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Views & Comments

Neg-Entropy Mechanism as a Target for Natural Medicines

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Current strategies for drug discovery research mainly focus on molecular targets, in which structure biology plays a central role, such as the detailed mechanism of a drug–target interaction. The principle of this approach is the presumed molecular mechanism or genetic background of the disease being treated. Although this approach has brought progress in understanding the mode of action for some drugs, most prevalent illnesses—especially chronic diseases—are multifactorial and present with a group of symptoms, as is often the case in cardiovascular diseases, metabolic disorders, cancers, and so forth. The newly emerging term "multi-morbidity" (i.e., multiple co-occurring diseases) describes a grand challenge for this strategy, and successful drug intervention for multi-morbidity should be multifaceted [1]. So, our research team has shifted its attention to a new direction that views the disease as a whole instead of a single-molecule abnormality, and focusing on drugs with multiple targets.

From this perspective, our team is paying close attention to natural compounds, as they are in a symbiotic system that is usually in harmony with humans. Although natural medicine covers compounds derived from plants, microbes, animals, and the soil, along with their analogues, metabolites, effective fractions, and herbal remedies, research often prioritizes single compounds, as their chemical structures can be identified. Interestingly, many of these compounds offer multiple and synergistic-style therapeutic effects for patients, but their mode of action is complicated, with their primary target(s) yet to be discovered. Aspirin, metformin, rapamycin, and thalidomide are well-known examples. It might present a great opportunity for finding new strategies to treat diseases.

To us, the most interesting natural drugs are those with good clinical efficacy (both effective and safe) despite having unknown mechanisms, such as berberine (BBR). BBR is an iso-quinoline alkaloid from medicinal plants like *Coptis chinensis* Franch. and others; it was originally approved as an over-the-counter (OTC) drug for bacterial-caused diarrhea in China [2]. Since 2004, we—and other researchers—have found BBR to be a safe and effective drug for the clinical treatment of hyperlipidemia, type 2 diabetes (T2D), fatty liver, and more, and for preventing colon cancer in high-risk populations [2–4]. The identified working targets of BBR include the low-density lipoprotein receptor (LDLR), insulin receptor (InsR), adenosine 5′-monophosphate-activated protein kinase (AMPK), proprotein convertase subtilisin/kexin type 9 (PCSK9), galectin3, leptin, and eukaryotic translation initiation factor 2-alpha kinase 2 (EIF2AK2), all of which relate to energy metabolism or inflammation [2,3,5–8]. At the same time, oral BBR interacts favorably with the gut microbiota, enhancing the production of short-chain fatty acids (SCFAs), *L*-dopa/dopamine, and bile acids within the intestine [5,9]. These intestinal metabolites enter the bloodstream and complement the action of BBR in target organs. Thus, our research team has used the drug cloud (dCloud) concept to express the synergistic effect of BBR, its metabolites, and related metabolites derived from gut microbiota [10]. We used bio-entropy calculation to evaluate the therapeutic efficacy of BBR, in a comprehensive comparison with that of metformin [5], through which we found bio-entropy to be a potential efficacy indicator for drugs with multiple targets.

Entropy is a concept of disordered state in physics, where lower entropy indicates a preferable state. In fact, all independent systems (with no external forces) tend to evolve toward a chaotic and disordered state, in what is known as the law of entropy increase. Despite entropy increasing in nature, the human body maintains its biological complexity in good order and health for many decades, indicating the body's ability to achieve negative entropy, or "neg-entropy" [11]. Indeed, humans can recover from illnesses or injury without drug treatment. Effective drugs may accelerate recovery by stimulating neg-entropy mechanisms, which can be classified into at least five groups: metabolism and self-organization, defense, self-healing, wear resistance, and adaptability [11]. Of these mechanisms, metabolism and self-organization are the ability to adjust cellular energy metabolism to assemble macromolecules, promote growth or/and differentiation, and maintain normal organ functions; the defense system involves the immune response and memory (T and B cells, etc.), as well as the inflammatory response against external threats; the self-healing ability, aided by stem cells and their secretions, resolves inflammation, repairs injuries, and promotes tissue growth; wear resistance is an inherent machinery to address abnormalities or errors in life by regulating signals, detoxifying harmful chemicals, repairing DNA mutations, and correcting folding or conformation errors in proteins; and adaptability

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denotes the capability to engage with changes that the body may face (e.g., disruptions to gut microbiota homeostasis) and ultimately reshape its function or metabolism to cope with the altered environment.

Theoretically, a useful drug should be able to activate one or more neg-entropy mechanisms in order to promote the healing process through the inherent power of the human body. In other words, the mechanism of neg-entropy in the body should be the ideal target of drugs. Vaccines are good examples, as they utilize antigens to activate the immune system and mount a defense response. In the case of BBR, the intestinal flora and the body energy metabolism are the treatment target as a whole and are responsible for the compound's clinical therapeutic efficacy [10]. A recent example is azvudine, a nucleoside analog clinically used to treat coronavirus disease 2019 (COVID-19). Azvudine was originally developed to treat human immunodeficiency virus-1 (HIV-1) infection, but it was found—in our laboratory—to be active against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in early 2020 [12]. Although the antiviral potency of azvudine *in vitro* was moderate, the *in vivo* therapeutic effect against COVID-19 was significant, in both monkeys and humans [12]. Mechanism studies showed that azvudine was converted into its triphosphate form (the active form against SARS-CoV-2) mainly in the thymus, thus favorably protecting the thymus and T cells from SARS-CoV-2 attack [12]. The protected T-cell immunity then became the major neg-entropy force to alleviate COVID-19. This two-phase mode of action (antiviral + immune protective response) partially explained why 3 $mg{\cdot}d^{-1}$ of azvudine (oral) achieved a therapeutic effect at least comparable to that of 600 $mg{\cdot}d^{-1}$ of paxlovid (oral) [13,14]. In this case, thymus-mediated T cell immunity appears to be the key target of azvudine [12].

In fact, the pool of natural compounds might be a rich source from which to discover drugs that activate the body's neg-entropy abilities. Such drugs often treat diseases for both symptoms (e.g., high blood glucose in T2D) and root causes (e.g., gut microbiota disruption and inflammation) in a relatively safe fashion. We believe the underlying principle to be that natural medicines are part of the ecology and are thus usually beneficial to humans. This principle reveals a profound connection between humans and nature that can help us to discover effective drugs to trigger the body's neg-entropy mechanisms.

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Compliance with ethics guidelines

Tian-Le Gao, Hui-Hui Guo, and Jian-Dong Jiang declare that they have no conflict of interest or financial conflicts to disclose.

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