Molluscivorous and Vermivorous Conus Species

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It is generally believed that more than 700 Conus species have evolved during the last 50 million years. With the highest species abundance occurring in southeast Asia, most Conus can be found in the shallow waters of tropical and subtropical oceans. Conus is widely distributed in rocky shores, sandy beaches, coral reefs and intertidal waters, with depths reaching up to over 600 m. Nowadays, Conus species are generally overexploited, and some species are now endangered. Exploring these waters of potentially high species diversity could enrich our understanding of their population's genetic structure and provide the missing pieces for clarifying Conus evolution. As the conotoxin compounds vary greatly throughout the growth stages and across geolocations within the same species, further investigation of these species-specific regional distribution differences may provide crucial insights for artificial breeding and harvesting specific bioactive compounds in the future.

Conus   feeding habit   phylogenetic tree   distribution map   biomedical compounds   COVID-19

1. Introduction

It is generally believed that more than 700 *Conus* species have evolved during the last 50 million years [1][2]. With the highest species abundance occurring in southeast Asia, most *Conus* can be found in the shallow waters of tropical and subtropical oceans [3]. *Conus* is widely distributed in rocky shores, sandy beaches, coral reefs and intertidal waters, with depths reaching up to over 600 m [4]. However, geophysical environment is not the only factor that influences the *Conus* species distribution. For example, despite similar oceanic and climate conditions, more than 77 *Conus* species have been discovered in Indian coastal waters, especially in the Tamil Nadu Coast and the Andaman Islands [4][5][6], with fewer than 20 species reported on the eastern side of the Andaman Sea [7]. Nowadays, *Conus* species are generally overexploited, and some species are now endangered. As the conotoxin compounds vary greatly throughout the growth stages and across geolocations within the same species, further investigation of these species-specific regional distribution differences may provide crucial insights for artificial breeding and harvesting specific bioactive compounds in the future.

With intraspecies variation of the venom cocktails, a huge array of remarkably diverse conopeptides, ranging from 50,000 to 140,000 venom peptides, are estimated to be produced in the *Conus* genus [8]. With a unique repertoire of 100–200 venom peptides for each species, *Conus* could presumably specifically target a wide range of vertebrate and invertebrate physiological receptors, assisting their prey hunting or defense from potential predators and competitors [9]. Different prey targets come along with different venom recipes. Yet, despite the species diversity of *Conus*, their feeding habits can be categorized into three main types, often with associated differences in the radula morphology [6][10]. The radula of the vermivorous (V) *Conus* usually have two barbs or the second barb replaced by a blade; spur and serration are present, with or without waist. Spur is absent in the molluscivous (M) radula; serrations are longer and terminate at a prominent cusp. The radula of the piscivorous (P) *Conus* has three barbs, with a recurved tip on the third barb with no serration, waist, cusp or spur [6]. Exceptionally, in some vermivore species, the radula was found to be similar to the molluscivous radula, indicating a more complex relationship between the radula morphology and feeding habit [11].

Alongside radula changes, *Conus* also developed complex venom compositions and envenom system. The venom gland of the sea snails can be divided into three sections: bulb, duct and radular sac [12]. To hunt and defend themselves, each *Conus* species can produce a cocktail of conotoxins (reaching hundreds of small polypeptides with very complex post-transcriptional modifications, alongside some paralytic small molecules) in their venom glands and inject the precise amount of venom cocktail through the duct anchored on its prey by the harpoon [13][14][15]. The prey will be instantly paralyzed through rapid stabbing with such an efficient venom cocktail [16]. Previous studies also proposed that modern *Conus* species can produce venom peptides with different functions at different parts of the venom gland, even for different parts of the venom duct. For example, the distinct defense cabal was identified from bulb-proximal and predation-evoked cabal from the bulb-distal end of the specialized venom ducts [17][18]. The diverse conotoxins allow *Conus* to precisely adjust their cocktail recipes for each attack (hunting, defending or threatening competitors) [19] or become specialized in a local prey according to geographic variation [20]. Recent studies further illustrated that the defensive compositions of venom cocktails of the worm-hunting species may be the driving factor for the emergences of fish- and mollusc-hunting species [21][22]. Consequently, conotoxin compositions are also expected to vary from lab culture to natural conditions.

In general, the small polypeptides (mostly 10 to 40 amino acid residues) are rich in disulfide bonds and act on the nervous system of the target organism, interfering with signal transmission in cells and neurons [23]. Specific types of cysteine residues

and disulphide bond arrangements have been found in different gene superfamilies, with each venom gene superfamily usually having unique corresponding binding sites from different pharmacological target families (**Table 1**) [3][24]. The targets of conotoxins include: (i) presynaptic membrane calcium channel or G protein receptor, (ii) voltage-gated potassium channel, (iii) adrenal hormone receptor, (iv) serotonin receptor, (v) somatostatin receptor, (vi) norepinephrine receptor, (vii) voltage-gated calcium ion channels and (viii) other targets [25][26]. These receptors are ubiquitous when it comes to drug research. Conopeptides, with their abundant diversity, novel chemical structure, biological sensitivity and target selectiveness, are of great potential as drug precursors, as well as an important neuroscience tool [27].

Table 1. Conopeptides gene superfamilies, cysteine framework and their pharmacological families [3][28][29].

| Conotoxin Family	Definition	Gene Superfamily	Cysteine Framework
α (ALPHA)	Nicotinic acetylcholine receptor (nAChR)	A, B3, D, J, L, M, S	I, II, III, IV, VIII, XIV, XX, XXV
γ (GAMMA)	Neuronal pacemaker cation currents (inward cation current)	O1, O2	VI/VII
δ (DELTA)	Voltage-gated Na Channel (agonist, delay inactivation)	O1	VI/VII
ε (EPISILON)	Presynaptic calcium channels or G protein-coupled presynaptic receptor	T	V
I (IOTA)	Voltage-gated Na Channel (agonist, no delayed inactivation)	I1, M	III, XI
κ (KAPPA)	Voltage-gated K Channel (blocker)	A, I2, J, M, O1	III, IV, VI/VII, XI, XIV
μ (MU)	Voltage-gated Na Channel (antagonist, blocker)	M, O1,T	III, IV, V, VI, VII
ρ (RHO)	Alpha 1 adrenoreceptor (GPCR)	A	I
σ (SIGMA)	Serotonin-gated ion channels (GPCR)	S	VIII
τ (TAU)	Somatostatin receptor	T	V
χ (CHI)	Neuronal noradrenaline transporter	T	X
ω (OMEGA)	Voltage-gated calcium channel	O1, O2	VI/VII, XVI, XXVI

Additionally, nerve system agents and anticancer drugs are research hotspots, and conotoxins are drawing more attention after the entry of Ziconotide (Prialt®) on the market [30]. Because the physiological system of fish is more similar to other vertebrates, such as human [31], in comparison to benthic organisms, such as worms and mollusks, many studies focus exclusively on the piscivorous species and their venom production. To better categorize the complex conopeptides, the primary structure of 222 conotoxins has been identified and classified into several gene superfamilies, according to precursor signal peptides and amino acid sequences [25][32]. Apart from their genetic diversity, the precursor RNA splicing process contributes greatly to the conotoxin diversity. With just over 30 gene superfamilies, more than 7000 conopeptides have been discovered [33][34][35]. Not all of these peptides, however, are of equal importance. Compounds from A, M, O1 and T gene superfamilies account for the bulk of venom cocktails. Moreover, the expression of some conopeptides is so low that their presence cannot even be detected in traditional proteomic experiments [18][36]. Perhaps it is the seemingly redundant venom compounds that are providing abundant raw materials for natural selection and contributing to the rapid speciation and quick adaptation of the *Conus.* Therefore, to understand the rich proteomic and toxicological resources in *Conus*, genomic and transcriptomic approaches are required to assist conotoxin identification and classification [37], as they are more sensitive and accurate for capturing the trace amount of conopeptides. Hence, the biggest obstacles now hindering the use of multi-omic approaches in *Conus* studies are data analysis and the scarcity of well-annotated genomes.

2. Feeding Habits and Evolution Path

Apart from the 190 species from three other genera (1 from *Californiconus*, 159 from *Conasprella* and 30 from *Profundiconus*) in the Conidae family, there are currently 728 species recognized in the *Conus* genus, making it one of the most diversified species in the Conoidea superfamily (Supplementary Table S1, could be found in https://www.mdpi.com/1660-3397/20/2/105#supplementary). In this study, the feeding habits of known species are categorized based on radula morphology, field reports and dissection of digestive chambers. Only 506 species in the Conidae family were classified into the staple feeding habits. For *Conus*, it is obvious that worm eating is the dominant feeding behavior, accounting for more than 72% of total species diversity, including most basal species, and thus likely to have first emerged in their evolutionary history. This trend was followed by the most recent fish-eating group (20%) and molluscivore group (12%). Interestingly,

several polyphagous species have also been found scattered among the three monophagous groups, indicating a more complex hunting behavior of the *Conus* species in natural environments.

The phylogeny tree constructed with barcode sequences (12S, 16S and COI) is consistent with previous studies, and researchers further highlighted the feeding habits using a color-coded pattern across the various species studied here with the same feeding habits (**Figure 1**). As shown in the phylogenetic tree, following the vermivorous group, the first batch of fish-hunting species appeared in the Neogene period (around 23 million years ago) [38]. Unlike the cluster of molluscivorous *Conus* species that share one collective root on the phylogenetic tree, the emergence of the piscivores seems to be independent and recurrent along with speciation.
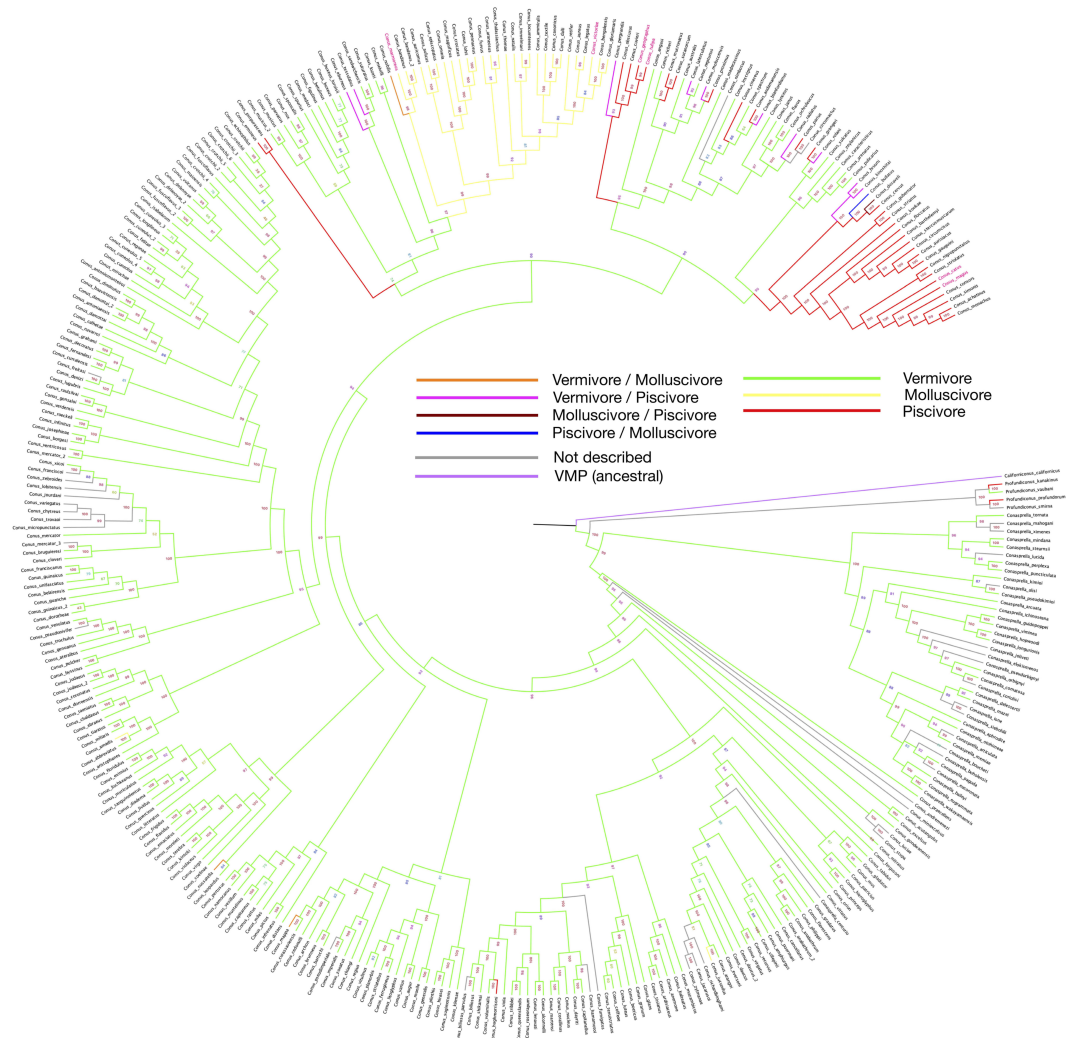
Figure 1. Phylogeny tree of 335 *Conus* species, constructed by using barcode sequences (12S, 16S and COI). Branch colors are set according to the feeding habit from Supplementary Table S1. Bootstrap values are presented by the numbers next to each branch. Species with feeding habits found have been assigned with branch colors accordingly. Names of species that have been involved in drug development are labeled in red.

According to the latest taxonomy update from the WoRMS website, several species have been categorized into the same species, as indicated by trailers in the graph (**Figure 1**). As shown in the tree, polyphagy is most likely to occur on restricted branches, where fish-hunting species have secondarily recurrently emerged from the worm-eating species. As a true omnivore, *Californiconus californicus* not only feeds on marine worms, fish and mollusks; it is also a scavenger. Positioned on the proximal branch of the phylogenetic root, the mentioned *Californiconus californicus* is considered as an ancestral state species to others in the family. Therefore, it is interesting to see that the majority of *Conus* species become specialized in only one particular prey category, which makes the few polyphagous species outliers, or more interestingly, transitive species.

Many studies have suggested that the venom cocktail composition for each preference is highly distinguishable. The venoms of fish-hunting species are well selected to target vertebrate nervous system, in which receptors are very different from invertebrates. If we look at *Conus* alone, vermivores are obviously plesiomorphic, and molluscivores and piscivores originate

from them. Furthermore, the distinguishable evolutionary patterns between the fish- and mollusc-hunting species indicate that the determining factors for different feeding habits may be separately located in the genomes, where gene silencing or gene lost mechanism could play an important role. Otherwise, it would be difficult to explain the seemingly random occurrences of the fish-hunting species.

However, there are also cases of one *Conus* species hunting various preys, or even some individual showing omnivorous behavior. This suggests that *Conus* feeding habit is not monophagous and far more complex than simple hunting/defense venom recipes. Indeed, other factors, such as environmental pressure and prey abundance, could also play important roles in venom secretion.

Conus evolution is subject to both convergence and divergence. Different groups in *Conus* could share similar evolutionary patterns due to comparable selection pressure in a confined geographical region. Previous molecular phylogenetic analysis has confirmed that *Conus* species constitute a largely heterogeneous group, despite their overall morphological homogeneity [39]. This may explain that, although the selective pressure on the venom is acting in different directions, vermivorous species, which are close to the fish-hunting clade, show great potential in accepting both worm and fish as prey.

On the phylogeny tree, some vermivorous sister species exhibit a fish-eating behavior or can also feed on other molluscs, suggesting a loose hunting strategy. Given that the roots of most divergent species are very recent, it indicates an ongoing adaptive process of some *Conus* clusters [40]. This phenomenon could be caused by both genetic plasticity and environmental pressure. It is also intriguing that fish-hunting and mollusc-hunting strategies were both developed at the same period of geological time, and the two clusters are genetically close to each other.

The origin of the Conidae family dates back to around 59 (73–55) million years ago, and the radiation of some analyzed species within the *Conus* genus was estimated to have occurred between 24–15 (30–12) million years ago [41]. The explosive fish speciation movement [42] in this period (Neogene) became the ultimate driving force and selection pressure for some clades of *Conus*. The emerge of massive Pleistomollusca species [43] occupied ecological niches and stiffened the competition, potentially leading to the clade of molluscivores.

However, questions remain on the *Conus* feeding habits. Normally, most specimens were dissected right after being collected for further multi-omics studies, and stomach contents and radula shapes were kept for feeding habit analysis. Only a small number of individual species have been kept for feeding behavior studies. The phylogeny and feeding habit results described in this work suggest a more complicated relationship between feeding habits and morphology.

Replicates are rare for most transcriptome datasets online, and gene expression can be influenced by environmental conditions, individual sample difference and other batch effects, making it challenging to compare datasets from various projects. Therefore, designed experiments should be carried out to retrieve precise transcriptome data for different tissues, and most importantly, the venom glands. Further studies could also explore venom cocktail composition difference induced by different pressures, such as constant defensive pressure, and how *Conus* would cope with the pressure when food options are limited, especially for the polyphagous clades labeled on the phylogenetic tree (**Figure 1**).

3. Distribution

Geographical coordinates of the *Conus* species from the last clade on the phylogeny tree are pinpointed on the map. On the map, *Conus* species that prey on both worm and fish (V+P) are spread largely in the shallow waters of southeast Asia, Australia and African east coast, corresponding to the distribution areas of the most diversified *Conus* species [3]. Apart from ocean currents, which may prevent the species from dispersing globally, the distribution pattern of V+P species could result from a high competitive pressure and diversity of potential food sources in these areas. The geographical landform of islands has also accelerated evolutionary diversification [40].

Interestingly, despite geological and hydrologic conditions being very similar to the surrounding waters, in south and southeast Asia, comprising the most species-rich area, few *Conus* species have been reported on the east coast of the Burma (or Andaman) Sea and the Gulf of Thailand (**Figure 2**). Little research and few scientific reports have been conducted in these areas, which could flag a potentially species-rich region for further studies.
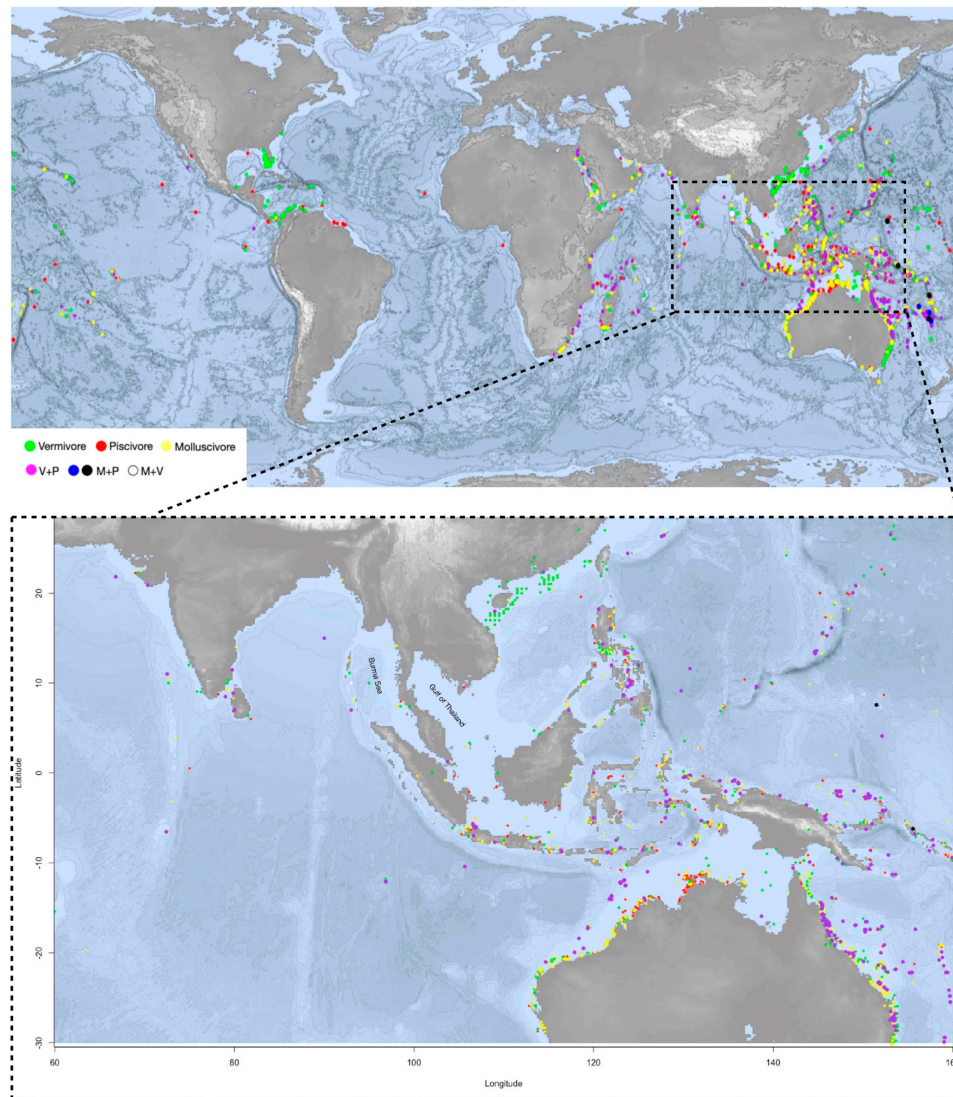
Figure 2. The upper map shows the distribution of the monophagous and polyphagous *Conus* species clades from the phylogenetic tree (species listed in the Supplementary Table S2). Orange for molluscivous (M), red for piscivorous (P), green for vermivorous (V). Purple-color dots indicate the feeding habit of V+P (vermivorous and piscivorous); blue and black dots are for M+P (molluscivous and piscivorous); and the white dot is V+M (vermivorous and molluscivous). *Conus* species V+P are spread largely in the shallow waters of southeast Asia and Australia and African east coast, corresponding to the distribution areas of the most diversified *Conus* species. The distribution pattern of V+P species could result from a high competitive pressure and diversity of potential food sources in these areas. The lower map highlights the region where *Conus* species are most abundant and diversified, including the north coast of Australia and south and southeast Asia.

4. Conservation Status

Despite *Conus* resources being relatively abundant, it is of great ecological and biological necessity to protect them. Shell hunting of the *Conus* has already driven some of the rare species to the edge of extinction. According to the International Union for the Conservation of Nature (IUCN) Red List, 26 *Conus* species are Near Threatened, 27 species are Vulnerable, and 14 more species have already been Endangered or Critically Endangered, accounting for 9.2% of the total *Conus* species globally. The number seems to be relatively small, but some regions are suffering huge depletion. For instance, all three of the Critically Endangered species, along with another four (out of 11) Endangered species, are located in the Cape Verde waters; 45.3% of the 53 species are assessed as Threatened or Near Threatened with extinction. It is shocking to find that 61% of the 41 *Conus* species are threatened with extinction in the west Africa area [44][45]. Shell hunting and habitat degradation are the main threatening factors for the *Conus*. Human activities, such as tourism and industrial and residential effluent pollution, have severely affected local *Conus* communities. In west Africa, there has been an observable reduction in species abundance and body size.

5. Drug Discovery

Venomous animals are widely distributed in the biosphere, and over time, a positive selection between venom and its target has been driven by the predator and prey arms race. Venoms are usually composed of novel chemical structures with various targets. Therefore, they encompass a pool of broad molecular structures highly relevant for novel drug discovery.

Marine toxins are one of the most rapidly growing research areas in bioactive substances. As unique chemical structures are more often found in venoms, the structure–function relationship of marine toxins is a valuable clue for discovering new targets and pathways. The most common marine toxins can be found in pufferfish and crabs; some toxic shellfish can also produce paralytic neurotoxins. Polyether toxins can be easily transmitted to humans through the food chain and cause food poisoning, such as palytoxin, dinophysistoxin and ciguatoxin. Other marine toxins include alkaloids, for example, saxitoxin. Among all the marine toxins, polypeptide toxins are so far the most effective and deadly (tetrodotoxin and conotoxin). They are usually highly selective with the nervous system, digestive system, cardiovascular system and cell membrane, with especially strong cardiotoxicity and cytotoxicity. This makes venom peptides very prominent for drug discovery. As a widely studied marine invertebrate, its diversified conopeptides make *Conus* promising animals for the discovery of antimicrobial peptides, analgesics and anti-cancer drugs.

Many works have committed to decipher the secrets of conopeptides. **Figure 3**A shows the top 100 keywords in the field for the past two decades. It is obvious to see that most publications are related to the ion channels (Ca^{2+}, sodium, voltage gated) and peptides–receptor interactions (acetylcholine receptor, inhibition, block). The most studied conotoxins are from alpha and omega pharmaceutical families. Protein structures and animal-trials-related topics are less reported.
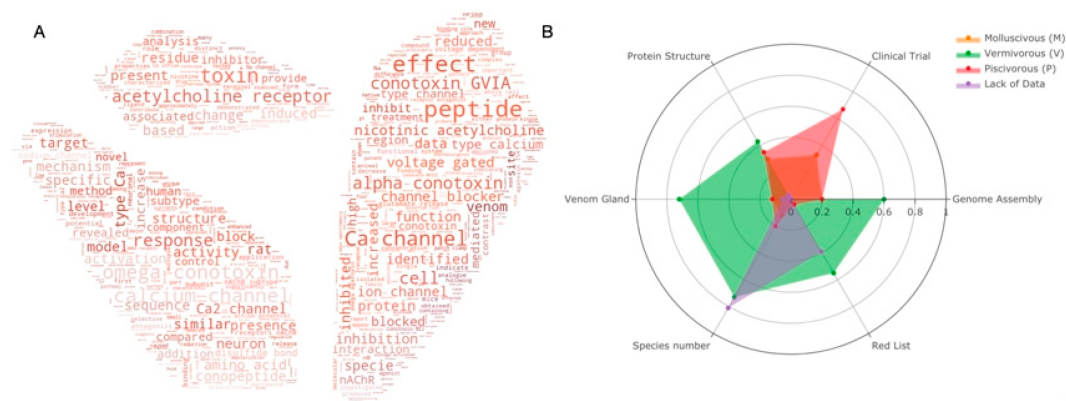
Figure 3. (**A**) Keyword cloud from the abstract of *Conus* studies over the past 20 years; (**B**) Statistics of current *Conus* studies. Ratio of six categories (genome assemblies, species under clinical trials, characterized protein structures, venom glands, species number and red list species) for *Conus* species of each feeding habit are presented in the radar plot. Orange for molluscivous (M), red for piscivorous (P), green for vermivorous (V) and species with insufficient data are presented in purple. Species with more than one feeding habit are counted separately in each group. Raw statistics can be seen in Supplementary Tables S3 and S4.

As mentioned, worm-eating *Conus* species (V) is the largest group of the three genera. It also has the highest number of venom glands (31 out of 43 transcriptomes, Supplementary Table S4) and genome assemblies (2 out of 3), and it is the most endangered species. In contrast, there is no genome assembly so far in the mollusc-hunting group. Even though most of the data are for the worm-hunting species, mollusc- and fish-hunting species are more favored in clinical research. It is notable that a number of species are in danger with little data reported.

In the past 20 years, with Ziconotide being approved by the FDA, a number of conotoxins have been selected for clinical research (**Table 2**). This is justified, since the prey for piscivorous *Conus* species is vertebrate, whose physiology system is more similar to the human system. Therefore, most drug-related research has focused on this group. Interestingly, mollusc-hunting *Conus* sourced molecules are also seen on the list, even if their prey is invertebrate. An important question to investigate now is whether the worm-hunting species, believed to be less promising for drug discovery, underestimated.

Table 2. Drug development with conotoxins.

	Conopeptide	Commercial Name	Comment	Target	Stage	Company	*Conus* Species (**)	Reference
1	α-Vc1.1	ACV1	Neuropathic pain	nAChR (α9α10)	Phase II *	Metabolic Pharmaceuticals, Melbourne, Australia	*Conus victoriae* (m)	[3]
2	ω-CVID	AM336	Neuropathic pain	Ca^{2+} channel (CaV2.2) N-type calcium channels/blocker	Phase IIa *	Relevare Pharmaceuticals LTD., Australia	*Conus catus* (p)	[3]
3	μO-MrVIB	CGX-1002	Neuropathic pain	Sodium channels/subtype selective blocker	Preclinical *	Cognetix Inc, Salt Lake City, USA	*Conus tulipa* (p)	[3]
4	Conantokin-G	CGX-1007	Intractable epilepsy / pain	NMDA receptor (NR2B)	Preclinical *	Cognetix Inc, Salt Lake City, USA	*Conus geographus* (p)	[3]
5	Contulakin-G	CGX-1160	Neuropathic pain	Neurotensin receptor	Phase Ib *	Cognetix Inc, Salt Lake City, USA	*Conus geographus* (p)	[3]
6	ω-MVIIA	SNX-III, C1002, Ziconotide, Prialt	Intractable pain	Ca^{2+} channel (CaV2.2) N-type calcium channels/blocker	FDA-approved	Elan Corporation (Elan Pharmaceuticals), CA, USA	*Conus magus* (p)	[3]
7	χ-MrIA	Xen2174	Neuropathic pain	Norepinephrine transporter/inhibitor	Phase IIa *	Xenome, Ltd., Brisbane, Qld., Australia	n.a.	[3]
8	κ-PVIIA	CGX-1051	Acute Myocardial Infarct, Cardioprotection	K^{+} channel (KV1)/blocker	Preclinical	n.a.	n.a.	[46]
9	n.a.	CGX-1204	Muscle relaxer / pain	Nicotinic acetylcholine receptors/antagonist	Preclinical	n.a.	n.a.	[46]
10	μ-SIIIA	PEG-SIIIA	Inflammatory pain	Sodium channels/blocker	Preclinical	n.a.	n.a.	[46]
11	ρ-Conotoxin TIA	n.a.	n.a.	α-1 adrenergic receptors	Preclinical	Xenome, Ltd., Brisbane, Qld., Australia	*Conus tulipa* (p)	[47]
12	χ-conopeptides (χ-CTX MrIA/B)	n.a.	Neuropathic pain	Neurotransmitter transporters	Preclinical	Xenome, Ltd., Brisbane, Qld., Australia	*Conus marmoreus* (m)	[47]

blications on other venomous animals have shown significant potential in antibacterials, cancer therapy, nervous system and cardiovascular diseases [48][49][50][51][52][53][54][55]. Given the vast application of other venoms, conopeptides are very under-explored and of such great potential. Yet, it remains difficult to isolate the most effective molecules with minimal side effects. Apart from Prialt, all other candidates present many unaddressed issues.

6. Structural and Functional Studies of Conotoxins with Their Receptors

The realization of conotoxins application in the pharmacological industry depends heavily on the structural and functional studies of conotoxins with their receptors. The physiological functions of conotoxins are fairly well understood, although the well-defined functions and structures account for only a small part of the entire toxin pool. The difference in cysteine skeletons and peptide structures determines the reactive sites of conotoxins. The identified targets mainly include ligand-gated ion channels (acetylcholine receptors, NMDA receptors), voltage-gated ion channels (sodium, potassium, calcium channels) and G protein-coupled receptors.

*indicates that further research has been known as terminated; ** Prey preference for *Conus* species: p = piscivorous (fish hunting); m = molluscivorous (mollusk hunting); v = vermivorous (worm-hunting).

Acetylcholine receptors (AChRs) are widely expressed in the nervous systems, playing critical roles in various physiological processes. nAChRs are associated with various neurological diseases, such as Parkinson's disease, Alzheimer's disease, neuralgia and epilepsy [56]. According to pharmacological activities, AChRs are classified into nicotinic (nAChR) and muscarinic (mAChR) types. α-conotoxins have become an ideal tool for studying nAChR. They usually contain two loop structures formed by two pairs of conservative disulphide bonds (except for three pairs for α-SII) and can selectively inhibit neuronal or muscle-type nAChRs. There are three known conotoxin families (α-, αA- and ψ- conotoxins), which can selectively react to nAChRs. For example, conotoxin Vc1.1 has significant analgesic activity for nAChR rat subtype α9α10 [57]. It has been used as an analgesic and entered clinical phase II study [58][59]. However, the project was eventually terminated due to low affinity for the human subtype [60]. On the other hand, GeXIVA is in the preclinical stage as an analgesic for the neuralgia treatment, indicating that α9α10 nAChR blockers have a good prospect for the development of analgesia [61]. Other prominent compound target at nAChRs includes recently discovered octaoligoarginine R8, α-conotoxins RgIA and previously isolated LvIA and LvIF from *Conus lividus* (V) [56][62][63][64]. In particular, LvIA and LvIF are being intensively studied, have exhibited great binding ability to the α3β2 nAChR receptor and have great potential as new candidate tools for studying α3β2 nAChR-related neurophysiology and pharmacology [56][62].

Conotoxin is also an ideal tool for studying ion channels and membrane receptors. For example, ω-GVIA has become an identification tool for N-type voltage-gated calcium ion channels [26]. Conantokin, as a highly selective antagonist of NMDA receptors, is expected to be a promising candidate for the treatment of epilepsy.

In short, conotoxin drug discovery depends on the variation of conopeptides. Fortunately, there is a large number of *Conus* species and an even larger amount of conopeptides that remain to be filtered. For the vermivorous species, there are far more data than for the other two groups to investigate. Multi-omics data provide a great scope for discovering novel mechanisms and pathways, and there is a hidden value for worm-hunting species in drug discovery. On the other hand, a considerable number of *Conus* species are facing survival difficulties. If they become extinct, venom peptides diversity will decrease as well. So far, only few *Conus* species have been thoroughly studied, and some of them are closely related (**Figure 1**).

▍ 7. Potential Value in COVID-19 and Other Diseases

Recently, one of the vermivorous species, *Conus nux*, has shown breakthrough from a different research angle. A newly published study suggested an anti-adhesion adjunct therapy against malaria and the potential of conotoxins in mitigating, or even curing, fatal diseases, such as AIDS and COVID-19, as some of the conopeptides are potential inhibitors of the specific protein of these viruses [65].

Furthermore, an intriguing correlation has been found between the toxin-like peptides and the samples collected from COVID-19 patients. Among all the peptides identified, conotoxin-like peptides are ubiquitous: sequences from *Conus tulipa* (P), *Conus geographus* (P), *Conus marmoreus* (M), *Conus radiatus* (V/P), *Conus virgo* (V), *Conus quercinus* (V), *Conus pulicarius* (V), *Conus flavidus* (V), *Conus catus* (V) and *Californiconus californicus* (V/M/P) have been identified in plasma, urine and fecal samples of COVID-19 patients [66]. This might explain the occurrence of many neurotic related symptoms observed in some COVID-19 patients, such as hyposmia, hypogeusia and signs typical of the Guillain–Barre syndrome. Some of the conotoxins target ion channels and nicotinic acetylcholine receptors, causing dysfunction of the receptors, and alter acetylcholine levels. Furthermore, a potential interaction between spike protein of the SARS-CoV-2 and nicotinic acetylcholine receptors has been reported [67]. Understanding how the different nAChRs are affected by the S-peptide and acetylcholine-related conopeptides may be relevant to uncovering COVID-19 pathophysiology. Therefore, if researchers know that the produced conotoxin-like molecules can cause the symptoms, it also provides insight into finding clues for neutralizing antibodies in the *Conus*-related studies. The coevolution between the *Conus* and their prey, which has existed for a long time, may also warrant further research. By studying the prey, there might be a chance to discover a coping strategy and then use it on patients.

So far, the findings from the worm- and mollusc-eating *Conus* species have shown a direct correlation with current global health emergencies. In future studies, with more conotoxin 3D structures constructed and protein–protein interaction simulation improved, the potential for developing medical treatments and pharmaceutical molecular tools from the worm- and mollusc-eating species, alongside the fish-hunting ones, is enormous.

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