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Lizard venom composition and therapeutic properties (Reptilia: Squamata: Lacertilia).

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1.Inroduction

1.1. Class Reptilia

The name “reptile” comes from the Latin “reptare”, whose translation is close to “crawl”. This means that most animals belonging to this classification usually move by crawling which may be on small paws or, in the case of snakes, just “dragging” on the ground. In addition to being oviparous, other characteristics of reptiles include lung breathing and thick skin. These animals are also called “cold-blooded” [1-2].

Most of these animals are carnivorous, with a very diverse diet. Some are herbivores and omnivores, but they are rare. Each of the species is adapted to capture its prey in the best possible way. A curious fact about them is that they have the so-called “double” blood circulation. This occurs because blood passes through the heart twice to complete the cycle [2-3].

1.2. Class Reptilia - order Squamatta

The lizard belongs to the Lepidosauria lineage a sister lineage of birds, crocodiles, and non-avian dinosaurs, Phylum Chordata, Class Reptilia. Together with snakes, they make up the order Squamatta, which is a Latin term for the plural of scaled, referring to the main external characteristic of lizards, which is having their skin covered in scales. One of the main differences between lizards and reptiles from the dinosaur and bird lineage is the positioning of the limbs, in lizards they are positioned laterally to the body while in reptiles from the dinosaur and bird lineage, the limbs are positioned below the body (Figure 1) [3-5].

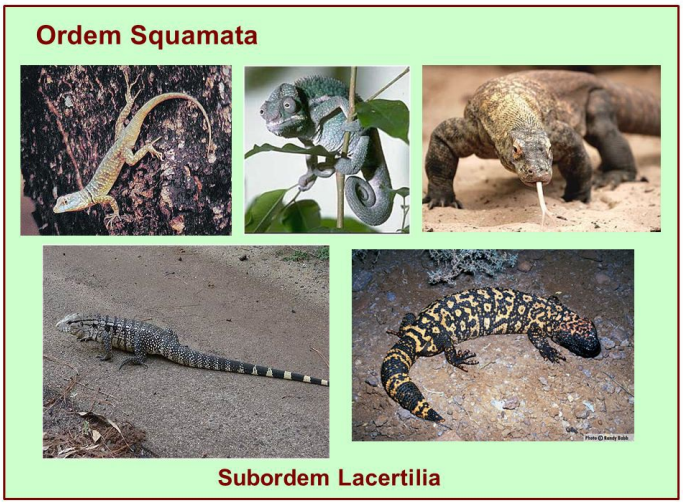

Figure 1. CLasse Repteis, Ordem Squamata, Subordem Lacertília. Source: https://slideplayer.com.br/slide/387764/.

Lizards vary more in size and shape than any other group of reptiles. Some measure just a few centimeters. But the largest lizard of all, the Komodo dragon, can reach 3 meters in length. Most lizards have four strong legs, but some have no legs. Thus, they look like snakes or serpents and are often confused with them. However, they have eyelids and ear openings, that is, ears. They also generally have a long tail. Most lizards have dry scales covering their bodies. Scales are small smooth or rough plates, often brown, green, or gray [4-5].

Many lizards have unique characteristics. Some have horns or spines. Others have a bony plate around their neck. These characteristics help them to frighten their enemies and keep them at bay. Some species have folds of additional skin on the sides of the body; When they open them, they look like wings, and these lizards can glide from one tree to another [5-6].

Most species of lizards are terrestrial, inhabiting dry land, however, it is also possible to find several species with arboreal and even semi-aquatic habits, such as the Madagascar marine iguanas, which feed on seaweed and can dive and stay submerged for several minutes. Lizards are ectotherms, which means that they need help from the environment's temperature to regulate their own, so it is quite common to see lizards in the hottest hours of the day on rocks absorbing heat [6-7].

Lizards can be found on every continent except Antarctica, and they live in all habitats except extremely cold areas and oceans. Most of these animals live on the ground, but others can make their home in a tree, in burrows, or water. Different species of lizards eat different types of food. They feed on a wide variety of foods, including fruits and vegetation, insects, small mammals, birds and amphibians, carrion, and even (in the case of large predatory lizards) large prey such as deer and other large animals (Figure 2) [8-9].

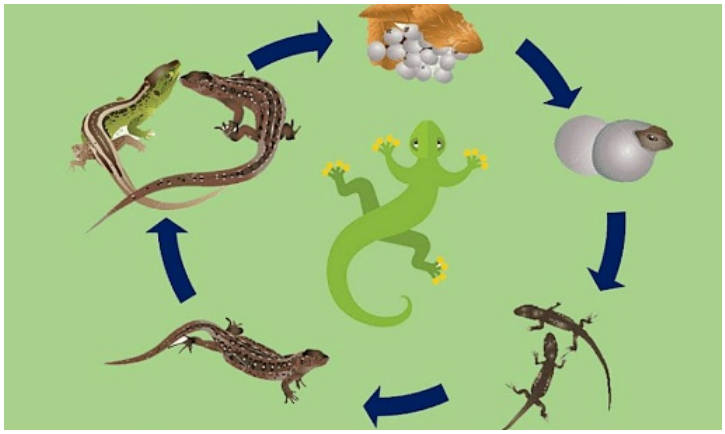

Figure 2. Lizards Life Cycle. Source: https://collegedunia.com/exams/lizard-and-moth-life-cycle-biology-articleid-2529.

Most lizards lay eggs, although some species are capable of producing a legless lizard that resembles a small snake. Slow worms reproduce from eggs that the female incubates inside her body. The incubation period is about 90 to 100 days. In smaller egg-laying lizards, females lay 8 to 12 soft-shelled eggs in a clutch a set of eggs laid at the same time. Some species, such as the dragon, dig a hole in the ground and lay 20 to 40 eggs. Then cover them with dirt. The eggs hatch in about 7 months. The young eat mainly insects and live in trees. Finally, chameleons lay white, oval, hard-shelled eggs, which are buried in hot sand until they hatch [9-11].

According to the Encyclopedia of Life, all lizards can change color in response to their environment or in times of danger. The most typical example is the chameleon. Some species can break off their tails when they are in danger or captured by a predator. This ability is called autotomy and, when this happens, the tail regenerates, although, the vertebrae are replaced by a cartilaginous tube [11-12].

Some species of lizards, called snakes or glass lizards, do not have functional legs, despite having vestigial skeletal legs. Although they may resemble snakes, these animals are distinguished from them by the presence of tympanic openings and eyelids. According to the Encyclopædia Britannica, only one genus of lizard is poisonous: the *Heloderma* (Wiegmann. 1829, which includes the species: Gila monster *Heloderma suspectum* Cope, 1869, and the beaded lizard *Heloderma horridum* (Wiegmann, 1829) [13-14].

Both species are inhabitants of western Mexico and southern Texas, in the United States. Furthermore, the comments that the Komodo dragon, found in the forests of Indonesia, can also be poisonous. According to Encyclopædia Britannica an education platform in the United Kingdom, lizards are the group of modern reptiles with the greatest diversity of shapes and sizes. Lengths vary from a few centimeters, in the case of some Caribbean geckos, for example, to almost 3 meters, as with the Komodo dragon (Figure 3) [15-17].

Figure 3. *Heloderma horridum* (Wiegmann, 1829). https://ca.wikipedia.org/wiki/Heloderma_horridum.

2. Lizard poisons

2.1. Group of poisonous lizards.

The Komodo dragon is considered the largest lizard in the world. This is because it is, on average, three meters long. Also called the land crocodile, the Komodo dragon originates from Indonesia and is capable of killing large prey, such as the Asian buffalo. This bovine species weighs more than half a ton. The Komodo dragon has a deadly lizard venom, which it delivers to its prey through its bite (Figure 4) [17-18].

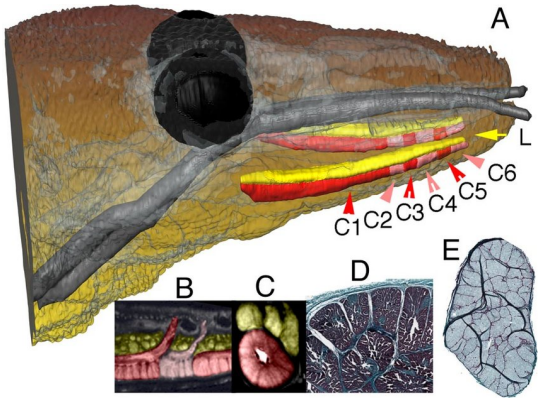

Figure 4. Anatomical investigation of the *Varanus komodoensis* Ouwens, 1912, venom system. (A) Magnetic resonance imaging of the V. komodoensis head showing the protein-secreting mandibular venom gland, with the 6 compartments colored in alternating red and pink (C1-C6), and the mucus-secreting infralabial gland in yellow (L). (B) Longitudinal MRI section showing the large duct emerging separately from each compartment of the mandibular venom gland and threading between the mucus lobes of the infralabial gland to terminate between successive teeth (black oval areas). (C) Transverse MRI section showing the large central lumen of the mandibular venom gland and individual lobes of the labial gland. (D) Transverse histology of Masson's Trichromestained section showing the intratubular lumina of the mandibular venom gland that feeds into the large central lumen. (E) Transverse histology of Masson's Trichrome-stained section of a mucus infralabial gland showing numerous tightly packed internal lobules (note that the 6 large dark folds are histology artifacts). Source: https://www.researchgate.net/figure/Anatomical-investigation-of-the-Varanus-komodoensis-venom-system-A-Magnetic-resonance_fig3_24436454.

The name “Komodo dragon” was given because of its robust and frightening appearance. Furthermore, Komodo is the name of one of the islands in Indonesia where this animal lives. The Gila monster is another species among the dangerous lizards that also exist in the wild. Found in the United States and Mexico, it has an immediate venom, capable of killing its prey. Unlike snakes, it has two incisor teeth in the lower jaw, where the inoculated venom is located. In snakes, it is located in the upper jaw. Gila Monster under the Rock: The Gila monster has powerful claws that help it attack its prey. With straight pink stripes, it can reach up to 60 cm in length. It is another lizard that you should not have physical contact with, as it has potent venom (Figure 5) [19-22].

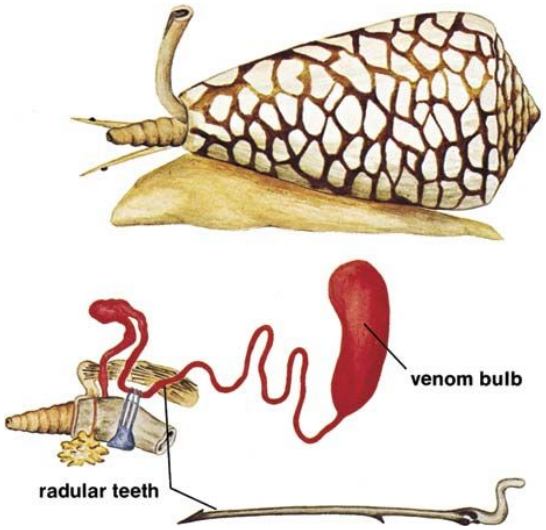

Figure 5. Venomous gland of the Heloderma (Wiegmann. 1829), lizard, Source: https://www.britannica.com/animal/venomous-lizard.

The billed lizard is found mainly in Mexico and southern Guatemala. It is another animal among the lizard species that is poisonous. Its jaw and bite are extremely strong to release venom from the glands. Therefore, a bite, even a superficial one, can cause damage. With a calm appearance, the lizard may not generate suspicion in people. However, you need to be careful, as it is a venomous animal. Its color is black with yellow stripes spread across the body. The beaded lizard can reach up to 1 meter in length (Figure 6) [22-23].

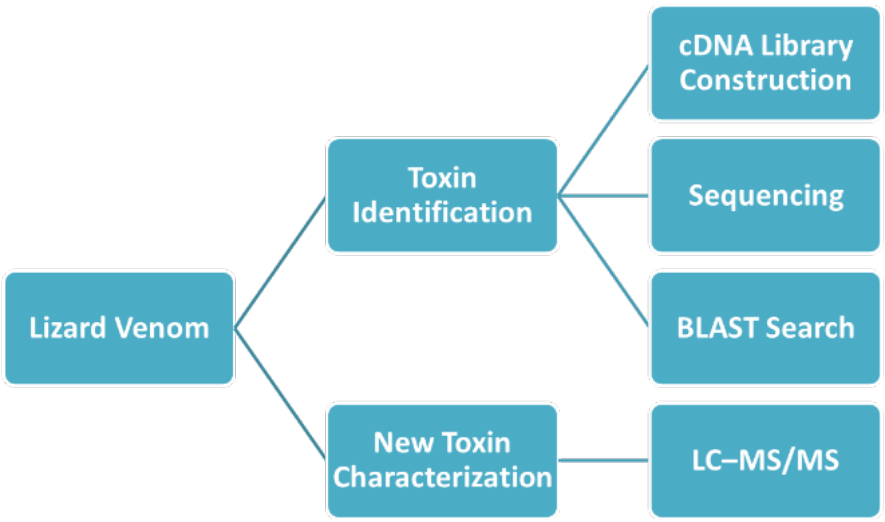

Figure 6. Analyze and identify proteins/peptides whose sequences have sequence homology with previously characterized toxins and maximize the identification of protein sequences in lizard venom to identify the types of new toxins that exist. Source: Molecular & Cellular Proteomics. 2010; 9(11):2369-2390.

The venom of these lizards has a content and effect very similar to that of some venomous snakes, even when the symptoms tend to be much less severe and the bite does not pose a fatal risk. Unlike most snakes, the Gila monster and beaded lizard clamp down firmly when they bite and introduce the venom into the victim by chewing rather than injecting it through their fangs. It may be difficult to release the lizard [23-24].

Common symptoms include pain, swelling, and discoloration in the area around the bite, as well as swollen lymph nodes. The affected person may become weak and sweat profusely, have thirst, a headache, and a ringing sensation in the ears (tinnitus). In severe cases, a drop in blood pressure may occur. Gila monsters are poisonous. Besides them, the only lizards on Earth capable of killing humans are their cousins of the Gila monsters are poisonous. Besides them, the only lizards on Earth capable of killing humans are their cousins of the species *Heloderma horridum* (Wiegmann, 1829) (Squamata: Helodermatidae). These are some of the factors that caught the attention of zoologists and breeders (Figure 7) [24-27].

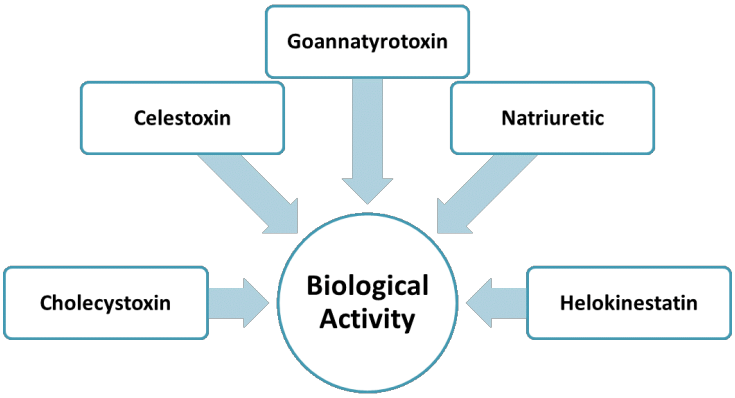

Figure 7. A detailed understanding of the diversification of different toxin types and structural and functional innovations in lizard venom can give lizard venom more attention in medical applications. Source: Molecular & Cellular Proteomics. 2010; 9(11):2369-2390.

3. Lizard venom for medicine production Therapeutic possibility).

Gila monster venom has therapeutic functions such as:

1. Exenatide is extracted from a substance found in saliva, a synthetic compound that is the first drug in a new class of drugs to hit the market, incretin hormone mimetics, for the treatment of type 2 diabetes.

2. Acting on the pancreas, injected before meals, exenatide mimics the effects of incretin, naturally responsible for the release of insulin after food consumption and the consequent elevation of blood glucose.

3. This lizard's venom is being studied for the possible treatment of Alzheimer's disease. species.

4. Research on the treatment of blood diseases. Many lizard venoms have selective effects on fibrinogen chains of different clotting proteins.

5. Research on the treatment of diabetes and hypertension. The new protein/peptide found in lizard venom may help drug development for diseases hypertension (Figure 8) [28-30].

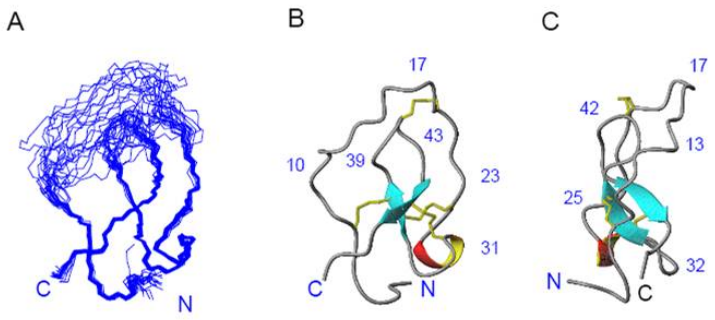

Figure 8. Waprins have recently identified three novel proteins of this family. One of the members, Omwaprin exhibited antibacterial activity against gram-positive bacteria. They are homologous to whey acidic proteins and secretory leukocyte proteinase inhibitors. We will examine their structure and function. Source: https://www.dbs.nus.edu.sg/lab/kini/NewToxins.htm.

Its venom is neurotoxic: it affects the central nervous system, produces cardiopulmonary paralysis, and is cytolytic, destroying the cells with which the saliva comes into contact. In addition, it causes stains on the shredded tissue and ruptures cell membranes. These are some of the consequences caused by the bite of the Gila Monster, a lizard that lives in the arid and hot regions of northern Mexico [31-32].

There is currently no medication developed to combat the venom of this carnivore. This lizard's venom contains several

enzymes and 30 different components, however, most of them have not been analyzed and could perhaps help in the treatment of various human diseases. Obtaining the antidote will not be complicated, as three decades ago this substance was produced by researchers from the then National Institute of Hygiene, a federal agency that produced 20 doses [32-33].

Exenatide is extracted from a substance found in saliva, a synthetic compound that is the first medicine in a new class of medicines to hit the market, that of incretin hormone mimetics, for the treatment of type 2 diabetes. With action on the pancreas, injected before meals, exenatide mimics the effects of incretin, naturally responsible for the release of insulin after food consumption and the consequent increase in blood glucose. The venom of this lizard is being studied for the possible treatment of Alzheimer's disease (Figure 9) [33-34].

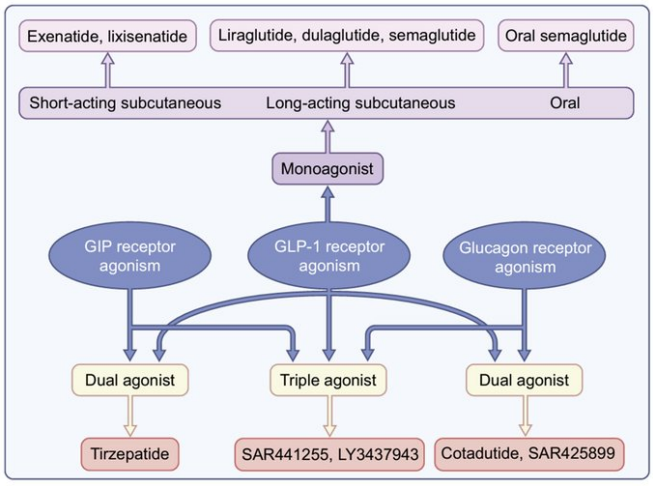

Figure 9. Gut hormone-based therapies have revolutionized the management of type 2 diabetes and obesity and hold great promise in this field. Source: https://link.springer.com/article/10.1007/s00125-023-05929-0.

One example is semaglutide, known under the brands Wegovy and Ozempic. Folk medicine, used to treat overweight and obesity, was inspired by the venom of the lizard known as the Gila monster. Scientists have discovered that a hormone from this reptile's venom, called exendin-4, could be used to treat type 2 diabetes. Exendin-4 is similar to a hormone found in humans called GLP-1, released after eating and important for controlling blood sugar levels.

Exenatide mimics the action of a hormone found in the desert lizard*H. suspectum* or Gila monster, one of the few venomous lizards found in nature. According to experts, the results of studies on ways to combat diabetes are carried out by a pharmaceutical company [35-38].

One of the main causes of type 2 diabetes, the most common form of the disease, is the failure of the beta cells in the pancreas to function. The researchers found that a hormone from the Gila monster behaved similarly to a hormone in the human digestive system called GLP-1, which helps maintain a moderate flow of glucose in the blood. GLP-1 stimulates the body to produce insulin in response to rising blood glucose levels, inhibits the release of glucose from the liver after meals, slows the absorption of nutrients, and reduces appetite (Figure 10) [37-39].

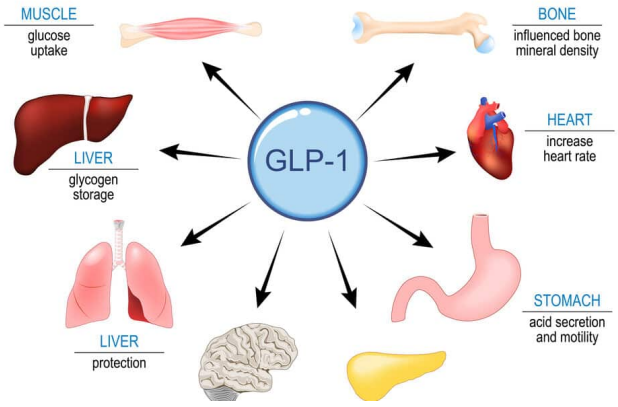

Figure 10. Weight management has evolved to become a pressing concern in today's health-centric society. Over the years, medical researchers have introduced several therapeutic agents to curb the epidemic of obesity. One such agent that has captured significant attention is GLP-1 agonists. Source: https://pennmedicalgroup.com/glp-1-agonists/what-are-glp-1-agonists-for-weight-loss/.

Scientists have discovered that the hormone that plays a similar role in the body of Gila monsters exendin-4 remains in the body for longer periods. Based on these discoveries, two companies, Amylin Pharmaceuticals and Eli Lilly have developed synthetic versions of the hormone found in the reptile. The most recent tests show that Exenatide improves the ability of beta cells to release insulin when there is an influx of glucose into the bloodstream. Three studies carried out on around 1,400 people showed that the drug reduced the average level of blood sugar and also the average weight of patients [37-39].

References

[1] Ribeiro PHP. Lizards. [Internet]. Recife: InfoEscola; @2005 [cited 2024 Apr 23]. Available from https://www.infoescola.com/biologia/lagartos/#google_vignette.

[2] Lizards [Internet]. Florianopolis: Federal University of Santa Catarina: @2024 [cited 2024 Apr 23]. Available from https://gestaoambiental.ufsc.br/.

[3] Bérnils RS, Costa HC [internet]. Porto Alegre: Brazilian reptiles: List of species; @2012 [cited 2024 Apr 23]. Available from http://www.sbherpetologia.org.br/. Brazilian Society of Herpetology.

[4] Pough HF, Janis CM, Heiser JB. The life of vertebrates. 4st ed. São Paulo: Atheneu. 2008.

[5] Freitas LM. 5. Macro- and microscopic brain anatomy of the amazon lava lizard (*Tropidurus torquatus*) (Wied, 1820). Brazilian Animal Science. 2023; 24: e-74091.

[6] Tojal SD. Parasitism by *Amblyomma rotundatum* on Teiidae lizards in the eastern part of the state of Acre, Brazil. Brazilian Journal of Veterinary Parasitology. 2023; 32(3): e004923.

[7] Ferreira FS, et al. Topical anti-inflammatory activity of body fat from the lizard*Tupinambis merianae*. Journal of Ethnopharmacology. 2010; 130(3): 514-520.

[8] Fitzgerald LA. Tupinambis lizards and people: a sustainable use approach to conservation and development. Conservation Biology. 1994; 8(1): 12-16.

[9] Rocha CFD. Introduction to the ecology of Brazilian lizards. Herpetology in Brazil [Internet]. Belo Horizonte: Pontifical Catholic University of Minas Gerais; Biodiversitas Foundation; Ezequiel Dias Foundation; @1994 [cited 2024 Apr 23]. Available from https://www.pucminas.br/destaques/Paginas/default.aspx.

[10] Rocha CFD. Introduction to the ecology of Brazilian lizards. In: Nascimento LB, Bernardes AT, Cotta GA, eds. Herpetology in Brazil 1. 1st ed. Belo Horizonte: Fundação Biodiversitas; 1994. p. 39-57.

[11] Barish RUA, Arnold DE. Lizard bites [Internet]. Rahway: MSD Manual; @2024 [cited 2024 Apr 23]. Available from https://www.msdmanuals.com/pt-br/casa/les%C3%B5es-e-envenenamentos/mordidas-e-picadas/picadas-de-centopeias-e-mil%C3%ADpedes.

[12] Pianka ER, VITT LJ. Lizards: windows to the evolution of diversity. 1st ed. Berkeley: University of California Press. 2006.

[13] Silva VN, Araújo AFB. Ecology of Brazilian lizards. 1st ed. Rio de Janeiro: Technical Books. 2008.

[14] Sluys MV, Rocha CFD. *Tupinambis merianae* (Common Tegu) activity. Herpetological Review. 1999; 30(1): 42-43.

[15] Pough HF, Janis CM, Heiser JB. The life of vertebrates. 1st ed. São Paulo: Atheneu. 2008.

[16] Environment warns about caring for lizards in urban areas [Internet]. Ivoti: Ivoti City Hall; @ 2024 [cited 2024 Apr 23] Available from https://www.ivoti.rs.gov.br/noticia/meio-ambiente-alerta-para-os-cuidados-com-lagartos-na-zona-urbana.

[17] Klemens MW, Thorbjarnarson JB. Reptiles as a food resource. Biodiversity & Conservation. 1995; 4(3): 281-298.

[18] Lee JC. The amphibians and reptiles of the Yucatan Peninsula. 1st ed. Ithaca: Cornell University Press.1996.

[19] National Geographic Society. The 5 interesting facts you didn't know about lizards, the most diverse group of reptiles [Internet]. Washington: Encyclopedia of Life (EOL); @2024 [cited 2024 Apr 23]. Available from https://www.nationalgeographicbrasil.com/animais/2023/08/as-5-curiosidades-que-voce-nao-sabia-sobre-os-lagartos-o-grupo-mais-diversificado-entre-os- reptiles.

[20] Fry BG, et al. A central role for venom in predation by*Varanus komodoensis* (Komodo Dragon) and the extinct giant *Varanus* (*Megalania*) *priscus*. Proceedings of the National Academy of Sciences of the United States of America. 2009; 106(22): 8969-8974.

[21] Brizuela S, Albino AM. Dental variations in*Tupinambis merianae* (Squamata: Teiidae). Herpetology Notebooks. 2010; 24(1): 1-5.

[22] Haddad JR, Duarte VMR, Garrone Neto D. Tegu (Teiu) Bite: Report of human injury caused by a Teiidae Lizard. Natureza Selvagem e Medicina Ambiental. 2008; 19: 111-1

[23] Martins M. Defensive tactics in lizards and snakes: the potential contribution of Neotropical fauna. Anais do XIV Encontro Anual de Etologia. 1996: 14: 185–199.

[24] Russell C. Ozempic and other remedies inspired by animal venom [Internet]. Goiânia: BBC News Brazil; @2023 [Cited 2024 Feb 23]. Available from https://www.bbc.com/portuguese/articles/c515q5neqdgo.

[25] Iberoamerican Agency for the Diffusion of Science [internet]. Salamanca: University of Salamanca; @2024 [cited 2024 Apr 23]. Available from https://www.dicyt.com/noticia/elaborado-antidoto-para-secrecao-venenosa-do-monstro-de-gila.

[26] Alves RRN, et al. Reptiles are used for medicinal and magical religious purposes in Brazil. Applied Herpetology. 2009; 6(3): 257-274.

[27] Alves RRN, et al. A review on human attitudes towards reptiles in Brazil. Environmental Monitoring and Assessment. 2012; 84(11): 6877-6901.

[28] Alves RRN, et al. A zoological catalog of hunted reptiles in the semiarid region of Brazil. Journal of Ethnobiology and Ethnomedicine. 2012; 8(1): 27-40.

[29] Passos DC, et al. Calangos and lizards: conceptions on lizards among High School students in Fortaleza, Ceará, Brazil. Sciences and Education. 2015; 21(1): 133-148.

[30] Martins E. Journalist MI-Medicos at Internet {Internet]. Vila Nova de Gaia: Alert life sciences Computing; @2024 [cited 2024 Apr 23]. Available from https://www.alert-online.com/br/contacts.

[31] Vicente-Ferreira GS, Martins GS, Keys NA, Silva DGH, Bonini-Sunday CR. Oxidative and osmotolerant effects of *Salvator merianae* (Squamata: Teiidae) red blood cells during hibernation. Brazilian Journal of Biology. 2024; 84: e249617.

[32] Arshad M, et al. An antimicrobial activity of oil extracted from Sahara hardwickii. Brazilian Journal of Biology. 2024; 84: e253508.

[33] Freitas LM. 5. Macro- and microscopic brain anatomy of the amazon lava lizard (*Tropidurus torquatus*) (Wied, 1820). Brazilian Animal Science. 2023; 24: e-74091.

[34] Tojal SD. Parasitism by *Amblyomma rotundatum* on Teiidae lizards in the eastern part of the state of Acre, Brazil. Brazilian Journal of Veterinary Parasitology. 2023; 32(3): e004923.

[35] Alves RRN, Rosa IL, Santana GG. The role of animal-derived remedies as complementary medicine in Brazil. BioScience. 2007; 57(11): 949-955.

[36] Alves RRN, Vieira WLS, Santana GG. Reptiles used in traditional folk medicine: conservation implications. Biodiversity and Conservation. 2008; 17(8): 2037-2049.

[37] Fry BG, et al. Functional and structural diversification of the *Anguimorpha* lizard venom system. Molecular & Cellular Proteomics. 2010: 9(11): 2369-2390.

[38] Rubino DM, et al. Step 8 Investigators. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the step 8 randomized clinical trial. JAMA. 2022; 1327(2): 138-150.

[39] Wilding JPH, et al. Step 1 study group. Once-weekly semaglutide in adults with overweight or obesity. The New England Journal of Medicine. 2021; 384(11): 989-1002.