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From Venom To Cure: The Therapeutics And Pharmacological Insights Of Komodo Dragon Toxin In Medicine

[1]Dr Azher sharif,

[1]Doctor of pharmacy (Pharm-D), Medical writer, Orcimed life sciences Private Limited, Jubilee hills check post, Jawahar colony, Hyderabad, Telangana 500033, India.

Abstract: The Komodo dragon (Varanus komodoensis), the largest extant lizard species, has garnered scientific attention due to its potent venom and unique physiological attributes. This review explores the composition and potential applications of Komodo dragon venom, which contains bioactive compounds such as AVIT peptides, CRISPs, kallikrein, natriuretic peptides, and phospholipase A2. These toxins exhibit diverse effects, including anticoagulation, hypotension, and antimicrobial properties, suggesting significant therapeutic potential. Notably, the venom's fibrinogenolytic activity aids in prey subjugation while holding promise for anticoagulant therapy. The review also highlights antimicrobial peptides like DRGN-1, which accelerate wound healing and combat infections, and discusses parallels between Komodo dragon venom and compounds like Exendin-IV from Gila monster venom, already used in diabetes management. Despite these advancements, challenges persist in ethical venom sourcing, toxicity mitigation, and peptide stabilization. Future research directions include recombinant production, personalized medicine applications, and clinical trials to unlock the full therapeutic potential of Komodo dragon venom for treating infections, chronic conditions, and metabolic disorders.

Index Terms **- Component, formatting, style, styling, insert.**

I. INTRODUCTION

The Komodo dragon, scientifically known as Varanus komodoensis, holds the title of being the largest extant lizard species globally. Belonging to the Varanidae family, it is native to Komodo Island and a few nearby islands within the Lesser Sunda Islands of Indonesia. With its imposing size and predatory behavior, the Komodo dragon has captured the fascination of many, leading to its status as an ecotourist attraction and consequently, increased conservation efforts.

 [i]

These formidable creatures can reach lengths of up to 3 meters (10 feet) and weigh approximately 135 kg (about 300 pounds). Despite typically reproducing through sexual means, it's noteworthy that isolated females can still produce offspring via parthenogenesis. They are known to dig burrows reaching depths of around 9 meters (29.5 feet) and lay their eggs, which typically hatch in April or May. Once hatched, the young dragons, measuring about 45 cm (18 inches) in length, spend several months residing in trees.

Adult Komodo dragons primarily subsist on carrion, although they're known to lie in wait along game trails to ambush prey such as pigs, deer, and cattle. Their venomous bite is their primary means of subduing prey, delivering toxins that hinder blood clotting and often inducing shock from rapid blood loss in their victims. Additionally, physical trauma from the bite and the introduction of bacteria from the dragon's mouth to the wound further contribute to the prey's demise. It's not uncommon for Komodo dragons to scavenge for prey in the process of dying or shortly after death.[ii]

The smallest monitor lizard achieves a maximum length of only 20 cm (8 inches), yet numerous species grow to impressive sizes. Among these, notable examples include the Komodo dragon (V. komodoensis) from Indonesia, renowned as the largest lizard globally, reaching lengths of up to 3 meters (10 feet). Other large monitor species include the two-banded, or water, monitor (V. salvator) from Southeast Asia, reaching lengths of 2.7 meters (9 feet); the perentie (V. giganteus) from central Australia, growing to 2.4 meters (8 feet); and V. bitatawa from the island of Luzon in the Philippines, reaching lengths of 2.0 meters (about 7 feet). Additionally, partial fossils of Megalania prisca, an extinct Australian monitor from the Pleistocene Epoch, suggest it exceeded 7 meters (23 feet) in length and likely weighed nearly 600 kg (about 1,300 pounds).

The Komodo dragon possesses serrated teeth, which are curved akin to a scalpel blade. These teeth are capable of slicing through the leg muscle of a mature water buffalo (Bubalus bubalis), ultimately leading to fatal bleeding.[iii]

Predator ecology-

The Komodo dragon attacks its prey when it approaches a distance of about one meter, typically hunting large animals like deer, wild pigs, goats, water buffaloes, and more through ambush tactics. Its teeth inflict damage to the integument of the prey's body, affecting the skin, hypodermis, muscles, blood vessels, and nerves. Furthermore, the teeth penetrate tissues with venom produced by venom glands located near the mandible. Despite having a relatively low bite force, the Komodo dragon strategically avoids contact between its teeth and skeletal elements while feeding. Instead, its teeth are specialized for cutting soft tissues, causing additional injury due to their microstructure. The venom primarily contributes to killing the Komodo dragon's prey.[iv,v]

Composition of venom-

To gain further insight into the potential role of envenomation in the predatory behavior of V. komodoensis, the researchers investigated the biochemical composition and toxicological properties of its venom. Mass spectrometry analysis revealed a complex mixture of proteins comparable to that found in snakes undergoing similar analyses. Examination of the mandibular venom gland cDNA library unveiled a diverse transcriptome with approximately 35% of the 2000 transcripts encoding known toxin types from other Toxicofera venoms[vi]. The molecular complexity and expression levels were found to be similar to those documented for venomous snakes. The identified toxin classes included AVIT, cysteine-rich secretory proteins (CRISP), kallikrein, natriuretic peptide, and type III phospholipase A2 protein scaffolds (GenBank accession nos. EU195455–EU195461). Isoforms isolated from V. komodoensis retained the biochemical properties of these coagulopathic, hypotensive, hemorrhagic, and shock-inducing toxins. Cardiovascular studies conducted on crude venom revealed potent hypotensive effects, primarily mediated by an endothelium-independent vasodilator effect on vascular smooth muscle. Pure V. komodoensis natriuretic toxin exhibited a similar potent endothelium-independent hypotensive effect as the crude venom isoforms from V. varius and Oxyuranus microlepidotus venoms.[vii]

Molecular biodiversity of toxin types detected in V. komodoensis venom[viii,ix]	
Toxin type	**Previously characterized bioactivities**
AVIT	Causes potent constriction of intestinal smooth muscle leading to painful cramping, along with the induction of hyperalgesia.
CRISP	The basal toxic activity involves the paralysis of peripheral smooth muscle and the induction of hypothermia by blocking L-type Ca2+ and BKCa K+ channels. This activity further includes the blockade of cyclic nucleotide-gated calcium channels.
Kallikrein	The basal toxic activity entails an increase in vascular permeability and the production of hypotension, along with the stimulation of inflammation. Derived effects impact the blood by cleaving fibrinogen.
Natriuretic	The basal activity involves the potent induction of hypotension, leading to loss of consciousness. Derived activities encompass cardiovascular effects that are independent of the GC-A receptor and antiplatelet activities adapted for emergent domains upstream of the natriuretic peptide domain.
PLA_2 (T-III)	Leads to anticoagulation via platelet inhibition.

Potential anti-coagulation effects-

Crude venoms from V. komodoensis and V. varius were observed to cause hypotension, with B-type natriuretic peptides identified as partially responsible for this effect. However, varanids were found to lack the gene for helokinestatins, which are toxins that affect blood pressure and evolved within the propeptide region of hypotension-inducing BNP peptides in the last common ancestor of anguids and helodermatids, following the split with the last common ancestor of lanthanotids and varanids. This supports the proposed closer relationship of helodermatid lizards with anguids and suggests active evolution within the Toxicofera clade.[x]

Norman et al[xi]. conducted a comparative study examining the venom of snakes and lizards, as well as the presence of venom toxins in two additional lizard lineages, Monitor Lizards and Iguania. They demonstrated that all lineages possessing toxin-secreting oral glands form a clade, indicating a single early origin of the venom system in lizards and snakes. The study's findings, encompassing combined cDNA analysis, LC/MS techniques, molecular modeling, and pharmacological experiments, align with reported effects of varanid bites. These effects include severe pain, breathing difficulties, skeletal muscle weakness, and tachycardia. One of the authors has also served as a consultant on three varanid bites caused by captive bred specimens, including Varanus komodoensis (Komodo Dragon), V. scalaris (Spotted Tree Monitor), and V. varius (Lace Monitor). Each incident resulted in rapid swelling, noticeable within minutes, along with symptoms such as dizziness, localized disruption of blood clotting, and shooting pain extending from the affected digit up to the elbow. Some symptoms persisted for several hours. The speed of onset and observed pathology suggest the involvement of bioactive secretions rather than bacterial infection. Furthermore, varanid venom has demonstrated the capability to swiftly paralyze small animals such as birds.

Dobson et al[xii]. conducted a study aimed to quantify the fibrinogenolytic activity of varanid lizard venoms using thromboelastography. They found that varanid lizard venom exhibits coagulotoxic activities comparable to those of helodermatid lizards, such as inducing hypotension, promoting bleeding by blocking platelets, and inhibiting blood coagulation. They observed that purified Group III PLA2 from V. varius venom promotes bleeding by inhibiting platelet aggregation through a similar pathway as Heloderma venoms. Additionally, crude venoms from V. komodoensis and V. varius were found to induce hypotension, partly attributed to B-type natriuretic peptides. However, varanids lack the gene for helokinestatins, which are blood pressure-regulating toxins evolved in the propeptide region of hypotension-inducing BNP peptides in the anguid/helodermatid.

Another potential mechanism by which anticoagulants may function is through the destructive cleavage of fibrinogen chains. Fibrinogen cleavage by thrombin, the final step in the clotting cascade, results in the formation of a fibrin clot[xiii]. Each fibrinogen molecule consists of two sets of three chains (Aα, Bβ, and γ), which are cleaved in a specific manner to expose polymerization sites for fibrin crosslinking. If fibrinogen is cleaved indiscriminately by a proteinase unlike thrombin, it can greatly reduce or entirely prevent fibrin chain crosslinking and clot formation. In snake venoms, anticoagulation can result from either the non-clotting cleavage of fibrinogen or the production of a transient, weak clot that leads to fibrinogen consumption[xiv].

Koludarov et al[xv]. reported on the fibrinogenolytic activity of varanoid lizard venoms using gel electrophoresis. While helodermatid lizards displayed minimal activity despite the presence of proteolytic kallikreins, certain varanid lizard venoms appeared to exhibit potent fibrinogenolysis.

The phylogenetic analysis of fibrinogenolytic activity suggests that this trait is actively selected for under positive selection pressures. While this toxic effect is non-lethal, when combined with other previously described activities and mechanical damage from the teeth, it may aid in subduing the lizard's prey. Weakening prey sufficiently to facilitate consumption could be as effective a method for acquiring a meal as killing the prey outright, as both achieve the same ultimate goal. Thus, fibrinogenolytic activity may play a predatory role in varanid venoms by facilitating blood loss initiated by mechanical damage from their large teeth and violent head movements, thereby contributing to their combined predatory arsenal[xvi].

Other potential functions of fibrinogenolytic activity in varanids include digestion or defense. This venom activity may be attributed to indiscriminate proteolytic enzymes that aid in digestion. However, the observed phylogenetic pattern does not support the notion of arbitrary activity with a digestive role. While stimulating pain is an effective predator deterrent found in many animal venoms, fibrinogenolytic activity does not induce pain. Therefore, based on the biochemical modes of action, the venom enzymes that destructively cleave fibrinogen suggest a predatory role[xvii,xviii].

According to Auffenberg W[xix]. venom from V. komodoensis amplifies bleeding and lowers blood pressure caused by deep lacerations by inducing anticoagulative changes in blood chemistry (PLA2 toxins) and lowering blood pressure through shock-inducing mechanisms (CRISP, kallikrein, and natriuretic toxin types). Additionally, prey immobilization is facilitated by AVIT toxins causing hyperalgesic cramping. In vivo studies demonstrate that an intravenous dose of 0.1 mg/kg results in significant hypotension, while 0.4 mg/kg induces hypotensive collapse. Consequently, a typical adult V. komodoensis prey, such as a 40-kg Sunda Deer, would require 16 mg of protein to induce complete hypotensive collapse, but only 4 mg to induce immobilizing hypotension. This quantity is feasible for delivery, considering that even rear-fanged snakes, with a relatively inefficient venom delivery system, can dispense more than half of their venom load. Such a significant drop in blood pressure, combined with blood loss, would incapacitate envenomed prey, rendering them unable to flee. These findings align with observations of prey displaying unusual quietness and rapid onset of shock.

Anti-diabetic effects of the venom-

The Komodo dragon and Gila monster are known to produce venom within their salivary glands. When these creatures bite their prey, the venom is transferred into the victim's bloodstream through the teeth. This venom has the remarkable ability to stimulate insulin production while also slowing down glucose production. With approximately two hundred million individuals worldwide affected by diabetes, a condition characterized by inadequate insulin production leading to uncontrolled blood sugar levels, the significance of this discovery becomes apparent. Insulin plays a crucial role in regulating blood sugar levels, preventing spikes that could potentially damage vital organs such as the liver, kidneys, eyes, and limbs.

Gila monster, despite consuming as few as three substantial meals annually, maintains a steady blood sugar level post-meal. This phenomenon is attributed to a chemical compound found in its venom, known as

Exendin-IV. This compound has the remarkable ability to stimulate the body's insulin production. Remarkably, Exendin-IV shares properties with a human gut hormone called GLP-1, which is of great interest of research. GLP-1 not only triggers insulin secretion from the pancreas in response to high blood sugar levels but also demonstrates the ability to refrain from stimulating insulin secretion when blood sugar levels are normal. Leveraging this discovery, Xenatide or Byetta, a medication developed by Amylin Pharmaceuticals (Eli Lilly & Co.), utilizes a synthetic version of Gila monster venom as its primary component in treating type II diabetes. This drug mirrors the properties of the human hormone GLP-1, which has been extensively studied for its role in diabetes management. Unlike the human hormone, however, which degrades rapidly, exendin-4 remains stable in the body for a period ranging from 4 to 24 hours.[xx]

Antimicrobial benefits-

Antimicrobial peptides, including magainin, have been discovered in the skin of frogs, toads, and Komodo dragons. Researchers are investigating these peptides for their capacity to permeabilize cell membranes, trigger pore formation, and potentially enhance the effectiveness of beta-lactam antibiotics.[xxi]

Author's message- My interest in the Komodo dragon and its venom was sparked by a video I stumbled upon while randomly scrolling through YouTube by BBC EARTH UNPLUGGED[xxii]. In the video, a zoologist named Bryan G. Fry extracts venom from the teeth of a Komodo dragon named Monty. He does this by inserting a synthetic rubber tube into Monty's mouth between his teeth. When Monty applies pressure to the rubber tube between his teeth, venom oozes out, which Bryan carefully collects.

After collecting the semi-viscous, lathery venom in a test tube, Bryan adds his own blood, withdrawn at the site, to the mixture. In another test tube, Bryan adds his own blood but not with Monty's venom, labeling it as a blank. After allowing the two test tubes to sit for some time, it becomes evident that in the blank test tube containing only Bryan's blood, the blood clots at the bottom, while in the other test tube containing Bryan's blood along with Monty's venom, no change is observed; the blood remains unclotted, like when it was initially added to the test tube.

This small experiment and its results have intrigued me ever since. I have been searching for literature supporting this phenomenon. Unfortunately, there is limited data on the benefits of the Komodo dragon's venom. However, it holds significant potential for medical advancements, making it a valuable contribution from nature to the field of medicine.

Talking about Bryan, Bryan G. Fry is an associate professor in the School of Biological Sciences at the University of Queensland leading the Venom Evolution Laboratory, working on venoms from a wide diversity of reptiles, centipedes, cnidarians, insects, scorpions, spiders, and even venomous mammals. He has published extensively on venom systems evolution and how they can be harnessed for therapeutic use. Bryan's publications have appeared in prestigious scientific journals, including Nature. He has led field expeditions to over forty countries and he is a member of the Explorers Club. His work has been featured in over seventy natural history documentaries appearing on Animal Planet, BBC, Discovery Channel, National Geographic TV, and others.[xxiii]

Wound healing properties-

Chung EMC et al[xxiv], conducted an in-vitro study to evaluate the antimicrobial and anti-biofilm activities of VK25, a histone H1-derived peptide from the Komodo dragon (*Varanus komodoensis*), and its synthetic derivative, DRGN-1, against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. In the study, female mice were induced with wounds using a 6-mm biopsy punch. Both peptides were applied topically every 48 hours: DRGN-1 in a 20 μg dose in a 20 μL gel form, and VK25 in a 1% hypromellose (hydroxypropyl methyl cellulose, HPMC) solution.The results showed that wounds treated with DRGN-1 exhibited a more rapid healing process compared to those treated with VK25. After 6 days, the bacterial counts of *S. aureus* and *P. aeruginosa* were significantly reduced in the DRGN-1-treated group. By day 11, wounds treated with DRGN-1 were fully healed, demonstrating not only its superior antimicrobial properties but also its ability to accelerate wound healing and enhance wound closure. In contrast, the healing process was slower in wounds treated with VK25. These findings suggest that DRGN-1 offers enhanced wound healing properties, effectively reducing bacterial load and promoting faster tissue recovery, making it a promising candidate for future therapeutic applications in wound care.

Some examples of Human Exposures to Monitor lizards-

Monitor Lizard Bite-Induced Acute Kidney Injury (AKI):

Monitor lizards are venomous reptiles that can cause coagulopathy, hemolysis, rhabdomyolysis, and sepsis in humans. However, acute kidney injury (AKI) due to monitor lizard bite has not been reported before.[xxv]

Vikrant S et al[xxvi], reported a case of a 55-year-old woman was bitten by a monitor lizard (Varanus bengalensis) on her right leg. She developed severe pain, bleeding, coagulopathy, hemolysis, rhabdomyolysis, sepsis, and AKI. She was treated with supportive care and peritoneal dialysis but died of a sudden cardiac arrest. Kidney biopsy showed acute tubular injury with pigment nephropathy.

From this case, the author mentions that a monitor lizard venom can cause AKI by multiple mechanisms, such as intravascular hemolysis, rhabdomyolysis, sepsis, coagulopathy, and direct nephrotoxicity. No specific antivenom is available and treatment is mainly supportive. Early hospitalization, saline hydration, and urine alkalization may prevent or treat pigment-induced AKI.

From the study, it is concluded that a monitor lizard bite-induced AKI is a rare but serious complication that should be recognized and managed promptly.

Life-Threatening coagulopathy due to Monitor Lizard bite:

Kumar et al,[xxvii] reported a case of a 12-year-old boy presented to the emergency department with severe pain at the bite site, vomiting, bleeding gums, and hematuria following a reptile bite. Upon examination, active bleeding from the gums was noted, along with laboratory findings indicating thrombocytopenia, prolonged prothrombin time, elevated D-dimer levels, and a prolonged 20-minute Whole Blood Clotting Time (WBCT). Initially, the medical team considered the possibility of a snake bite and administered a trial of Anti-Snake Venom (ASV), starting with 10 vials. However, after six hours, WBCT remained prolonged, and bleeding symptoms persisted. Consequently, an additional 10 vials of ASV were administered upon discovering that the reptile responsible for the bite was a monitor lizard. After a total of 20 vials of ASV were given, WBCT

returned to normal, and bleeding manifestations ceased. The child's laboratory parameters normalized within 48 hours, and he was observed for 96 hours before discharge.

Lizard bites and envenomation are very uncommon occurrences in pediatric patients. While monitor lizard bites were traditionally deemed non-venomous, current study demonstrates their potential to induce life-threatening coagulopathy akin to that observed in hemotoxic snake bites. And use of ASV in treating monitor lizard bite can be a better treatment option as envenomation.

Challenges and future directions-

Komodo dragon venom holds considerable promise for developing new medical treatments, but several obstacles must be addressed before it can be widely used. The venom's intricate mixture of bioactive compounds makes it challenging to isolate and identify the specific substances responsible for its therapeutic effects. Ethical concerns about obtaining venom from protected species, as well as the potential toxicity of these peptides to human cells, need to be resolved. Additionally, ensuring the stability, pharmacokinetics, and regulatory approval of these peptides is critical to confirm their safety and effectiveness. Future studies should focus on synthesizing or producing these peptides through recombinant methods to mitigate sourcing issues, along with developing stable and effective delivery systems. There is also potential for these peptides to be used in treating a broader range of conditions, such as chronic infections, cancer, or autoimmune disorders. Investigating their combined use with traditional antibiotics, exploring personalized medicine, and conducting extensive clinical trials will be key for advancing their use. Finally, adopting sustainable production methods and ensuring ethical sourcing are essential for the continued development and success of these therapies.

References-

[i] https://www.scmp.com/week-asia/article/3185546/indonesias-komodo-dragons-are-endangered-are-tourists-willing-pay-us250

[ii] Britannica, T. Editors of Encyclopaedia. "Komodo dragon." Encyclopedia Britannica, December 25, 2023. https://www.britannica.com/animal/Komodo-dragon.

[iii] Gorman, G. C. and Vitt, . Laurie. "lizard." Encyclopedia Britannica, January 8, 2024. https://www.britannica.com/animal/lizard.

[iv] Fry BG, Vidal N, Norman JA, Vonk FJ, Scheib H, Ramjan SF, Kuruppu S, Fung K, Hedges SB, Richardson MK, Hodgson WC, Ignjatovic V, Summerhayes R, Kochva E. Early evolution of the venom system in lizards and snakes. Nature. 2006 Feb 2;439(7076):584-8. doi: 10.1038/nature04328. Epub 2005 Nov 16. PMID: 16292255.

[v] Janeczek M, Goździewska-Harłajczuk K, Hrabska L, Klećkowska-Nawrot J, Kuropka P, Dobrzyński M, Melnyk O, Nikodem A. Macroanatomical, Histological and Microtomographic Study of the Teeth of the Komodo Dragon (*Varanus komodoensis*)-Adaptation to Hunting. Biology (Basel). 2023 Feb 3;12(2):247. doi: 10.3390/biology12020247. PMID: 36829525; PMCID: PMC9953444.

[vi] Fry BG, Vidal N, Norman JA, Vonk FJ, Scheib H, Ramjan SF, Kuruppu S, Fung K, Hedges SB, Richardson MK, Hodgson WC, Ignjatovic V, Summerhayes R, Kochva E. Early evolution of the venom system in lizards and snakes. Nature. 2006 Feb 2;439(7076):584-8. doi: 10.1038/nature04328. Epub 2005 Nov 16. PMID: 16292255.

[vii] Fry BG, Wroe S, Teeuwisse W, van Osch MJ, Moreno K, Ingle J, McHenry C, Ferrara T, Clausen P, Scheib H, Winter KL, Greisman L, Roelants K, van der Weerd L, Clemente CJ, Giannakis E, Hodgson WC, Luz S, Martelli P, Krishnasamy K, Kochva E, Kwok HF, Scanlon D, Karas J, Citron DM, Goldstein EJ, McNaughtan JE, Norman JA. A central role for venom in predation by Varanus komodoensis (Komodo Dragon) and the extinct giant Varanus (Megalania) priscus. Proc Natl Acad Sci U S A. 2009 Jun 2;106(22):8969-74. doi: 10.1073/pnas.0810883106. Epub 2009 May 18. PMID: 19451641; PMCID: PMC2690028.

[viii] Fry BG, Scheib H, van der Weerd L, Young B, McNaughtan J, Ramjan SF, Vidal N, Poelmann RE, Norman JA. Evolution of an arsenal: structural and functional diversification of the venom system in the advanced snakes (Caenophidia). Mol Cell Proteomics. 2008 Feb;7(2):215-46. doi: 10.1074/mcp.M700094-MCP200. Epub 2007 Sep 12. PMID: 17855442.

[ix] Fry BG. From genome to "venome": molecular origin and evolution of the snake venom proteome inferred from phylogenetic analysis of toxin sequences and related body proteins. Genome Res. 2005 Mar;15(3):403-20. doi: 10.1101/gr.3228405. PMID: 15741511; PMCID: PMC551567.

[x] Fry BG, Winter K, Norman JA, Roelants K, Nabuurs RJ, van Osch MJ, Teeuwisse WM, van der Weerd L, McNaughtan JE, Kwok HF, Scheib H, Greisman L, Kochva E, Miller LJ, Gao F, Karas J, Scanlon D, Lin F, Kuruppu S, Shaw C, Wong L, Hodgson WC. Functional and structural diversification of the Anguimorpha lizard venom system. Mol Cell Proteomics. 2010 Nov;9(11):2369-90. doi: 10.1074/mcp.M110.001370. Epub 2010 Jul 14. PMID: 20631207; PMCID: PMC2984233.

[xi] Norman, Janette A.; Vonk, Freek J.; Scheib, Holger; Ramjan, S. F. Ryan; Kuruppu, Sanjaya; Fung, Kim; Blair Hedges, S.; Richardson, Michael K.; Fry, Bryan G.; Vidal, Nicolas (2005). *Early evolution of the venom system in lizards and snakes. , 439(7076), 584–588.* doi:10.1038/nature04328

[xii] Dobson, J.S.; Zdenek, C.N.; Hay, C.; Violette, A.; Fourmy, R.; Cochran, C.; Fry, B.G. Varanid Lizard Venoms Disrupt the Clotting Ability of Human Fibrinogen through Destructive Cleavage. *Toxins* **2019**, *11*, 255. https://doi.org/10.3390/toxins11050255

[xiii] Wolberg AS. Thrombin generation and fibrin clot structure. Blood Rev. 2007 May;21(3):131-42. doi: 10.1016/j.blre.2006.11.001. Epub 2007 Jan 8. PMID: 17208341.

[xiv] Debono J, Bos MHA, Nouwens A, Ge L, Frank N, Kwok HF, Fry BG. Habu coagulotoxicity: Clinical implications of the functional diversification of Protobothrops snake venoms upon blood clotting factors. Toxicol In Vitro. 2019 Mar;55:62-74. doi: 10.1016/j.tiv.2018.11.008. Epub 2018 Nov 22. PMID: 30471431.

[xv] Koludarov I, Jackson TN, Brouw BOD, Dobson J, Dashevsky D, Arbuckle K, Clemente CJ, Stockdale EJ, Cochran C, Debono J, Stephens C, Panagides N, Li B, Manchadi MR, Violette A, Fourmy R, Hendrikx I, Nouwens A, Clements J, Martelli P, Kwok HF, Fry BG. Enter the Dragon: The Dynamic and Multifunctional Evolution of Anguimorpha Lizard Venoms. Toxins (Basel). 2017 Aug 6;9(8):242. doi: 10.3390/toxins9080242. PMID: 28783084; PMCID: PMC5577576.

[xvi] Jackson TN, Fry BG. A Tricky Trait: Applying the Fruits of the "Function Debate" in the Philosophy of Biology to the "Venom Debate" in the Science of Toxinology. Toxins (Basel). 2016 Sep 7;8(9):263. doi: 10.3390/toxins8090263. PMID: 27618098; PMCID: PMC5037489.

[xvii] Sweet SS. Chasing flamingos: Toxicofera and the misinterpretation of venom in varanid lizards. InProceedings of the 2015 interdisciplinary world conference on monitor lizards 2016 (pp. 123-149). Institute for Research and Development.

[xviii] Arbuckle KE. Ecological function of venom in Varanus, with a compilation of dietary records from the literature. Biawak. 2009;3(2):46-56.

[xix] Auffenberg W. The behavioral ecology of the Komodo monitor. (No Title). 1981.

[xx] Wolpert, H. D. (2011). Snake oil and venoms for medical research. Bioinspiration, Biomimetics, and Bioreplication. doi:10.1117/12.871107

[xxi] Varaz Bozoghlanian, MD, and Matthew Butteri, MD. THE DIVERSE AND PROMISING WORLD OF ANIMAL DERIVED MEDICATIONS. The Pharos of Alpha Omega Alpha honor medical society /Winter 2015. Pg no- 18-22. https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=3ff22f6040a099d8286027ee206a99f9c3645974#page=18

[xxii]https://www.bing.com/videos/riverview/relatedvideo?&q=komodo+dragon+venom+benefits&&mid=712EADBD5F5E491A418D712EADBD5F5E491A418D&&FORM=VRDGAR

[xxiii] Föreläsare Bryan G Fry – Stockholms Herpetologiska Förening (sthlm-herp.net)

[xxiv] Chung EMC, Dean SN, Propst CN, Bishop BM, van Hoek ML. Komodo dragon-inspired synthetic peptide DRGN-1 promotes wound-healing of a mixed-biofilm infected wound. NPJ Biofilms Microbiomes. 2017 Apr 11;3:9. doi: 10.1038/s41522-017-0017-2. PMID: 28649410; PMCID: PMC5445593.

[xxv] Auffenberg W. The bengal monitor. Univ Pr of Florida; 1994.

[xxvi] Vikrant S, Verma BS. Monitor lizard bite-induced acute kidney injury--a case report. Ren Fail. 2014 Apr;36(3):444-6. doi: 10.3109/0886022X.2013.868223. Epub 2013 Dec 16. PMID: 24341640.

[xxvii] Kumar, V., KS, A., Gupta, S.K. et al. Monitor Lizard Envenomation Treated with ASV. Indian J Pediatr 90, 847 (2023). https://doi.org/10.1007/s12098-023-04673-y