Journal of Comparative Pathology. 1989 Apr 1;100(3):231–6.

[217] Li T, Peng T. Traditional Chinese herbal medicine as a source of molecules with antiviral activity. Antiviral Research. 2013 Jan 1;97(1):1–9.

[218] Luo H, Vong CT, Chen H, Gao Y, Lyu P, Qiu L, Zhao M, Liu Q, Cheng Z, Zou J, Yao P. Naturally occurring anti-cancer compounds: shining from Chinese herbal medicine. Chinese medicine. 2019 Dec;14(1):1-58.

[219] Fowler III AA, Kim C, Lepler L, Malhotra R, Debesa O, Natarajan R, et al. Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. World J Crit Care Med. 2017 Feb 4;6(1):85–90.

[220] Oudemans-van Straaten HM, Spoelstra-de Man AM, de Waard MC. Vitamin C revisited. Crit Care. 2014 Aug 6;18(4):460.

[221] Mulloy B, Forster MJ. Conformation and dynamics of heparin and heparan sulfate. Glycobiology. 2000 Nov 1;10(11):1147–56.

[222] Suter E, Munoz JJ. Effect of BCG Infection on Sensitivity of Mice to Histamine, Serotonin and Passively Induced Anaphylaxis. Proceedings of the Society for Experimental Biology and Medicine. 1963 Oct 1;114(1):211–3.

[223] Cassaro CM, Dietrich CP. Distribution of sulfated mucopolysaccharides in invertebrates. Journal of Biological Chemistry. 1977;252(7):2254–61.

[224] Rabenstein DL. Heparin and heparan sulfate: structure and function. Natural product reports. 2002;19(3):312–31.

[225] Li S, Li M, Liu X, Yang Y, Wei Y, Chen Y, Qiu Y, Zhou T, Feng Z, Ma D, Fang J. Genetic and chemical screenings identify HDAC3 as a key regulator in hepatic differentiation of human pluripotent stem cells. Stem cell reports. 2018 Jul 10;11(1):22-31.

[226] Deutsch JC, Santhosh-Kumar CR, Hassell KL, Kolhouse JFred. Variation in ascorbic acid oxidation routes in hydrogen peroxide and cupric ion solution as determined by GC/MS. Anal Chem. 1994 Feb;66(3):345–50.

[227] Deutsch JC. Ascorbic acid oxidation by hydrogen peroxide. Anal Biochem. 1998 Jan 1;255(1):1-7. doi: 10.1006/abio.1997.2293. PMID: 9448835.

[228] Hmiel LK, Brorson KA, Boyne MT. Post-translational structural modifications of immunoglobulin G and their effect on biological activity. Anal Bioanal Chem. 2015 Jan 1;407(1):79–94.

[229] Mittal S, Saluja D. Protein Post-translational Modifications: Role in Protein Structure, Function and Stability. In: Singh LR, Dar TA, Ahmad P, editors. Proteostasis and Chaperone Surveillance [Internet]. New Delhi: Springer India; 2015 [cited 2022 Apr 3]. p. 25–37. Available from: https://doi.org/10.1007/978-81-322-2467-9_2

[230] Jayachandran_2018_PES.pdf - R ES E A RC H RESEARCH ARTICLE ◥ ECONOMICS Cash for carbon: A randomized trial of payments for ecosystem services to reduce | Course Hero [Internet]. [cited 2022 Oct 16]. Available from: https://www.coursehero.com/file/118160353/Jayachandran-2018-PESpdf/

[231] Jayachandran P, Koshy L, Sudhakaran PR, Nair GM, Gangaprasad A, Nair AJ. Dysregulation of miRNA and its reversal with l-ascorbic acid during AGE-BSA induced ER stress in Mus musculus neuronal cells. Gene Reports. 2020 Dec 1;21:100841.

[232] Ruberti F, Pezzola S, Barbato C. Advances in MicroRNAs and Alzheimer's Disease Research. Alzheimer's Disease Pathogenesis-Core Concepts, Shifting Paradigms and Therapeutic Targets. 2011 Sep 12;14(2):273-94.

[233] Wu J, Wang Y, Zhang Y, Li L. Association Between Interleukin-16 Polymorphisms and Risk of Coronary Artery Disease. DNA and Cell Biology. 2011 May;30(5):305–8.

[234] Yamamoto N, Yang DL. Helical magnetic effect and the chiral anomaly. Phys Rev D. 2021 Jun 4;103(12):125003.

[235] Sahoo SC, Kundu T, Banerjee R. Helical Water Chain Mediated Proton Conductivity in Homochiral Metal–Organic Frameworks with Unprecedented Zeolitic unh-Topology. J Am Chem Soc. 2011 Nov 9;133(44):17950–8.

[236] Mukherjee A, Vanderhaeghen M. Helicity-dependent twist-two and twist-three generalized parton distributions in light-front QCD. Phys Rev D. 2003 Apr 24;67(8):085020.

[237] Mukherjee A, Saha MK, Nethaji M, Chakravarty AR. Helical supramolecular host with aquapores anchoring alternate molecules of helical water chains. Chem Commun. 2004 Mar 5;(6):716–7.

[238] Verlangieri AJ, Mumma RO. In vivo sulfation of cholesterol by ascorbic acid 2-sulfate. Atherosclerosis. 1973 Jan 1;17(1):37–48.

[239] Hatanaka H, Egami F. Sulfate Incorporation from Ascorbate 2-Sulfate into Chondroitin Sulfate by Embryonic Chick Cartilage Epiphyses. The Journal of Biochemistry. 1976;80(6):1215–21.

[240] Mumma RO. Ascorbic acid sulfate as a sulfating agent. Biochimica et Biophysica Acta (BBA) - General Subjects. 1968 Oct 15;165(3):571–3.

[241] Hirschmann JV, Raugi GJ. Adult scurvy. Journal of the American Academy of Dermatology. 1999 Dec 1;41(6):895–910.

[242] Schwartz ER, Adamy L. Effect of ascorbic acid on arylsulfatase activities and sulfated proteoglycan metabolism in chondrocyte cultures. J Clin Invest. 1977 Jul 1;60(1):96–106.

[243] Njoroge FG, Chen KX, Shih NY, Piwinski JJ. Challenges in modern drug discovery: a case study of boceprevir, an HCV protease inhibitor for the treatment of hepatitis C virus infection. Accounts of chemical research. 2008;41(1):50–9.

[244] Chen KX, Njoroge FG. A review of HCV protease inhibitors. Curr Opin Investig Drugs. 2009 Aug;10(8):821–37.

[245] Antonopoulou I, Sapountzaki E, Rova U, Christakopoulos P. Inhibition of the main protease of SARS-CoV-2 (Mpro) by repurposing/designing drug-like substances and utilizing nature's toolbox of bioactive compounds. Comput Struct Biotechnol J. 2022;20:1306–44.

[246] Romeo I, Mesiti F, Lupia A, Alcaro S. Current Updates on Naturally Occurring Compounds Recognizing SARS-CoV-2 Druggable Targets. Molecules. 2021 Jan;26(3):632.

[247] Ferrazzini G, Maggiorini M, Kriemler S, Bärtsch P, Oelz O. Successful treatment of acute mountain sickness with dexamethasone. Br Med J (Clin Res Ed). 1987 May 30;294(6584):1380–2.

[248] Huang S, Yu H, Li Q. Supramolecular Chirality Transfer toward Chiral Aggregation: Asymmetric Hierarchical Self-Assembly. Advanced Science. 2021;8(8):2002132.

[249] Roomi MW, Ivanov V, Kalinovsky T, Niedzwiecki A, Rath M. In vitro and in vivo antitumorigenic activity of a mixture of lysine, proline, ascorbic acid, and green tea extract on human breast cancer lines MDA-MB-231 and MCF-7. Med Oncol. 2005 Jun 1;22(2):129–38.

[250] Li JP, Kusche-Gullberg M. Chapter Six - Heparan Sulfate: Biosynthesis, Structure, and Function. In: Jeon KW, editor. International Review of Cell and Molecular Biology [Internet]. Academic Press; 2016. p. 215–73. Available from: https://www.sciencedirect.com/science/article/pii/S193764481630020X

[251] Chini CCS, Peclat TR, Warner GM, Kashyap S, Espindola-Netto JM, de Oliveira GC, et al. CD38 ecto-enzyme in immune cells is induced during aging and regulates NAD+ and NMN levels. Nat Metab. 2020 Nov;2(11):1284–304.

[252] Tan A, Doig CL. NAD+ Degrading Enzymes, Evidence for Roles During Infection. Frontiers in Molecular Biosciences [Internet]. 2021 [cited 2022 Apr 6];8. Available from: https://www.frontiersin.org/article/10.3389/fmolb.2021.697359

[253] Ehrlich P. Man with the magic bullet. Singapore Med J. 2010;51(11):842.

[254] Strebhardt K, Ullrich A. Paul Ehrlich's magic bullet concept: 100 years of progress. Nature Reviews Cancer. 2008;8(6):473–80.

[255] Winau F, Westphal O, Winau R. Paul Ehrlich—in search of the magic bullet. Microbes and Infection. 2004;6(8):786–9.

[256] Tan SY, Grimes S. Paul Ehrlich (1854-1915): man with the magic bullet. Singapore Med J. 2010 Nov;51(11):842–3.

[257] Wu H, Wu Y, Ai Z, Yang L, Gao Y, Du J, et al. Vitamin C Enhances Nanog Expression Via Activation of the JAK/STAT Signaling Pathway. Stem Cells. 2014 Jan 1;32(1):166–76.

[258] Schmittel M, Abufarag A, Luche O, Levis M. α-Umpolung of Ketones via Enol Radical Cations: A Mechanistic Study. Angewandte Chemie International Edition in English. 1990;29(10):1144–6.

[259] Schmittel M. Umpolung of ketones via enol radical cations. In: Mattay J, editor. Electron Transfer I. Berlin, Heidelberg: Springer; 1994. p. 183–230. (Topics in Current Chemistry).

[260] Hamer M, Suarez SA, Neuman NI, Alvarez L, Muñoz M, Marti MA, et al. Discussing Endogenous NO • /HNO Interconversion Aided by Phenolic Drugs and Vitamins. Inorg Chem. 2015 Oct 5;54(19):9342–50.

[261] Ebrahimi S, Dabbagh HA, Eskandari K. Nature of intramolecular interactions of vitamin C in view of interacting quantum atoms: The role of hydrogen bond cooperativity on geometry. Physical Chemistry Chemical Physics. 2016;18(27):18278–88.

[262] Mayorga Burrezo P, Jiménez VG, Blasi D, Ratera I, Campaña AG, Veciana J. Organic Free Radicals as Circularly Polarized Luminescence Emitters. Angewandte Chemie International Edition. 2019;58(45):16282–8.

[263] Mayorga-Burrezo P, Jiménez VG, Blasi D, Parella T, Ratera I, Campaña AG, et al. An Enantiopure Propeller-Like Trityl-Brominated Radical: Bringing Together a High Racemization Barrier and an Efficient Circularly Polarized Luminescent Magnetic Emitter. Chemistry. 2020 Mar 23;26(17):3776–81

[264] Avalos M, Babiano R, Cintas P, Jiménez JL, Palacios JC. From parity to chirality: chemical implications revisited†Dedicated to the memory of André Collet (1945–1999).†. Tetrahedron: Asymmetry. 2000 Jul 28;11(14):2845–74.

[265] Yuan H, Stratton CF, Schramm VL. Transition State Structure of RNA Depurination by Saporin L3. ACS Chem Biol. 2016 May 20;11(5):1383–90.

[266] Gaurav, A. & Al-Nema, M. Chapter 10 - Polymerases of Coronaviruses: Structure, Function, and Inhibitors. in Viral Polymerases (ed. Gupta, S. P.) 271–300 (Academic Press, 2019). doi:10.1016/B978-0-12-815422-9.00010-3.

[267] Geller C, Varbanov M, Duval RE. Human coronaviruses: insights into environmental resistance and its influence on the development of new antiseptic strategies. Viruses. 2012;4(11):3044–68.

[268] Brosey CA, Houl JH, Katsonis P, Balapiti-Modarage LPF, Bommagani S, Arvai A, et al. Targeting SARS-CoV-2 Nsp3 macrodomain structure with insights from human poly(ADP-ribose) glycohydrolase (PARG) structures with inhibitors. Prog Biophys Mol Biol. 2021 Aug;163:171–86.

[269] Haake PC, Westheimer FH. Hydrolysis and Exchange in Esters of Phosphoric Acid 1a,b. J Am Chem Soc. 1961 Mar;83(5):1102–9.

[270] Westheimer F. Additions and Corrections. Pseudo-Rotation in the Hydrolysis of Phosphate Esters. Acc Chem Res. 1968 Dec 1;1(12):381–381.

[271] Sajenko I, Pilepic V, Jakobušić Brala C, Uršić S. Solvent dependence of the kinetic isotope effect in the reaction of ascorbate with the 2, 2, 6, 6-tetramethylpiperidine-1-oxyl radical: tunnelling in a small molecule reaction. The Journal of Physical Chemistry A. 2010 Mar 18;114(10):3423-30.

[272] Karković A, Brala CJ, Pilepić V, Uršić S. Solvent-induced hydrogen tunnelling in ascorbate proton-coupled electron transfers. Tetrahedron Letters. 2011 Apr 13;52(15):1757–61.

[273] Karković Marković A, Jakobušić Brala C, Pilepić V, Uršić S. Kinetic Isotope Effects and Hydrogen Tunnelling in PCET Oxidations of Ascorbate: New Insights into Aqueous Chemistry? Molecules. 2020 Jan;25(6):1443.

[274] Baccolini G, Boga C, Micheletti G. The Phosphoenolpyruvate Phosphorylation: A Self-Organized Mechanism with Implications to Understand the RNA Transformations. Phosphorus, Sulfur, and Silicon and the Related Elements. 2010 Oct 28;185(11):2303–15.

[275] Baccolini G. The Possible Role of Cyclic Pentacoordinate Phosphorus Intermediates in the Origin and Evolution of Life. are Phosphoric Anhydride and Trimetaphosphates Prebiotic Reagents? Phosphorus, Sulfur, and Silicon and the Related Elements. 2015 Dec 2;190(12):2173–86.

[276] Cabral J, Haake P, Kessler K. Rearrangement of 3-Acyl Derivatives of L-Ascorbic Acid. Journal of Carbohydrate Chemistry. 1998 Dec 1;17(9):1321–9.

[277] Sauve AA. NAD+ and vitamin B3: from metabolism to therapies. Journal of Pharmacology and Experimental Therapeutics. 2008;324(3):883–93.

[278] Makarov MV, Trammell SAJ, Migaud ME. The chemistry of the vitamin B3 metabolome. Biochemical Society Transactions. 2018 Dec 17;47(1):131–47.