Review

Modifying Effect of Products Derived from Vibration-Gradual Technology

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Modifying Effect of Products Derived from Vibration-Gradual Technology

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Abstract

Research demonstrates that highly diluted solutions can modify the physicochemical and biological properties of the substance from which they are derived. This modifying effect is attributed to the mechanical vibration (such as stirring or shaking) applied during preparation process. By subjecting the initial substance and a neutral carrier directly to vibrational treatment, "vibrational iterations" had been developed that retain these modifying properties while bypassing the serial dilution process entirely. The development and application of these approaches to obtain products that modify the properties of the initial substance is hereafter defined as vibration-gradual technology. This technology has facilitated the development of therapeutics based on high dilutions of antibodies and, more recently, vibrational iterations derived from diverse complex biological structures. Evidently, vibrational iterations offer substantial potential for the treatment of various pathologies, including oncological diseases. This review outlines the research milestones leading to these developments, summarizes current experimental data, and proposes the 'supramolecular matrix' hypothesis to explain the mechanisms underlying the modifying effect.

Keywords: modifying effect; vibration; vibrational iterations; post-vibrational activity; post-vibrational interactions; supramolecular matrix; solution theory; high dilutions; antibodies; interferon-gamma

Introduction

At the end of the 20th century, a systematic study of high dilutions (HDs) of biologically active substances as potential therapeutics led to the discovery of modifying effect (ME). ME is characterized by the ability of HDs of an initial substance to alter the physicochemical and biological properties of that same substance in its non-vibrated state. Using HDs of antibodies as a model, it was established that ME is based on conformational changes in target molecules. These changes are induced by HDs of antibodies specific to that molecule, thereby modulating the activity of the corresponding molecular pathway [1,2]. Consequently, the primary advantage of the ME is its ability to exert a specific influence on any target molecule or associated biological process. This research has already facilitated the clinical introduction of a new class of biological drugs, alongside the development of in vitro analytical methods for quantifying the ME in units of modifying activity (UMA) [1,3–6].

Recently, it was established that the ME originates from vibrational treatment of the initial substance. By utilizing non-contact interaction between the initial substance and a neutral carrier (such as water or lactose), a novel technological product termed a vibrational iteration (VI), was obtained, and the technology for producing these iterations was termed vibrational crossing [7]. Like HDs, VIs of any substance exert a specific ME on the same substance. During each dilution step of the HD preparation process, the intact solvent is effectively subjected to vibrational influence from the initial substance and its subsequent dilutions. Therefore, it became clear that HDs are essentially a *mixture* of VIs.

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For a long time, the study of HD products, which contain virtually no initial substance molecules, was hindered by conceptual and ideological barriers. The discovery of the role of vibration, returns HDs to the realm of material objects accessible to rational scientific study, and, remarkably, closes the history of their independent study. As a more refined and effective application of vibrational technology, VIs are poised to supersede traditional HDs in the near future. Notably, unlike traditional HDs, VIs can be obtained from intact biological objects, such as cell cultures [8]. In vitro results suggest the potential use of such VIs for the treatment of various pathologies, including cancer (**publication in preparation**).

Vibrational crossing is a relatively new technology, and current publications on the topic remain limited [7–11]. Therefore, to demonstrate the properties of vibration-gradual technology products, this review presents data obtained during a nearly thirty years of research into pharmaceuticals based on HDs (**Figure 1**). Presented chronologically, each stage of this research offers both theoretical and practical insights.

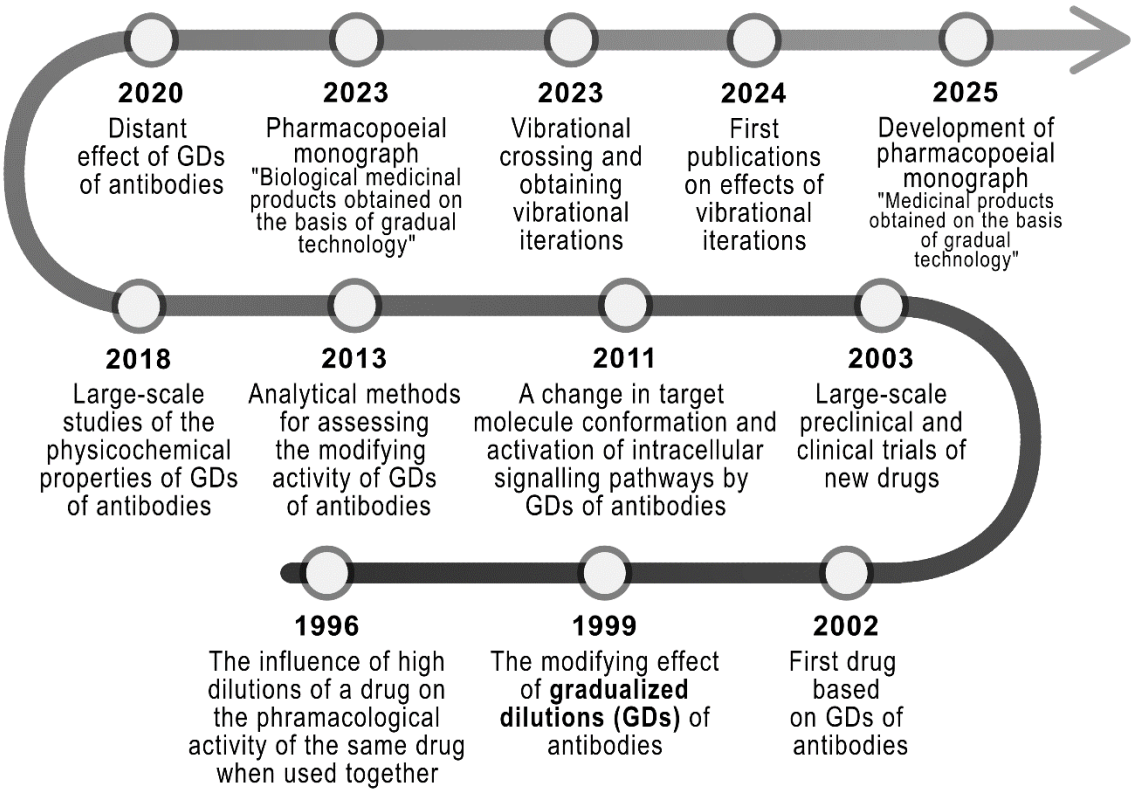

Figure 1. From highly diluted solutions to vibrational iterations: major milestones.

The discovery of the ME naturally necessitates a rigorous investigation into its underlying physical mechanisms and the establishment of its theoretical foundations. To this end, the author proposes the supramolecular matrix hypothesis, a theoretical framework for supramolecular regulation based on the observed biological activity of vibration-gradual technology products. This hypothesis represents a philosophical attempt to understand the nature of the discovered ME. While several research groups of physicists are currently exploring this phenomenon, the consensus suggests that explaining the ME may require a revision of traditional physical models and an expansion of solution theory to include the role of vibration. This article invites specialists in a wide range of fields studying or using solutions, primarily physicists, to engage in dialogue, in the hope that joint discussion will help formulate more fundamental concepts of the ME.

Stage 1. Discovery of the modifying effect of high dilutions

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The ME of HDs was discovered in 1996 during an investigation into "small" doses of established pharmacological agents. The study sought to determine the feasibility of utilizing low-dose "classical" drugs as safe therapeutic alternatives. At that time, two independent lines of research had already begun accumulating data regarding the unique effects of HD substances.

The first historical direction was homeopathy, which emerged in the 18th century and utilized HDs, often termed "small" doses, prepared by the serial dilution of an initial substance (**Figure 2**).

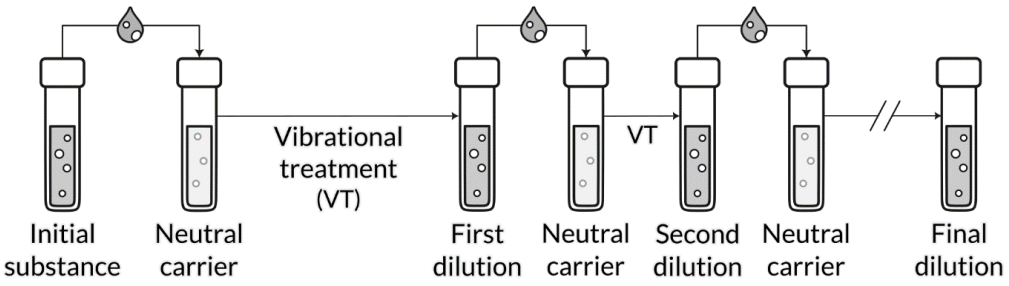

Figure 2. Conventional methodology for the preparation of high dilutions [7].

An analysis of the available homeopathic literature led to several key conclusions:

1. Most HDs or "small doses" used in homeopathy are calculated to be devoid of the initial substance molecules.
2. HDs in homeopathy are typically studied through administration to healthy volunteers in order to elicit and characterize a specific *individual reactions*. The phenotypic traits of those who react (responders) serve as markers of individual sensitivity.
3. Based on the markers identified for each HD drug, one of them is then individually selected for the patient to elicit a unique response. Only if such a response is successfully elicited does the drug exert a symptom-modifying effect, leading to clinical improvement.

A subsequent shift occurred with the investigation of *the physiological* properties of HDs. During the 1970s and 1980s, data emerged demonstrating the ability of HD solutions of various substances to produce *reproducible* molecular and cellular effects, distinguishing them from the isolated individual reactions observed in homeopathy [12–16]. These effects were *specific*; in a reduced form, they reproduced the biological properties of only the initial substance [17]. However, due to the lack of the hypothesis explaining the ability of HDs to exhibit such activity without a "material" carrier, these findings were largely dismissed by the scientific community [18,19].

Integrating these two approaches led to the hypothesis that HD substances might not only exert a symptom-modifying effect on a disease but also directly influence the molecular pathways of the substance from which the HD was derived. This could explain the physiological effects observed by researchers.

To test this hypothesis, the first stage of the study involved co-administering known drugs at therapeutic (or toxic) doses alongside HDs of those same drugs to animals using standard pharmacological models, i.e., the simultaneous use of conventionally "high" and "small" doses. It was found that HDs altered the pharmacological properties of the original drugs, including the severity of their toxicity [20–22]. Most cases demonstrated a positive combination of increased pharmacological activity and decreased toxicity of the original drugs. Thus, it was demonstrated that the effects of HDs are based on their ability to exert MD on the biological properties of the initial substance.

It was later established that the mechanism underlying HD is the repeated vibrational treatment invariably applied during the process of their preparation [7]. Consequently, the terms "high dilution" and "small dose" do not accurately reflect the nature of these products. Given the role of repeating vibrational cycles, the production method was termed "*vibrational -gradual*" technology. Products resulting from combined vibration and serial dilution are termed *gradualized dilutions* (GD), while those prepared via vibration alone are called *vibrational iterations* (VI).

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Subsequently, it became apparent that the newly acquired quality (ME) was a consequence of the HD preparation technology. This insight reframed the fundamental question regarding the activity of HDs: rather than considering how the properties of the initial substance are preserved in a HD solution, attention shifted to identifying the mechanisms by which qualitatively new, technologically induced properties emerged. To emphasize the role of preparation technology, our group initially introduced the term *"released-activity"* [1], which was later replaced by the more precise term *"post-vibrational activity"* [7].

Stage 2. Development of drugs based on gradualized dilutions of antibodies and investigation of their molecular mechanisms

The impetus for studying GDs of antibodies arose from the use of a well-known model of long-term post-tetanic potentiation in hippocampal slices [23]. Ordinarily, the incubation of slices in a medium containing antiserum to S100B protein results in a complete blockade of post-tetanic potentiation. However, preincubation of hippocampal slices with GDs of antibodies to S100B prevented this inhibitory effect, thereby preserving the dynamics of post-tetanic potentiation [23,24].

These data allowed for the hypothesis that GDs of antibodies are capable of direct ME on the target antigen, occurring independently of the presence of the original antibody molecules. Thus, while any GD exerts ME on its initial substance, GDs of antibodies selectively modify the corresponding antigen. Unlike monoclonal antibodies, primarily used in oncology and rheumatology to exert a suppressive effect on molecular targets (antigens), the effects of GDs of antibodies are adaptive. This allows their use as a gentle regulatory therapy for a broad range of infectious diseases and psychosomatic conditions.

The primary focus of our investigations into the ME mechanisms was GDs of antibodies to interferon-gamma (IFN-γ). Research demonstrated that their ME is realized through the induction of conformational changes of the target molecule by influencing its hydration shell [2,25]. GDs of antibodies to IFN-γ alter the dimer structure at the interface between the two monomers and within their C-terminal regions, significantly impacting cytokine's function. This structural shift results in increased specific binding of IFN-γ to its receptors on U-937 monocytic cells (**Figure 3**). Furthermore, an increase in induced IFN-γ secretion was observed in human peripheral blood mononuclear cell cultures, reflecting the activation of the IFN-γ signaling pathway. Consequently, these effects translate into increased survival rates in mice infected with influenza A [2].

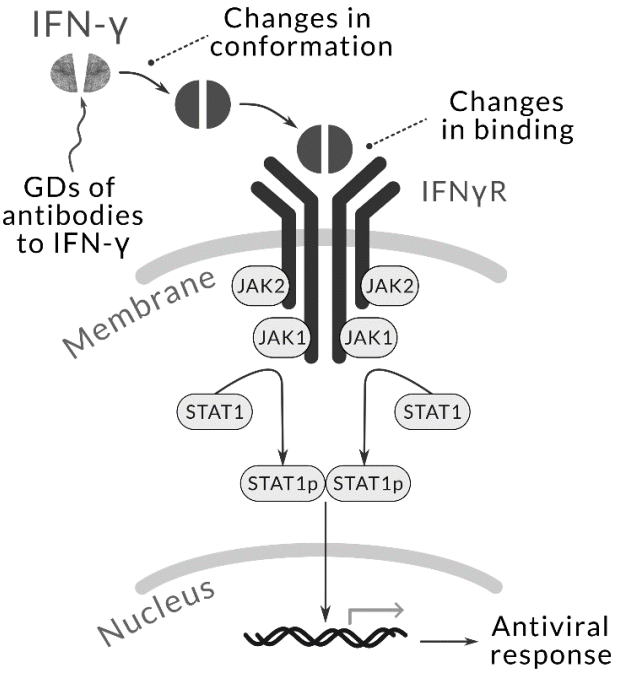

Figure 3. Proposed mechanism of action for GDs of antibodies to IFN-γ (adapted from [26]).

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Studying the molecular effects of HDs of antibodies has enabled the application of a pathogenetic approach, standard in modern pharmacology, to the development of safe preparations of GDs of antibodies. Currently, a group of gradualized oral drugs based on affinity-purified polyclonal antibodies has been approved for medical use. **Tables A1 and A2** provide a summary of preclinical and clinical studies investigating therapeutic agents based on GDs of antibodies.

Stage 3. Utilization of advanced analytical techniques to elucidate the mechanisms and modifying effects of gradualized dilutions

The development of modern analytical methods has prompted a surge in publications examining the diverse physical properties of HDs [27–32]. The primary methodologies employed for this purpose include conductometry [33]; radiometry [34,35], terahertz (THz) spectroscopy [36], infrared (IR) thermography [5], surface plasmon resonance spectroscopy [37], enzyme-linked immunosorbent assay (ELISA) [3], and kinetic analysis [4]. In addition, using dynamic light scattering [33,38,39] and IR emission spectroscopy [40], it has been shown that HDs contain structural heterogeneities, often referred to as nanoassociates [27,33,38], or less commonly, as clusters [41], mesoscale structures [42] or supramers [43]. These nanoscale objects are considered as potential carriers of the activity of HDs. While various hypotheses have been proposed regarding their origin and structure [42,44], it is evident that a central role is played by the formation and modification of hydrogen bonds between the solute and water molecules [45]. It is possible that external influences may drive changes in the macroscopic properties of aqueous solutions through quantum effects [32], alongside alterations in their ionic and molecular composition [46].

Recent studies have shown that structural heterogeneities [38,47]and new physicochemical properties [32,46,48–52]appear not only in HDs of the initial substance [27,29,33,53–58], but also in "classical" solutions containing "measurable" doses of the initial substance, provided they have been subjected to vibrational treatment.

Through the development of proprietary analytical methods, the activity of drugs based on GDs of antibodies, specifically their capacity to exert a ME, has been quantified in UMA [6]. The UMA is a relative value calculated by comparing the drug's effect on target molecules against a placebo. These methods subsequently allowed for the discovery of the role of vibration in the emergence of ME.

Stage 4. Evidence that the action of gradualized dilutions is based on structural modification of the exposed environment

Research has established that GDs primarily modify the structure of various media upon which they act. As a secondary effect, if the medium contains molecules of the initial substance, their spatial configuration is subsequently modified by the already-altered medium. Examples of GD-induced structural changes are summarized in **Table A3.**

Stage 5. Discovery of distant modifying effect

During the study of GDs of antibodies, it was discovered that they exert a ME on the corresponding antigens even without direct physical contact (distantly). Specifically, a distant effect occurs when the GDs of antibodies and the antigen solution are placed in adjacent vials (see **Table A4**).

Stage 6. Development of vibrational crossing technology

The discovery that GDs can interact at a distance without physical contact (distantly) made it possible to overcome a significant conceptual barrier by eliminating the requirement for serial dilution of initial substances. This led to the implementation of "vibrational crossing," a process where a neutral carrier, such as water or lactose, is sequentially exposed to the vibrations of an initial substance without directly mixing the components [7] (**Figure 4, upper panel**). Vibrational crossing is technically straightforward and indicates that behind the process of multiple dilutions, distant interactions occur between the initial substance and the neutral carrier.

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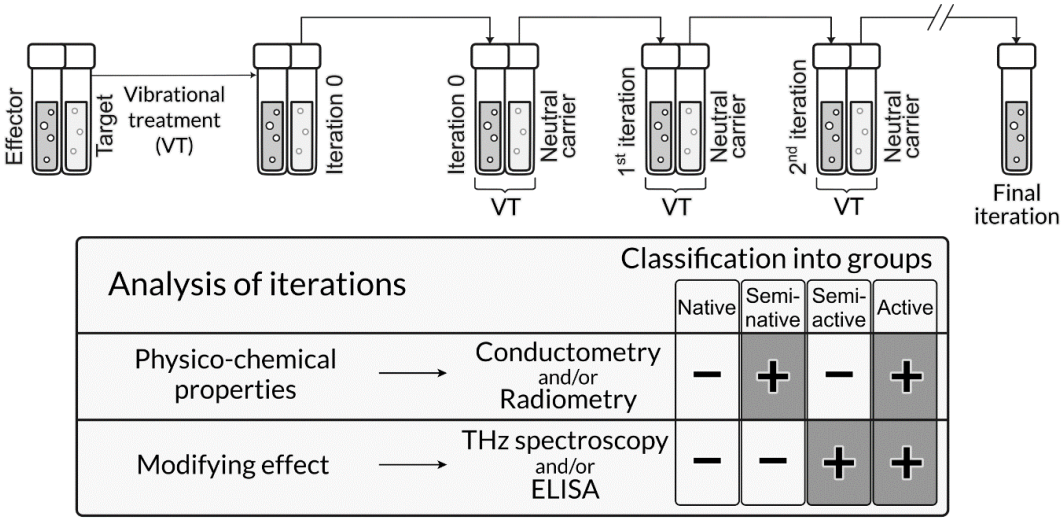

Figure 4. Schematic of vibrational crossing technology [7].

A series of samples obtained via vibrational crossing was analyzed for electrical conductivity, absorption/emission characteristics across multiple spectral ranges, and their influence on antibody-antigen interactions was assessed by ELISA. These analyses revealed that the physicochemical properties of the neutral carrier varied among these samples. Neutral carrier samples subjected to vibration that exhibit altered, long-term properties were denoted vibrational iterations (VIs) (**Figure 4, lower panel**). Based on deviations from the intact neutral carrier's (ultra-pure water) physicochemical properties, VIs were classified into four distinct groups (*fractions*):

1. Native: Exhibits no significant physicochemical changes via conductometry or radiometry compared to the intact neutral carrier and shows no ME on the target molecule in THz spectroscopy or ELISA.
2. Semi-native: Displays statistically significant physicochemical changes compared to the intact neutral carrier but lacks a ME on the target molecule in THz spectroscopy or ELISA.
3. Semi-active: Shows no significant physicochemical deviations from the intact neutral carrier yet, unlike the Native fraction, exerts a ME on the target molecule in THz spectroscopy or ELISA.
4. Active: Exhibits both statistically significant physicochemical differences and a consistent ME on the target molecule in THz spectroscopy or ELISA compared to the intact neutral carrier.

As with HDs [17,59,60], these effects are *specific*: each VI fraction reproduces a portion of the pharmacological spectrum of its initial substance.

While initial classification relied primarily on ELISA and THz spectroscopy, it was later confirmed that the fractions tentatively termed "Native" and "Semi-native" are also capable of modifying certain properties of the initial substance. This finding further supports the conclusion that the ME constitutes the fundamental basis of activity for products obtained using vibration-gradual technology, and implies that GDs represent a mixture of VIs.

Later, it was established that, under different experimental conditions, the ME of GDs and VIs manifests itself in changes in the various physicochemical properties of the initial substance. Thus, while a larger number of methods could expand this classification system, the current four-fraction model remains the most practical for this stage of research.

Stage 7. Practical applications and therapeutic potential of vibrational iterations

At this stage, it has been established that the use of individual VIs offer greater clinical promise than their use as a combination within GDs. For example, studies of VIs obtained from *chemical* compounds (including well-known drugs such as paracetamol, prednisolone, haloperidol, phenobarbital, benzodiazepine) or antibodies to these substances, demonstrate that two fractions, namely Active and Native, in reduced form reproduce the biological activity of the initial substance,

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while exhibiting maximum difference in spectrum and magnitude of their effects. The ability to generate distinct VI fractions enables the experimental selection of those with the most favorable potential pharmacological properties.

Furthermore, the co-administration of paracetamol with its corresponding VI has been shown to reduce paracetamol-related toxicity (**submitted for review**). This finding highlights the potential of VIs for use in pharmacology as modulators of the adverse effects associated with existing drugs.

A main advantage of vibrational crossing is its applicability to substances that cannot undergo traditional serial dilution without losing their integrity, such as biological materials ranging from isolated cells [8] to whole organs. The ability to generate VIs from intact cellular material is particularly attractive for applications in regenerative medicine, as it offers a route to the development of long-lasting, pathogen-free and *standardized* biological drugs. Such preparations are not expected to induce rejection reactions, thereby supporting their potential for widespread, rather than individualized, clinical use.

Preliminary in vitro studies suggest that VIs derived from biological materials are promising candidates for the treatment of hormonal disorders, cancer, and other serious diseases (**results are being prepared for publication**). To date, initial investigations have been conducted using various experimental models to evaluate the antitumor potential of VIs derived from both malignant cell lines (e.g., B16 melanoma, P-815 mastocytoma, RAW264.7 leukemia) and normal cells or cell lines (e.g., human lung fibroblast cells FLECH-104, human embryonic kidney cells HEK 293, Chinese hamster ovary cells CHO-S, mouse peritoneal macrophages, human prostate cells). Notably, iterations of "normal" human cells have demonstrated the ability to suppress tumor proliferation in vitro and tumor growth and metastasis in vivo.

Given that *water* constitutes approximately 60% of the human body and plays a central role in various biochemical reactions and thermoregulation, the pharmacological activity of various VI fractions of water has been investigated to determine their influence on physiological and biochemical processes occurring in water and bodily fluids. Selected effects identified for the Native fraction of VIs of water are presented in **Table A5** (**unpublished data**).

VIs can be obtained not only from chemical or biological substances, but also from "*physical*" factors. For example, water exposed to UV irradiation, as well as to magnetic [61], or electromagnetic fields [10], can serve as an initial substance for vibrational crossing. These "physical" VIs have been found to modify the impact of environmental impacts on biological systems.

Irrespective of the initial substance, all VIs can be consistently classified into the four established fractions: Native, Semi-native, Semi-active, and Active [7,8,10,61]. This consistency indirectly points to a predetermined, non-random mechanism underlying the crossing process. Thus, both GDs and VIs are capable of exerting a ME on the initial substance of any origin, which opens up prospects for their application in chemistry, medicine and engineering (**Table A6**).

Stage 8. Summary of findings

To date, theoretical studies addressing the mechanisms of post-vibrational activity remain relatively limited [62–78] and do not yet fully account for all observed data. Therefore, the main properties of preparations developed via vibration-gradual technology are summarized below:

1. A common feature of GDs and VIs obtained using the same initial substance is the *variability* in their physicochemical and biological properties. This variability depends on the number of dilution steps accompanied by solution mixing, or number of cycles of vibrational treatment [7,17,27,33]. Moreover, HDs prepared simultaneously and with the same dilution degree are known to exhibit fluctuations in their properties [79–82].
2. Current research identifies nanoassociates as the primary carriers of activity in both VIs and GDs [7,27,33,79]. The presence of nanoassociates does not depend on the degree of dilution of the solution; rather they are formed or their number increases in a solution with any concentration of a solute following vibration exposure [83,84]. This indicates that their formation is induced by a suprasystemic factor (i.e., vibration), which refutes the popular hypothesis of "water memory." In this context, it is more appropriate to refer not to the memory of water (or another

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conditionally neutral carrier such as lactose), but to the "memory" of a suprasystemic regulatory process that governs structural reorganization during vibrational treatment. It is also important to consider that the relaxation period of hydrogen bonds involved in the formation of nanoscale structures is in the order of a few picoseconds, which is less than the lifetime of nanoassociates themselves [45]. At the same time, GDs retain their specific biological properties over prolonged periods. This suggests that the structural basis of GD activity is associated not with the transient nanoassociates themselves, but rather with their dynamic spatial coupling [22], which is likewise governed by suprasystemic regulation.

3. It is known that the formation of nanoscale structures in HDs is dependent on electromagnetic field [33]. Both with "delicate" preparation without the use of vibration, and under hypomagnetic conditions, optical heterogeneities fail to form in HDs [27,85], and the resulting dilutions lack activity [86]. Vibrational treatment also affects the ability of HDs to emit electromagnetic radiation [34,35,40,83]. These observations led to the hypothesis that both the electromagnetic field and vibration are necessary for producing VIs and GDs, suggesting an intrinsic interconnection of these factors in nature. Perhaps vibration is also associated with other types of *known* factors, and not just with electromagnetic fields.
4. The most important feature of products obtained using vibration-gradual technology is the presence of MD, which determines the adaptive (normalizing) nature of their biological effects. Specifically, the *adaptive effect* is exemplified by GDs of antibodies to erythropoietin, which increase erythropoietin levels when they are low and decrease them when they are elevated [87]. VIs also exhibit an adaptive effect. For example, the Native fraction of VIs of water has been shown to suppress the metabolic activity in tumor cells while enhancing it in macrophages derived from healthy animals (**publication in preparation**). The adaptive effect of VIs and GDs demonstrates their ability to direct the biological system toward a *predetermined* multiparametric equilibrium state.
5. Another key feature of the effects of VIs and GDs is that they are always mediated through *a reorganization of the spatial structure* of the environment (or molecules present in the environment) into which these preparations are introduced. This influence is fundamental to understanding the effects of these drugs. In essence, their activity is realized at a structural or conditional geometric level. The observed adaptive effects of GDs and VIs lie in the normalization of the biological system's structure, potentially including changes in its electromagnetic characteristics. While the concept of the vibrational-resonance mechanism, whereby HDs influence electromagnetic processes in the organism, is widely discussed in the literature [41,88,89], it is obvious that these processes are secondary to the spatial restructuring of the organism.
6. Mathematical modeling indicates that the energy transferred during a 10-second vibration of a 20 ml sample (as used in vibrational crossing technology) corresponds to a temperature increase of only 0.06 °C [7]. Despite this minimal energy input, the process successfully "sets" adaptive parameters of the biological system. By bypassing a stage of thermodynamic "chaos," preparations based on GDs exert a uniquely gentle biological influence.

Stage 9. Hypothesis about the nature of the modifying effect.

A defining paradox of vibrational technology is, as stated above, that its ME is highly specific, reproducing the effects of the initial substance, despite the total absence of that substance in the final products of vibration-gradual technology (VIs and GDs). This suggests that their activity stems from the connection to a pre-existing supramolecular regulatory system or *supramolecular matrix*.

The central postulate of this hypothesis is that space itself controls any processes occurring within it, ensuring they conform to evolutionarily determined geometric frameworks. The vibration of any molecule activates this control, manifesting as the ME observed in "post-vibrational" molecules and the products of vibration-gradual technology (VIs and GDs).

In this model, evolution is viewed as the geometric (topological) self-complication of the absolute vacuum. The first stage in the formation of the Universe may have involved an initial geometric deviation (spatial curvature) of the vacuum from its initial state, the directional "vector"

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of which was then infinitely multiplied. This process would lead to the fractalization of space and its subdivision into an infinite number of cells, referred to as supramolecular matrices. Each matrix represents a unique deviation of space from the vacuum and its geometric structure simultaneously constitutes its semantic content. These matrices act as "corrective templates," ensuring the spatial coupling of all processes within their specific level of complexity. This spatial complication may have arisen from the competition between at least two evolutionary principles governing the development of the vacuum. Each of these principles operates in accordance with its own primary spatial algorithm, i.e., through the transfer of its specific principle of spatial organization to all manifestations of the Universe.

If we turn to the general principles of how an organism functions, the significant role of "spatial" control in biological activity becomes apparent. In a living cell, the flow of small, relatively simple ions is regulated by proteins with complex spatial structures. In turn, small protein fragments (epitopes) determine the specificity of antibodies, which themselves possess complex, domain-based spatial structures. On this basis, it has been hypothesized that long before biological evolution, at the stage of geometric complexification of the vacuum, mechanisms of spatial control of the evolutionary process must also have existed. Possibly this role was played by constant, inertia-free, energy-free self-oscillations of the supramolecular matrix. The "correct" deviation of the matrix from a certain axis of symmetry may have served as the primary control of the evolutionary "vector." This control itself was likely implemented through a feedback mechanism, the purpose of which was to distinguish "self" from "foreign."

The supramolecular matrix is regarded as a self-sufficient element of space, independent of molecules. Molecules appeared later in the evolutionary process, at a certain stage of the self-complexification (hypostasis) of the Universe. Consequently, all molecular elements are coupled into a single whole by the supramolecular matrix corresponding to their level of complexity. This hypothesis essentially expands the concept of "substance": it is a form of matter in which each particle composing the substance is embedded in a regulatory geometric matrix.

Through resonance mechanisms, artificially induced molecular vibrations allow the selection of a constantly vibrating supramolecular matrix corresponding to a given level of molecular complexity from the spatial continuum. In essence, a conditionally neutral carrier (lactose or water) is "introduced" into the supramolecular matrix and becomes directly exposed to the matrix. Consequently, the neutral carrier changes its original structure. Through mechanisms that are not yet fully understood, it maintains a long-term connection with the regulatory supramolecular matrix and, in effect, transmits the modifying (normalizing) effect inherent to the matrix.

It should be emphasized once again that the modifying (normalizing, adaptive) effect of products of vibration-gradual technology is their key feature.This new qualitative property is imparted by the small amount of energy transferred to the system during vibration. As a result, both the ME and its carrier are likely *pre-existent*, as the amount of energy transferred to the molecule is too small to generate new qualitative changes. Finally, the differences in properties between different VIs and GDs of the same substance can be explained by self-oscillations of the supramolecular matrix, since the state of the supramolecular matrix changes at any given moment. Thus, the supramolecular matrix hypothesis explains the main properties of gradualized preparations.

Previously, to explain the ability of GDs to elicit specific individual responses, it was suggested that all molecular processes in the organism are holographically (spatially) coupled [1,22,90]. Apparently, this coupling is due to the *holographic* organization of supramolecular regulation that controls the activity of biological systems.

The author believes that the discovery of a new role for vibration positions such research at the boundary between the material and ideal world. Perhaps the supramolecular matrix can be considered an element of essential coupling information, akin to concepts such as Naom Chomsky's generative grammar [91]and, even more broadly, to spatial memory.

A forthcoming paper reports on analysis of the intrinsic (induced) gigahertz emission of substances, such as interferon-gamma and water, which were not directly subjected to vibrational

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treatment. The emission changes occurred while identical samples were being processed on a vortex at a remote location (a laboratory in a separate building). While the effect consistently appeared in repeated trials, it would eventually fade, only to be reinstated by changing the vortexing mode (e.g., speed or duration). Such patterns of adaptation and tolerance to sustained stimuli are typical of biological systems that have memory properties.

Ultimately, it is not possible for two separate physical principles to operate within an organism. Regardless the physical mechanisms underlying the activity of gradualized preparations, at some subtle level they must be integrated with the mechanisms of action of pharmacological drugs administered in "classical" doses. This integrative level is proposed to correspond to the spatial (geometric) organization of the biological system.

Conclusions

1. A key advantage of gradualized preparations (VIs and GDs) over conventional pharmacological agents is that, during vibration treatment, the drug molecule is already transformed into a corresponding congruent structure of a neutral carrier, i.e., either lactose or water. Because VIs and GDs do not undergo traditional biotransformation, they are inherently free of toxicity and systemic side effects. However, like any class of drugs, gradualized preparations have their limitations, as they are only suitable for use in situations requiring a gentle regulatory effect.
2. The phenomenon of ME represents a significant challenge to modern physics. While the supramolecular matrix hypothesis is speculative and philosophical, it provides a necessary framework for physicists to develop a holistic approach to the problem of post-vibrational interactions. While alternative theories regarding vibrational effects will undoubtedly emerge, any complete theory of ME must account for two interrelated factors: 1) the physical changes in substance subjected to vibration, and 2) the pronounced adaptive, regulatory action of VIs and GDs.
3. The newly identified role of vibration as a determinant of the properties of gradualized preparations reveals prospects for the application of vibration-gradual technology not only in medicine, but also in engineering and materials science. Specifically, this approach may enable the modification of properties in a variety of materials, including superconductors, cement, and gasoline, among others [92–94]. It is anticipated that VIs will garner attention from a broader range of specialists more rapidly than GDs.

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Abbreviations

The following abbreviations are used in this manuscript:

ADHD	attention deficit hyperactivity disorder
ARVI	acute respiratory viral infections
CHO	Chinese hamster ovary
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
DLS	dynamic light scattering
ELISA	enzyme-linked immunosorbent assay
FTIR	Fourier transform infrared
GD	gradualized dilutions
HD	high dilutions
IFN-γ	interferon gamma
IR	infrared
LALLS	low-angle laser light scattering
ME	modifying effect
MHC	major histocompatibility complex
MoCA	Montreal Cognitive Assessment
NO	nitric oxide
THz	terahertz
UMA	units of modifying activity
UV	ultraviolet
VI	vibrational iteration

Appendix A

Table A1. Examples of preclinical studies of drugs based on gradualized dilutions of antibodies.

Model	Effect
Drug based on GDs of antibodies to IFN-γ	
A mouse model of acute pneumonia caused by the pandemic strain of influenza virus A/California/07/09 (H1N1)	Increased survival, average life expectancy, and protection index. Reduction in viral titer in the lungs, as well as decrease in pneumonia lesion size [95].
Models of pneumonia in mice caused by pandemic strains of influenza virus, A/California/07/09 (H1N1) and A/Equi2/Miami/1/63 (H3N8)	Increased survival [2].

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Infection in mice caused by the herpes simplex virus type 2 strain MS HSV-2	Reduced viral accumulation in the brain and increased survival [96].
Drug based on a mixture of GDs of antibodies to IFN-γ, CD4 and histamine	
Mouse model of respiratory syncytial virus infection	Reduced total inflammatory cell infiltration in the lungs, along with reduced numbers of infiltrating lymphocytes and macrophages compared with the control groups [97].
In vitro model of infection of MA-104 cells with rotavirus group A, strain 568	Reduced rotavirus titer in infected cells [98].
Drug based on a mixture of GDs of antibodies to the C-terminal fragment of the insulin receptor beta subunit and endothelial NO synthase	
Rat model of type 2 diabetes mellitus	Reduced plasma glucose levels and prevention of age-related impaired glucose tolerance [99].
Model of mixed type diabetes mellitus in rats	Decreased plasma glucose levels, restored glucose tolerance, decreased levels of ketone bodies in urine [100].
In vitro activation of insulin receptors in mature human adipocytes	Increased ratio of phosphorylated (active) to total insulin receptors [101].
In vitro secretion of adiponectin by mature human adipocytes	Increased production of adiponectin [102].
Drug based on GDs of antibodies to endothelial NO synthase	
Ex vivo endothelium-dependent vascular relaxation after preliminary phenylephrine-induced constriction of aortic rings in spontaneously hypertensive rats in response to a gradual increase in acetylcholine concentration	Increased relaxation of aortic rings compared to the control and comparable to the reference drug perindopril [103].
A model of decreased sexual function in aged rats	Increasing sexual motivation [104].
A model of sexual dysfunction in rats with low erectile function	Stimulating effect on copulatory behavior and sexual motivation [105].
Drug based on GDs of antibodies to brain-specific protein S100	
Model of stress and anxiety behavior in rats in the Vogel conflict test and elevated plus maze	Increased number of water intakes (punished by electric shock) and entries into stress zones (open arms of the elevated plus maze) [106].
Drug based on GDs of antibodies to prostate-specific antigen	
Rat model of androgen deficiency induced by gonadectomy	Enhanced testosterone androgenic effects on the prostate gland, evidenced by restoration of the

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	weight coefficients of the prostate gland ventral lobe to the level of the intact group [107].
Model of acute aseptic inflammation of the prostate gland in rats caused by suturing the gland with a silk thread	Reduced severity of hemodynamic disturbances in the prostate gland during inflammation, together with an increase in its functional activity (evidenced by an elevated zinc ion concentration) [107]
Drug based on GDs of antibodies to the C-terminal fragment of the angiotensin II receptor type 1 (AT_1)	
Model of hereditary stress-induced arterial hypertension (NISAG rats)	Reduced systolic blood pressure [108].
Drug based on GDs of antibodies to cannabinoid receptor type 1	
Model of obesity in mice induced by a long-term (5 months) high-calorie diet	Reduced body weight gain in animals throughout the study [109].
Drug based on GDs of antibodies to tumor necrosis factor alpha	
Collagen-induced rheumatoid arthritis (autoimmune joint inflammation) model in mice	Reduced severity of joint damage (determined using the scale for assessing clinical signs of arthritis), together with a reduced total score for the severity of joint inflammation (determined by the degree of changes in bone and cartilage tissue) [110].
Drug based on a mixture of GDs of antibodies to bradykinin, morphine, and histamine	
Guinea pig cough model induced by capsaicin or citric acid	Reduced number of cough shocks in one or both models [111,112].
Drug based on a mixture of GDs of antibodies to IFN-γ, CD4, β2-microglobulin of MHC class I molecule, β1-domain of MHC class II molecule	
Model of lethal infection with multidrug-resistant *Klebsiella pneumoniae* in neutropenic mice	Increased survival when combined with amoxicillin and clavulanic acid, reflecting enhanced antibiotic activity against resistant bacteria [113].
Mouse model of pulmonary infection caused by *Streptococcus pneumoniae*	Reduced bacterial load in the lungs [114].
Model of lethal infection by influenza virus A/California/07/09 (H1N1)pdm09 in mice	Increased survival and average life expectancy [115].
Model of mixed viral-bacterial infection in mice (influenza virus A/California/04/2009 (pdmH1N1 2009) followed by infection with *Staphylococcus aureus*)	Increased survival [115].
Drug based on GDs of antibodies to brain-specific protein S100, modified	

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Hemorrhagic stroke model in rats	Reduced area of brain damage and neurological deficit. Increased survival [116].
Ischemic stroke model in rats	Restored neurological status at the peak of neurological deficit [117] .
Assessment of cognitive functions using the slow alternation test in "young" and "old" rats	Improved learning and memorization processes (reduction of simple reaction time and choice time in “old” animals) [118].
Assessment of anxiety-like behavior using the open field test in rats	Increased exploration in the open field (distance traveled, time spent, and center entries) [119].
Evaluation of bioelectrical activity of the mouse brain	Changes in the bioelectrical activity of the brain (reduced electroencephalogram spectral power in the alpha and theta frequency ranges) (**article accepted for publication**)

Table A2. Examples of clinical trials of drugs based on gradualized dilutions of antibodies.

Study design	Results
Randomized clinical trials	
Drug based on a mixture of GDs of antibodies to IFN-γ, CD4, β2-microglobulin of MHC class I molecule, β1-domain of the MHC class II molecule	
A multicenter, double-blind, placebo-controlled, randomized, parallel group clinical trial on the efficacy and safety of the drug in the treatment of acute respiratory viral infection	One-day reduction in illness duration compared with a placebo. Four-fold increase in the proportion of patients recovering by day 3 of the study. On average, patients with PCR-confirmed ARVI who received the drug recovered within 4 d without complications or the need for antibacterial therapy[120].
Drug based on a mixture of GDs of antibodies to bradykinin, morphine, and histamine	
Multicenter, double-blind, placebo-controlled, randomized, parallel group clinical trial on the efficacy and safety of the drug in the treatment of cough in patients with chronic obstructive pulmonary disease	Reduced cough severity in a significantly higher percentage of patients compared with placebo therapy. Most patients suffering from a disruptive cough responded favorably to the drug. In combination with basic therapy, drug treatment for 4 weeks significantly reduced the impact of COPD on patients' lives, demonstrating the feasibility of “cough management” [121].
Drug based on GDs of antibodies to brain-specific protein S100, modified	
Multicenter, double-blind, placebo-controlled, randomized, parallel group clinical trial on the efficacy and safety of the drug in the treatment of mild cognitive	Improved cognitive function (as measured by the Montreal Cognitive Assessment [MoCA]) in 91.9% of patients. The average MoCA score increased by 3.8 over 24 weeks of treatment. Restoration of daily

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impairment in patients in the early recovery period of ischemic stroke	activities (as measured by the Barthel Scale) in 90.1% of patients with post-stroke movement disorders during treatment. No clinically significant changes in vital signs or laboratory abnormalities were observed during the study [122].
Multicenter, double-blind, placebo-controlled, randomized, parallel group clinical trial on the efficacy and safety of the drug in the treatment of asthenia in patients after acute novel coronavirus infection (COVID-19)	Notable 16.5-point reduction in the average Fatigue Severity Scale score in patients with post-COVID asthenia. Reduced severity of asthenia in 99.9% of patients during treatment. The antiasthenic effect of the drug was maintained in 90% of patients for one month after discontinuing therapy [123].
Multicenter, double-blind, placebo-controlled, randomized, parallel group clinical trial on the efficacy and safety of the drug in the treatment of cognitive, behavioral, and mental disorders in patients with vascular dementia	Significantly reduced severity of cognitive impairment in elderly and senile patients with vascular dementia. Reduced severity of mental and behavioral symptoms of vascular dementia (assessed by both physicians and caregivers). Improved socialization and reduced care requirements. The drug was well tolerated and did not cause negative interactions with basic therapy (beta-blockers, drugs affecting the renin-angiotensin system, calcium channel blockers, anticoagulants, lipid-lowering drugs, anti-inflammatory drugs, antirheumatic drugs, or analgesics) [124].
Multicenter, double-blind, placebo-controlled, randomized, parallel group clinical trial on the efficacy and safety of the drug in the treatment of attention deficit hyperactivity disorder (ADHD) in children	Reduced ADHD symptoms (≥25% reduction) in 55.9% of participants. Significantly reduced symptoms of inattention and hyperactivity/impulsivity. No serious adverse events or cases of drug incompatibility with medications used in pediatric practice were reported [125].
Drug based on a mixture of GDs of antibodies to the C -terminal fragment of the insulin receptor beta subunit and endothelial NO synthase	
Multicenter, double-blind, placebo-controlled, randomized, parallel group clinical trial on the efficacy and safety of the	Notable 1.99 mmol/L reduction in 2-h (postprandial) glycemia compared with placebo therapy in patients with impaired glucose tolerance (including those with excess body weight and

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drug in patients with impaired glucose tolerance	obesity) for 3 months. Normalization of blood sugar levels in >50% of cases, slowing progression of carbohydrate metabolism disorders. Clinically proven effect on weight stabilization [126].

Table A3. Examples demonstrating modification of medium properties by gradualized dilutions.

Method/Effect
Water
Thermogravimetry and calorimetry: Changes in the structuring of water in lactose crystals upon saturation with GDs of a substance, induced by variations in the number and strength of hydrogen bonds [127].
IR spectroscopy: Changes in the structural and dynamic characteristics of aqueous and aqueous–alcoholic solvents in a GDs of α-tocopherol [128].
THz spectroscopy: Reduction in the degree of water structuring under the influence of GDs of $CaCl_2$ and CsCl [54].
Lactose
FTIR spectroscopy: Changes in lactose conformation upon saturation with GDs of antibodies to IFN-γ [129].
X-ray structural analysis: Changes in the structural characteristics (crystal lattice parameters) of lactose under the influence of GDs of antibodies to IFN-γ [130].
DLS, LALLS: Change in the diameter of the water–lactose complex both in lactose powder and in its solution under the influence of GDs of antibodies to IFN-γ [131].
THz spectroscopy: Change in the size of the lactose hydration shell; GDs of antibodies to IFN-γ promote more rapid dissolution of lactose monohydrate at equivalent volumes compared with control samples [132].
THz spectroscopy: Changes in the optical properties (absorption spectrum in the THz range) of lactose upon its saturation with GDs of antibodies to IFN-γ [133].
Crystals
Single-crystal X-ray structural analysis: Changes in the crystal structure (triglycine sulfate) grown in GDs of antibodies to IFN-γ [134].
Measurement of volt–ampere characteristics: Changes in the superconducting properties of ceramics ($YBa_2Cu_3O_y$), in the preparation containing a GDs of $YBa_2Cu_3O_y$ [92].
Measurement of volt–ampere characteristics: Changes in the piezo- and pyroelectric properties of ceramics (Bi_3TiNbO_9) in the preparation containing a GDs of Bi_3TiNbO_9 [93].
Single-crystal X-ray structural analysis and luminescence studies: Changes in the structure of a grown Nd:$MgMoO_4$ crystal and its luminescence properties imparted by a GDs of the batch components [92] .

Table A4. Examples of distant effects of gradualized dilutions of antibodies.

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THz spectroscopy and IR emission spectroscopy: GDs of antibodies to IFN-γ alter the structural properties of IFN-γ solution located in a separate tube [36,135]. The magnitude of such changes increases proportionally with the duration of joint (non-contact) incubation [36]. The intrinsic IR emission of IFN-γ also increases following contactless incubation with GDs of antibodies to IFN-γ [40].
Cellular chemiluminescence: In a non-contact manner, GDs of antibodies to IFN-γ alter the ability of IFN-γ to stimulate the release of reactive oxygen species by neutrophils. This effect is proportional to the duration of non-contact incubation and depends on the parameters of the magnetic field parameters used during incubation [136].
Glucose uptake by cells: a preparation containing GDs of antibodies to the insulin receptor β-subunit, placed in the same container as a culture plate with Chinese hamster ovary (CHO) cells, increased glucose uptake by the cells in the presence of insulin [137].

Table A5. Examples of biological effects of the Native fraction of vibrational iterations of water.

Item No.	Activity	Model/Disease	Result
1.	Anti-inflammatory	Carrageenan edema in mice	Anti-inflammatory effect (reduces swelling growth)
2.	Antiproliferative	Mouse peritoneal macrophages and RAW 264.7 cells *in vitro*	Increases metabolic activity of mouse peritoneal macrophages and suppresses metabolic activity of RAW 264.7 cells
		Ehrlich carcinoma *in vitro*	Increases the cytotoxicity of cisplatin
3.	Regenerative	Skin *ex vivo*	Modulates proinflammatory gene expression and keratinocyte differentiation
4.	Anti-inflammatory	Patients with atopic dermatitis	Relives disease symptoms
5.	Immunotropic	Humoral immune response after immunization of mice with sheep red blood cells	Increases the number of antibody-producing cells (stimulating the immune response)
		Hypoxic stimulation of hematopoiesis in mice	Stimulates of leukopoiesis and erythropoiesis

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6.	Antiasthenic	Weight-loaded swimming test	Increases swimming time
7.	Antiallergic	Ovalbumin-induced allergy	Reduces the severity of anaphylaxis

Table A6. Prospects for the application of vibration-gradual technology (gradualized dilutions and vibrational iterations).

Use in biology and medicine	Use in chemistry and engineering
▪ Increasing the effectiveness of pharmacological drugs and reducing their toxicity [22] ▪ Antiviral therapy [2,95–98,115,120] ▪ Personalized therapies based on iterations of MHC molecules ▪ Overcoming antibiotic resistance [113] ▪ Antibacterial therapy without the use of antibiotics [114] ▪ Protection from physical factors ▪ Solving the bioavailability problem ▪ Antitumor potential [138,139] ▪ Anti-aging therapy ▪ Creation of standardized biological preparations with long shelf life [8]	▪ Chemistry, catalysis [11] ▪ Increasing the sensitivity of analytical methods (determination of impurities) ▪ Materials science (change in the properties of materials) [92–94]

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