

Provider Note

Humeomics is a challenging field of study, which makes a nutraceutical product based on one of its components, humic acid, equally challenging. Though too much complexity can render some natural molecules clinically inaccessible, we believe that a comprehensive appreciation of what we know and what we do not as it pertains to humic acid, and ultimately Humavir, is relevant for a clinician to make an informed clinical decision on behalf of their patient.

This FAQ will be updated periodically as additional clinical information becomes available.

What are the primary biological activities of humic acid?

Humic acids are characterized by various properties including anti-viral, anti-inflammatory, pro-fibrinolytic and estrogenic activities. They are also regarded as chelators of heavy metals, including lead, mercury, cadmium and iron.

Given the heterogeneous chemical nature of the soil humeome, the functional signature of humic acid varies from deposit to deposit, so not every humic acid sample has the same chemistry, activity spectrum or clinical efficacy.

References:

- 1) Hampf J, Herzig I, Vlcek J. Pharmacokinetics of sodium humate in chickens. *Vet Med (Praha)*. 1994;39(6):305-313.
 - 2) Piccolo A.; et al. (2018) "The Molecular Composition of Humus Carbon: Recalcitrance and Reactivity in Soils". In: *The Future of Soil Carbon*. Wiley and Sons. Pp.87-124. Doi:10.1016/B978-0-12-811687-6.00004-3. ISBN 9780128116876
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What makes the study of humic acid complex?

Spending some time with the humic acid literature can generate more questions than it answers. On the one hand, humic acid exhibits anti-viral and anti-inflammatory properties that we have shown in prior studies has clinical value. On the flip side, it has been linked to accelerating cigarette smoke induced lung emphysema in mice and IL-8 release in human monocytes.

At the root of this challenge is the complex and heterogeneous chemical nature of the soil humeome, which includes humic acid and other humic substances. Though our understanding of this chemistry is

always evolving, humeomics has advanced enough in recent years to provide a functional explanation for the variability of biological effects observed with humic acid. Ultimately the humeome is made up of smaller molecules that associate into larger supermolecules over millennia based on local physical factors and the biological degradation of the plant matter native to the local soil. The emphasis is on local. Hyperlocal. Because soil conditions and the pressure on it vary widely across the millennia from region to region, humeome deposits are similar but not identical. This valuable insight answers why some biological activities of humic acid are well conserved, while other features are not. "Humic acid" actually refers to a class of supermolecules rather than a particular molecule, per se. This fundamental reality of humeomics requires that each deposit of humic acid be investigated on a standalone basis to better understand its unique molecular, chemical and biological properties.

Aside: The classic model of humeomics regarded humic substances as high-molecular-weight macropolymers that were well conserved across deposits.

Reference:

- 1) van Eijl, Sven, et al. "Humic Acid Enhances Cigarette Smoke-induced Lung Emphysema in Mice and IL-8 Release of Human Monocytes." *Pulmonary Pharmacology & Therapeutics*, vol. 24, no. 6, 2011, pp. 682-9.
 - 2) Piccolo A.; et al. (2018) "The Molecular Composition of Humus Carbon: Recalcitrance and Reactivity in Soils". In: *The Future of Soil Carbon*. Wiley and Sons. Pp.87-124. Doi:10.1016/B978-0-12-811687-6.00004-3. ISBN 9780128116876
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Where does the humic acid in Humavir come from?

The humic acid in Humavir is sourced exclusively from deposits in the United States. It is the same humic acid that was studied for its anti-viral properties on behalf of the National Institutes of Health.

References:

- 1) Broad Spectrum Antiviral Effectiveness of Natural and Synthetic Humates; Virology Branch, Antiviral Research & Antimicrobial Chemistry Program, Division of Microbiology & Infectious Diseases; Screening & Testing Program for Antiviral, Immunomodulatory, Anti-tumor and/or Drug Delivery Activities, National Institutes of Allergy & Infectious Diseases, National Institute of Health (NIH), August 9, 2002
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Is the anti-viral mechanism of action linked to humic acid unique?

The anti-viral activity of Humavir relies on humic acid's primary activity as a **viral fusion protein inhibitor** that prevents viruses from entering the cell. This mechanism of action is not exclusive to humic acid. Enfuvirtide and maraviroc are two synthetic viral fusion protein inhibitors approved by the Food and Drug Administration for HIV therapy. Leronlimab and BMS-488043 are currently under investigation. Rhamnan sulfate, which is extracted from the green algae, *Momostroma nitidum*, exhibits similar activity.

The ability of humic acid to disrupt viral RNA polymerase is a minor secondary mechanism of action.

References:

- 1) <https://www.drugbank.ca/categories/DBCAT000219>
- 2) Terasawa M, Hayashi K, Lee JB, et al. Anti-Influenza A Virus Activity of Rhamnan Sulfate from Green Algae *Monostroma nitidum* in Mice with Normal and Compromised Immunity. *Mar Drugs*. 2020;18(5):254. Published 2020 May 13. doi:10.3390/md18050254

What is the relationship between humic acid and kidney disease?

Humic acid can be extracted from two natural reservoirs, fossilized coal deposits in the form of lignite (332), and decomposing organic matter that has not fossilized (491). The humic acid in Humavir comes from oxidized lignite, which is a form of low-grade coal.

Lignite-sourced humic acid was previously linked to Balkan endemic nephropathy (BEN), an irreversible kidney disease of unknown origin that is also associated with renal cancer. As the name suggests, the condition was initially identified in the Balkans, specifically across farming villages along tributaries of the Danube River spanning multiple countries.

It was previously thought that the proximity of lignite deposits and the contamination of drinking water with organic compounds from lignite coal was the cause of BEN. Drinking water from lignite aquifers in the United States had also been linked to renal cancer (481-484). Though there were multiple hypothesis in play to explain the cause of these findings, heavy metal contamination of water with uranium emerged as the dominant explanation for the disease until the 1990s, when 100 otherwise healthy Belgian women developed aggressive chronic kidney disease (CKD) while subscribing to a local weight loss program. Forensic studies ultimately uncovered that these women had been consuming *Aristolochia fangchi*, an herb used in Traditional Chinese Medicine, as a part of their weight loss routine. Molecular epidemiological studies later yielded that chronic dietary exposure to aristolochic acid (AA), the active molecule in *Aristolochia*, was the cause of the CKD in the Belgian women, and ultimately BEN and its associated renal cancers.

On a side note: About 1800 Belgian women had taken the weight loss regimen with *Aristolochia* daily over a 20-month interval. Similarly, the numbers of individuals with chronic dietary exposure to *Aristolochia* in Balkan farming villages dwarfs the number of individuals who developed BEN, at a prevalence rate of 3-7%. It is currently opined that genetic polymorphisms exist in some people that make some more susceptible to AA.

CLINICAL PEARL: TOXICITY AND CELL PROLIFERATION STUDIES OF THE HUMIC ACID IN HUMAVIR WERE INCLUDED IN THE 2002 NATIONAL INSTITUTES OF HEALTH EVALUATION OF HUMIC ACID'S ANTI-VIRAL PROPERTIES. THIS ITERATION OF HUMIC ACID WAS ESTABLISHED TO BE NON-TOXIC.

References:

- 1) Supplier, humic acid
- 2) Oxidized Lignite / Humic Acid Derivatives, Crops, Technical Evaluation Report, compiled by The Organic Center for the USDA National Organic Program, July 7, 2020; <https://www.ams.usda.gov/sites/default/files/media/Ox%20lig%20Technical%20Evaluation%20Report%20%282012%29.pdf>; lines 319-340, 386-392, 480, 491-513
- 3) Stiborová M, Arlt VM, Schmeiser HH. Balkan endemic nephropathy: an update on its aetiology. *Arch Toxicol.* 2016;90(11):2595-2615. doi:10.1007/s00204-016-1819-3
- 4) Giovanni B. Fogazzi, Cecilia Bellincioni, *Aristolochia clematitis*, the herb responsible for aristolochic acid nephropathy, in an uncultivated piece of land of an Italian nephrologist, *Nephrology Dialysis Transplantation*, Volume 30, Issue 11, November 2015, Pages 1893–1896, <https://doi.org/10.1093/ndt/gfv211>
- 5) Grollman AP, Marcus DM. Global hazards of herbal remedies: lessons from *Aristolochia*: The lesson from the health hazards of *Aristolochia* should lead to more research into the safety and efficacy of medicinal plants. *EMBO Rep.* 2016;17(5):619-625. doi:10.15252/embr.201642375

- 6) Broad Spectrum Antiviral Effectiveness of Natural and Synthetic Humates; Virology Branch, Antiviral Research & Antimicrobial Chemistry Program, Division of Microbiology & Infectious Diseases; Screening & Testing Program for Antiviral, Immunomodulatory, Anti-tumor and/or Drug Delivery Activities, National Institutes of Allergy & Infectious Diseases, National Institute of Health (NIH), August 9, 2002
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What is known about the absorption and elimination of Humavir?

An animal study examining the pharmacokinetics of sodium humate in chickens provides some insight. The findings of the study are as follows:

- One third of the oral dose of sodium humate is absorbed. The balance is excreted in the feces.
- The elimination half-life for sodium humate is 78.1 hours. The amount of sodium humate removed from blood per unit time, or the clearance rate, is 1.4 mL/min, and the time to achieve C_{max} , otherwise known as t_{max} , is 39 minutes.

Reference:

- 1) Hampf J, Herzig I, Vlcek J. Pharmacokinetics of sodium humate in chickens. Vet Med (Praha). 1994;39(6):305-313.
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What is the relationship between humic acid and heavy metals?

Every batch of humic acid that ultimately makes its way into Humavir has some trace metals, including lead. In order to ensure that those trace metals are within acceptable limits, we contract with third party laboratories to do an independent assessment to measure heavy metal content of each batch of humic acid that we include in Humavir.

In early 2020, our supplier modified its mining process for humic acid in consultation with us to reduce trace metal content to levels that had never been achieved before. We achieved this benchmark by performing heavy metal assays every 6 to 12 inches during the mining process to ensure that the harvesting process stayed within the preferred geological strata. This process modification reduced the lead content in Humavir by just over 80%.

Though minimizing heavy metals is essential, acknowledging the pharmacokinetic properties of humic acid and the intrinsic qualities of the molecule are also relevant to assessing attributable risk. Specifically, only one-third of ingested humic acid is absorbed. The balance is passed through the gut and excreted, which decreases potential load.

Given that the proprietary humic acid complex in Humavir is at minimum >95% humic acid, whatever potential competition would otherwise be presented by fulvic acid, the most common contaminant) is eliminated. This purification process may liberate humic acid to chelate heavy metals.

Humic acid has natural chelating properties, specifically for mercury, cadmium, lead and iron, that have been leveraged in a variety of clinical situations.

CLINICAL PEARL: *VENOUS LEAD TESTING OF INDIVIDUALS USING OUR PROPRIETARY HUMIC ACID COMPLEX TWICE DAILY FROM 8 DAYS TO 20 YEARS ARE ALL LESS THAN OR EQUAL TO 1 MCG/DL (LABORATORIES: QUEST DIAGNOSTICS & ACCESS MEDICAL LABS).*

DEVELOPMENT PEARLS:

- AS OF OCTOBER 2021, INTERNAL ASSESSMENTS ESTABLISHED THAT HUMAVIR SATISFIES ALL HEAVY METAL BENCHMARKS FOR [NSF CERTIFICATION](#) REGARDLESS OF DOSING. IN ADDITION, HEAVY METAL LEVELS IN HUMAVIR FALL BELOW CALIFORNIA **PROPOSITION 65** NOTIFICATION THRESHOLDS FOR ALL METALS AT MAINTENANCE DOSING. A CALIFORNIA **PROPOSITION 65** NOTICE FOR LEAD IS WARRANTED WHEN DOSING EXCEEDS 2 CAPSULES PER DAY (Pb THRESHOLD: 0.5 MCG/DAY)
- AS OF DECEMBER 2021, WE BEGAN ASSESSING MINERAL LEVELS IN INDIVIDUALS WHO HAVE BEEN USING HUMAVIR TWICE DAILY FOR >90 DAYS. ASSESSED BIOMARKERS INCLUDE IRON, MAGNESIUM, ZINC, CALCIUM AND PHOSPHORUS. RESULTS AS OF FEBRUARY 2022 HAVE BEEN NORMAL.

References:

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- 3) Hudák, A., et al. "Effect of the consumption of humic acid with bound complex micro elements in cases of occupational cadmium exposure." *Central European Journal of Occupational and Environmental Medicine*, 1997. 3(3): p. 175-186.
Klinghardt, D: Amalgam/Mercury Detox as a Treatment for Chronic Viral, Bacterial, and Fungal Illnesses. *Explore*. 1997 Vol 8 (3).

May Humavir be used in pregnant women?

Given the absence of any clinical studies, the use of Humavir during pregnancy is not encouraged.

Can Humavir be used for children, and if so, how?

Humavir may be used in children, but the unit dose should not be lower than 250mg of humic acid if the goal is to support the immune system.

CLINICAL PEARL: WE HISTORICALLY USED HUMAVIR IN CHILDREN SPARINGLY UNTIL THE AGGREGATED VENOUS LEAD DATA IN ADULTS WAS NOTED TO BE UNREMARKABLE. THE FURTHER REDUCTION IN BASELINE LEAD CONTENT OF THE PRODUCT (BY 80%) LIBERALIZED OUR USE IN THE PEDIATRIC POPULATION; HOWEVER, WE CONTINUE TO DEFER TO USE ON A PROPHYLACTIC BASIS BASED ON AN INDIVIDUAL'S UNIQUE RISK ASSESSMENT.

Does humic acid have an effect on coagulation?

In vitro and *in vivo* animal studies in mice and rats by Klöcking in 1991 established that humic acid promotes a dose-dependent release of tissue plasminogen activator (tPA) from vascular endothelial cells.

Follow up *in vitro* studies by Klöcking, et al. in 2013 established that humic acid has a bimodal effect on coagulation with thromboelastography (TEG) as the assessment tool. Higher concentrations of humic acid prolong coagulation times by 2-12-fold (anticoagulant effect). Low concentrations decrease the reaction time by an average of 25% (procoagulant effect).

Humic acid was found to inhibit coagulation factors IIa, VIIa and Xa by Klöcking, et al. in 2013. Prothrombiin time, or PT, measures the activity of Factors II, VII and X.

CLINICAL PEARL: COAGULATION PROFILES (PT, PTT, INR & FIBRINOGEN) COLLECTED ON PATIENTS USING HUMAVIR 250MG TWICE DAILY HAVE NOT RESULTED IN ABNORMAL CLOTTING TIMES. WE MAINTAIN OUR POSTURE OF ACTIVE SURVEILLANCE WHILE USING HUMAVIR IN PATIENTS ON ANTICOAGULATION THERAPY.

Special Note: The TEG assay used by Klöcking, et al. in 2013 “measures blood coagulation *in vitro* with or without an additional activator. An important component of the coagulation cascade, tissue factor, cannot be quantified *in vitro*. Moreover, blood coagulation potential is only one component in such complex processes as clinical thrombosis and bleeding. Blood coagulation also depends on the size of the injured vessel, blood flow characteristics, and local vessel wall biology that determines the quantity and functional activity of the membrane-bound pro- and anticoagulation factors. In other words, there are significant aspects of coagulation which are not components of the blood.”

References:

- 1) Klöcking HP. (1991) Influence of Natural Humic Acids and Synthetic Phenolic Polymers on Haemostasis. In: Chambers P.L., Chambers C.M., Wiezorek W.D., Golbs S. (eds) Recent Developments in Toxicology: Trends, Methods and Problems. Archives of Toxicology, vol 14. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-74936-0_33
- 2) Klöcking R., Helbig B. (2013) Medical Aspects and Applications of Humic Substances, in Biopolymers for Medical and Pharmaceutical Applications, Edited by A. Steinbüchel and R. H. Marchessault, 2005, Wiley-VCH Verlag GmbH & Co KGaA, Weinheim. ISBN: 3-527-31154-8
- 3) Klöcking H.P., Klöcking R. (2013) Application of Humic Substances in Medicine: Basic Studies to Assess Pro- and Anticoagulant Properties of Humic Acids. In: Xu J., Wu J., He Y. (eds) Functions of Natural Organic Matter in Changing Environment. Springer, Dordrecht. https://doi.org/10.1007/978-94-007-5634-2_205
- 4) Shaydakov ME, Sigmon DF, Blebea J. Thromboelastography (TEG) [Updated 2020 Apr 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK537061/>

What is the potential for humic acid to cross the blood brain barrier?

It is unlikely that humic acid crosses the blood brain barrier (“BBB”).

In the aggregate, brain microvascular endothelial cells form the bulk of the blood brain barrier. Astrocytes, pericytes, other glial cells and neurons complete the blood brain barrier and together regulate brain homeostasis.

Based on size and/or charge, ions and molecules have the option of passing through this barrier via one or more select mechanisms, including paracellular transport, passive diffusion, ion/water transport channels and active transport systems (receptor based, carrier-mediated & adsorption mediated). Paracellular transport and tight junctions are one and the same.

With the above in mind, here are some specific thoughts regarding Humavir, the blood brain barrier, and the various options that are available to cross the BBB.

- Paracellular transport and ion/water transport channels are limited to moving water and electrolytes. Think small. [The iteration of humic acid in Humavir is 50,000 Da, so it's too big.](#)
- Passive diffusion is a form of membrane transport. [A molecule that navigates this mechanism has to be able to negotiate the hydrophobic core of membrane phospholipids. Since humic acid is very hydrophilic, this mechanism seems unlikely without an active-transport bump.](#)

- Regarding active transport systems:
 - Receptor-mediated active transporters control the movement of discreet molecules, such as insulin (5800 Da), TNF-A (homotrimer, 17300 Da per subunit), and IgG (150,000 Da). This mechanism moves large molecules, but the key here is that there is a dedicated receptor. [We have not been able to find any information to substantiate that there is or is not a receptor that binds to humic acid. Quite frankly, we don't think anyone has ever looked.](#)
 - Carrier-mediated transporters include energy transport systems (think glucose), amino acid transport systems, and transporters for nucleosides and organic anions and cations. [Humic acid doesn't fit any of these criteria.](#)
 - Neuropeptides, proteins, liposomes and nanoparticles use adsorption-mediated transcytosis to pass through the blood brain barrier. This is the transport mechanism leveraged by the pharmaceutical industry. This transport mechanism is triggered by electrostatic interactions between net positively charged molecules and proteins in the outward-facing cell membrane and negatively charged regions of the cytoplasm-facing side of the endothelial cell membrane which makes up the BBB. [The iteration of humic acid in Humavir has a net positive charge, so this transport mechanism seems unlikely because it depends on positively charged proteins and peptides to pull the molecule through the system. Humic acid is likely to be repelled by the positive charge of these cell membrane molecules and proteins.](#)

References:

- Lu W. Adsorptive-mediated brain delivery systems. *Curr Pharm Biotechnol.* 2012 Sep;13(12):2340-8. doi: 10.2174/138920112803341851. PMID: 23016640.
- Wong, Andrew & Ye, Mao & Placone, Amanda & Rothstein, Jeffrey & Bergles, Dwight & Searson, Peter. (2013). The Blood-Brain Barrier: An Engineering Perspective. *Frontiers in neuroengineering.* 6. 7. 10.3389/fneng.2013.00007.

What are the potential clinical applications for Humavir?

In vitro studies established that the humic acid component in Humavir exhibits anti-viral activity against multiple viral lines, including HIV-1, HSV-1, HSV-2, RSV, VZV, EBV, influenza, HBV and hemorrhagic fevers. Additional in-vitro studies further established and then differentiated between humic acid's prophylactic effect when applied at the time of viral infection and its therapeutic activity in established and/or chronic infection.

Studies performed by Klöcking and Terasawa quantified the relative prophylactic activity of viral fusion protein inhibitors against a spectrum of viruses. The kinetics of this molecular class to bind viral surface glycoproteins and disrupt viral attachment to cell membrane receptors favors prophylaxis. Humic acid's anti-viral activity in established infection largely depends on the shedding of new viral particles from infected cells.

Human clinical studies with Humavir illuminate a more significant therapeutic effect against influenza than humic acid alone. The amino acid complex is responsible for improved outcomes in the Humavir study. This being said, anecdotal experience with Humavir in a variety of occupational and

clinical situations also suggests that the formulation has prophylactic and therapeutic potential against COVID-19.

References:

- 1) Broad Spectrum Antiviral Effectiveness of Natural and Synthetic Humates; Virology Branch, Antiviral Research & Antimicrobial Chemistry Program, Division of Microbiology & Infectious Diseases; Screening & Testing Program for Antiviral, Immunomodulatory, Anti-tumor and/or Drug Delivery Activities, National Institutes of Allergy & Infectious Diseases, National Institute of Health (NIH), August 9, 2002
 - 2) Klöcking R., Helbig B. (2013) Medical Aspects and Applications of Humic Substances, in Biopolymers for Medical and Pharmaceutical Applications, Edited by A. Steinbüchel and R. H. Marchessault, 2005, Wiley-VCH Verlag GmbH & Co KGaA, Weinheim. ISBN: 3-527-31154-8
 - 3) Klöcking, R., Sprössig, M. Antiviral properties of humic acids. *Experientia* 28, 607–608 (1972).
<https://doi.org/10.1007/BF01931906> (German)
 - 4) Terasawa M, Hayashi K, Lee JB, et al. Anti-Influenza A Virus Activity of Rhamnan Sulfate from Green Algae *Monostroma nitidum* in Mice with Normal and Compromised Immunity. *Mar Drugs*. 2020;18(5):254. Published 2020 May 13.
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 - 6) A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Pilot Study to Investigate the Effects of Humic Acid + Amino Acid Complex on Symptoms of Influenza. Unpublished, internal data.
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