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REVIEW ARTICLE

Exploring CNS Effects of American Traditional Medicines using Zebrafish Models

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Abstract: Although American traditional medicine (ATM) has been practiced for millennia, its complex multi-target mechanisms of therapeutic action remain poorly understood. Animal models are widely used to elucidate the therapeutic effects of various ATMs, including their modulation of brain and behavior. Complementing rodent models, the zebrafish (*Danio rerio*) is a promising novel organism in translational neuroscience and neuropharmacology research. Here, we emphasize the growing value of zebrafish for testing neurotropic effects of ATMs and outline future directions of research in this field. We also demonstrate the developing utility of zebrafish as complementary models for probing CNS mechanisms of ATM action and their potential to treat brain disorders.

Keywords: Zebrafish, American traditional medicine, behavior, brain effects, drug screening, animal models.

1. INTRODUCTION

While American traditional medicine (ATM) has been practiced for nearly 30 000 years [1-3], it continues to be widely used globally today. For example, 71% of Chileans and 40% of Colombians have received ATM therapy [4], whose medical, societal, and economic importance remains high [4, 5]. The consumption of ATMs is also expanding worldwide. In the US, it reached nearly $9 billion for antioxidant/anticancer herbal supplements [6-10].

Historically, ATM plants have long been used by various tribes for medical and religious purposes. For example, the Huichols of West Mexico eat fresh and dried peyote (*Lophophora williamsii* Lem) buttons [11]. The Yanomamos of Venezuela inhale powder of yakoana (*Virola elongata* Benth) [12] for their rituals. The Mayas have long used ritual enemas laced with various psychoactive plants (*e.g.*, hallucinogenic mushrooms teonanacatl, *Psilocybe mexicana* Heim) or seeds of ololiuhqui (*Turbina corymbose* Linn.) [13], also brewing them for drinking as tea [12]. A common South American shamanic tea, ayahuasca, contains two major alkaloids: harmine (from jagube, *Banisteriopsis caapi* Griseb.) and N,N-dimethyltryptamine, DMT (from angico, *Anadenanthera colubrina* Vell. or chacrona, *Psychotria viridis* Rubiaceae) [3, 12]. Ayahuasca has long been used ancestrally by Amazonian Indian populations, and more recently, by various religious groups globally [14-16], evoking euphoria, hallucinations, fear, paranoia, as well as some psychedelic and other beneficial effects [17, 18].

Although ATM has been practiced for millennia, its complex multi-target mechanisms of action remain poorly understood. In addition to clinical evidence, animal models have been instrumental in increasing our understanding of the effects and mechanisms of central nervous system (CNS) action of ATMs. For instance, the extract of aroeira (*Schinus terebinthifolius Raddi)* and the oil of crabwood (*Carapa guianensis Aublet*) improve gastric wound healing in rats [19]. In mice, chronic treatment with hydroethanolic extracts from leaves of yerba-mate (*Ilex paraguariensis* St. Hil.) induces anxiolytic-like effects and hyperlocomotion, whereas aqueous extracts given acutely prevent scopolamine-induced memory deficits in the avoidance task [20]. In rodents, etha-

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nolic extracts of sambaíba (*Curatella americana Linn*.) bark decrease the severity of gastric damage induced experimentally in several models [21]. The aqueous extract from cranberry (*Vaccinium macrocarpon* Aiton) given for 14 days ameliorates behavioral (psychotic-like) effects induced in rodents by MK-801 (dizocilpine), a potent N-methyl-D-aspartate (NMDA) glutamatergic antagonist that evokes acute psychosis, spatial memory deficits, and impaired synaptic plasticity [22].

2. EFFECTS OF AMERICAN TRADITIONAL MEDICINE IN ZEBRAFISH MODELS

Complementing rodent studies, the zebrafish (*Danio rerio*) is emerging as a promising aquatic model organism in biomedicine, including neuroscience and neuropharmacology research [23, 24]. Multiple advantages of zebrafish as a model system include in vitro fertilization, rapid development, easy maintenance, and high genetic and physiological homology to humans [25, 26]. Due to the small size of both larvae and adults, zebrafish also show promise as a high-throughput screening tool for drug testing [27].

Zebrafish have also been extensively used to elucidate mechanisms of action of various neuroactive drugs, further supporting their importance in studying human CNS diseases and their therapies [28, 29]. The use of zebrafish models to probe other folk medicines (*e.g.*, Chinese traditional medicine [30]) has also been discussed recently. Recognizing the growing importance of ATM in biomedicine, here we discuss the developing utility of zebrafish screens for ATM-based therapies for treating CNS disorders.

A popular ATM, ayahuasca improves mindfulness, mood, and emotional control and reduces addiction, anxiety, depression, and post-traumatic stress disorder (PTSD) clinically [31, 32]. In addition to harmine, this ATM mix is rich in DMT and monoamine oxidase inhibitors, whose serotonergic properties further contribute to its positive CNS effects [33]. In zebrafish, exposure to ayahuasca produces dose-dependent effects in the novel tank test, including hypoactivity (reduced swimming speed and distance), freezing and bottom-dwelling at high doses, and more top swimming at a low dose (Fig. **1**) [34]. The novel tank test is a popular zebrafish behavioral assay based on geotaxis (an innate fish preference for 'protective' bottom areas), where increased top dwelling and lower immobility indicate anxiolytic-like behavior [35]. Thus, ayahuasca appears to reduce anxiety-like behavior in zebrafish at low doses and induce anxiety and/or hypolocomotion in high doses [34]. Adult zebrafish chronically exposed to ayahuasca also display impaired discriminative performance and aberrant locomotion in the object discrimination memory task [36], demonstrating amnesic effects *in vivo*. Furthermore, zebrafish larvae acutely exposed to ayahuasca exhibit overt developmental anomalies, including hatching delay, loss of equilibrium, edema, and hypolocomotion [37].

The bushy matgrass (*Lippia alba* Mill.) is a multi-branched shrub native to North, Central and South America, whose extracts exert antiviral [38], analgesic, and anti-inflammatory activity in mammals [39, 40]. The lemon verbena's (*Aloysia triphylla* L'Herit.) is another bushy plant from South America, known for its analgesic, anti-inflammatory, antispasmodic, and antipyretic clinical activity [41, 42]. The essential oils from these ATM plants have shown anesthetic effects in various fish species, such as tambaqui (*Colossoma macropomum*) and red hook piranha (*Serrasalmus eigenmanni*) [43, 44]. Likewise, adult zebrafish acutely exposed to bushy matgrass' (150 μL/L) or lemon verbena's (100 μL/L) essential oils exhibit an anxiolytic-like profile [45], as do zebrafish chronically fed for 210 days a diet containing lemon verbena's essential oil (2 mL/kg) [46]. While extract from a different *Aloysia* species, burrito (*Aloysia polystachya* Griseb.), also produces anxiolytic/antidepressant-like effects acutely in rodents [47-49], the hydroethanolic extract from the leaves of this herb is likely anxiolytic in zebrafish, as it reverts anxiogenic-like effects of caffeine [50]. Together, this suggests potentially shared mechanisms of anxiolytic action of this and related ATMs from *Aloysia* plants that may involve purinergic, rather than the gamma-aminobutyric acid (GABA)-ergic [49], neurotransmission.

Hydroethanolic extract from hog plum (*Spondias mombin L.*), a plant growing in tropical regions of South America, especially in Northern Brazil and Peru, also induces anxiolytic-like effects in zebrafish [51]. Strikingly paralleling its flumazenil-sensitive anxiolytic-like and anti-aggressive effects in rodents [52], this profile suggests shared mechanisms and targets that involve the GABA-ergic system.

Lady salvia (*Salvia divinorum* Labiatae), a member of the *Lamiaceae* family, is remarkably rich in a hallucinogenic compound, salvinorin A, known for its high affinity for the kappa opioid receptor (KOP) [53]. Salvinorin A evokes overt, fast-onset psychotropic and dissociative effects clinically, blocking external sensory perception and modulating interoception and sense of body ownership [54]. This ATM compound also evokes anxiolytic- and antidepressant-like effects in rodents [55]. Recently, salvinorin A has been tested in adult zebrafish, in acute 0.1-0.2-μg/kg doses accelerating swimming, but causing 'trance-like' behavior at 5-10 μg/kg [56]. Pretreatment with a KOP antagonist norbinaltorphimine (10 mg/kg) and a cannabinoid type 1 (CB1) antagonist rimonabant (1 mg/kg) blocks these psychostimulant and inhibitory CNS effects, respectively [56], suggesting both opioidergic and endocannabinoid mechanisms of salvinorin A activity in zebrafish.

The cat's claw (*Uncaria tomentosa* Willd.) is another South American plant whose bioactive compounds with known beneficial properties [57] include 17 different alkaloids with antioxidant, anti-inflammatory, antiviral, and immune-modulating effects [58]. Adult zebrafish treated with extract of this ATM plant for 96-h show elevated total thiols and normalized lipid peroxidation in the model of neurotoxicity caused by 96-h exposure to Glyphosate-Roundup [59]. The rosemary (*Rosmarinus officinalis* Linn.) is another popular ATM plant used in food flavoring and in folk medicine for its antispasmodic, analgesic, antirheumatic, diuretic, and antiepileptic activity [60-62]. This herb contains several bioactive compounds with anti-inflammatory activity *in vitro* and *in vivo* [63], which has also been tested in zebrafish models [64].

Brazilian pepper-tree (*Schinus terebinthifolius* Raddi) is another potent anti-inflammatory, astringent, and antidiarrheal ATM [65]. In mammals, it exerts antifungal, healing,

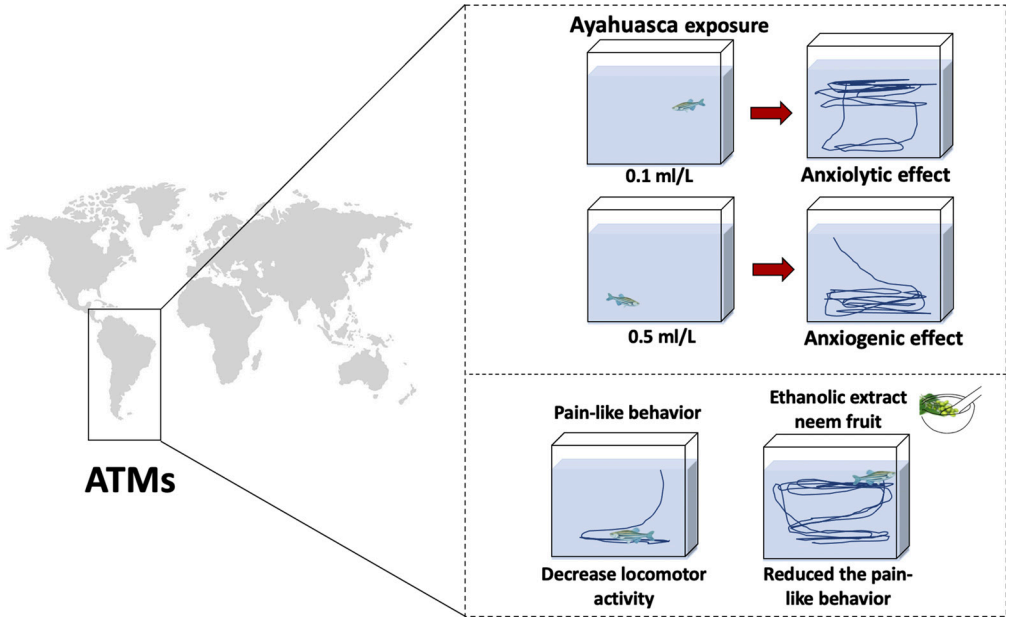

Fig. (1). Selected examples of CNS effects of American traditional medicines (ATMs) in zebrafish models. Low doses of ayahuasca reduce fish anxiety-like behavior, whereas its higher doses evoke an anxiety-like profile [34]. Exposure to ethanolic extract of neem fruit (*Azadirachta indica*) reduces pain-like behavior induced in adult zebrafish by formalin, glutamate, or acidic saline injections [74]. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

and anti-allergic effects [66-68], as well as anti-nociception in rats with chronic sciatic nerve injury-based model of neuropathic pain [69]. Paralleling its effects in rodents, the essential oil from leaves of this herb also evokes behavioral antinociceptive effects in the zebrafish formalin, cinnamaldehyde, capsaicin, glutamate, acidic and hypertonic saline models of pain [70].

The candle brush (*Cassia alata* Linn.) is an ATM commonly used to treat rheumatism, constipation, stomach pain, headaches and skin diseases [71, 72]. In larval zebrafish, exposure to leaf extract of this plant causes an anti-melanogenic activity, assessed by reduced ocular melanin [73]. Neem fruit (*Azadirachta indica* Juss.) is another tropical tree, native to the Indian subcontinent, but also found in South America (*e.g.*, in Brazil) [74], where it is used as an ATM for its antifungal, antibacterial, antiulcerogenic [75, 76], analgesic and anti-inflammatory properties [77]. In zebrafish, the ethanolic extract of neem fruit reduces pain-like behavior induced by formalin, glutamate, and acidic saline [74]. Importantly, neem fruit is rich in antioxidant flavonoids, increasing cytokine production and inhibiting protein kinases [78], hence likely contributing to antinociception by exerting general anti-inflammatory effects as well.

Finally, oil from another plant, batiputá (*Ouratea fieldingiana* Gardner), is used in ATM for the treatment of rheumatism, arthritis, and toothache [79]. In zebrafish, pre-treatment with kaempferol-3-*O*-rutinoside isolated from this plant evokes analgesic effects in formalin, cinnamaldehyde, capsaicin, glutamate, and acidic saline models of orofacial pain (Table **1**) [80]. Moreover, these effects are modulated by naloxone, ruthenium red, camphor, or acid amiloride [80]. Because kaempferol also inhibits formalin-induced licking in rats [81], this suggests shared, evolutionarily conserved molecular targets for these antinociceptive ATMs across taxa.

3. DISCUSSION

Mounting evidence discussed here and briefly summarized in Table **1** and Fig. (**1**) shows that experimental animal models, including both rodents and zebrafish, are particularly useful tools to elucidate mechanisms involved in the effects of various ATMs on brain and behavior, as well as for developing novel pharmacological therapies for CNS disorders based on ATMs. As already mentioned, because zebrafish have a high degree of genetic homology with humans [26], this model species may also represent a powerful vertebrate system to explore how ATMs modulate various evolutionarily conserved molecular targets and shared signaling pathways.

Furthermore, the small size of both larvae and adult zebrafish optimizes the screening of natural compounds and their respective biological fractions since small quantities of purified molecules can be directly added to the tank water, small well, or injected into the fish [82-84]. Other advantages of zebrafish include low cost, ease of experimental manipulations, and somewhat lesser sensitivity to testing environments (*e.g.*, experimenter identify) [85]. Furthermore, zebrafish display rich behavioral repertoire [86], enabling the assessment of all major neurobehavioral domains, including stress-related (*e.g.*, anxiety) [87], aggression-like [88, 89], cognitive [90], and pain-related phenotypes [91]. As such, these behaviors can all be utilized in zebrafish screens testing various ATMs. Moreover, zebrafish models are relevant to modelling other, more complex and specific brain conditions, such as autism [92], schizophrenia [93, 94], epilepsy [95], impulse control [96], neurodevelopmental [97] or attention deficit hyperactivity [98] disorders. As such, testing ATM effects in these models can also be both translationally relevant and practically important.

Table 1. Selected examples of CNS effects of American traditional medicine (ATM)-based therapies in zebrafish and rodent models.

ATM	Dose	Model	Effects	References
Zebrafish	-	-	-	-
Ayahuasca	0.1 ml/L	Novel tank test	Anxiolytic-like effect	[34]
Ayahuasca	1 and 3 ml/L	Novel tank test	Anxiogenic-like effect	[34]
Matgrass	150 µL/L	Novel tank test	Anxiolytic-like effect	[45]
Lemon verbena	100 µL/L	Novel tank test	Anxiolytic-like effect	[45]
Burrito	10 mg/kg	Novel tank test	Reverted caffein-induced anxiety-like behavior	[50]
Hog plum	25 mg/L	Novel tank test	Anxiolytic-like effects	[51]
Salvinorin A	0.1-0.2-µg/kg	Conditioned place preference test	Addictive behavior	[56]
Aroeira	20 µL	Pain model (induced by formalin, cinnamaldehyde, capsaicin, glutamate, acidic saline, and hypertonic saline)	Reduced the pain-like behavior	[70]
Neem fruit	1 and 2.5 mg/mL	Pain model (induced by glutamate)	Reduced pain-like behavior	[74]
Neem fruit	2.5 and 5 mg/mL	Pain model (induced by formalin)	Reduced pain-like behavior	[74]
Neem fruit	5 mg/mL	Pain model (induced by cinnamaldehyde)	Reduced pain-like behavior	[74]
Batiputá oil (kaempferol-3-O-rutinoside)	1, 2.5, and 5 mg/ml	Pain model (induced by formalin, capsaicin, acidic saline)	Reduced pain-like behavior	[80]
Batiputá oil	2.5 mg/ml	Pain model (induced by glutamate, cinnamaldehyde)	Reduced pain-like behavior	[80]
Rodents	-	-	-	-
Ayahuasca	2.5 mg/kg	Forced swimming test and open field test	Antidepressant-like effect	[113]
Matgrass	12.5 and 25 mg/kg	Elevated T-maze	Anxiolytic-like effect	[114]
Lemon verbena	15 mg/kg	Elevated plus maze	Anxiolytic-like effect	[115]
Burrito	100 mg/kg	Forced swim test	Antidepressant-like effect	[48]
Salvinorin A	0.001-1000 µg/kg	Elevated plus maze and forced swim tests	Anxiolytic-/antidepressant effects	[55]
Billygoat weed	0.5, 1 and 1.5 g/kg	Pain model (induced by formalin)	Reduced pain-like behavior	[116]
Brazil beauty-leaf	9.4 or 131 mg/kg	Pain model (induced by acetic acid)	Reduced pain-like behavior	[117]
Brazil beauty-leaf	47.9 mg/kg	Pain model (induced by glutamate)	Reduced pain-like behavior	[117]
Cranberry	50, 100, 200 mg/kg	Pain model (induced by L-arginine)	Reduced pain-like behavior	[118]

As with other animal models, zebrafish assays present certain limitations. For instance, teleost fish-specific genome duplication of some genes [26] may complicate analyses of molecular mechanisms of ATM action since genes for various putative targets may differ between species. Using experimental animal models is also limited due to the fact that animal studies do not necessarily predict human CNS phenotypes [99, 100]. For example, some adverse ATMs reactions in humans cannot be detected in animals (*e.g.*, headache, dizziness, and flushes) [101, 102] or can be problematic to mimic and record (*e.g.*, flashbacks). Moreover, there is also likely interspecies variation in pharmacokinetics and pharmacodynamics of ATM drugs (*e.g.*, the hepatobiliary toxicity in humans is poorly predicted (~50%) from animal studies [101]), that may result in the inappropriate extrapolation of animal dose to humans [103], and hence affect the overall translatability of zebrafish ATM findings to human trials.

Another general concern is the lower variability between subjects in experimental models since laboratory animals used in screening assays are often of homogenous genetic background and are housed, fed, and/or handled uniformly [101]. From this point of view, choosing more heterogenous animal populations (*e.g.*, wild-type outbred zebrafish strain) may be a potential solution based on population validity considerations [104]. Indeed, although genetically controlled inbred

Table 2. Selected open questions related the use of American Traditional Medicine (ATM) in zebrafish CNS models.

Questions
• Does acute and chronic ATM administration evoke similar (or different) effects on zebrafish neurobehavioral phenotypes?
• Are there sex-, strain- and individual differences in neurobehavioral responses to ATM therapies in zebrafish models?
• Are there transgenerational consequences (*e.g.*, epigenetic modulation) of ATM action in zebrafish CNS models?
• Pain and anxiety are common in ATM effects in zebrafish (Table **1**). Would neurobiological systems involved in pain and anxiety (*e.g.*, opioids and endocannabinoids) be most strongly impacted by ATMs, compared to other systems that are key for other CNS conditions?
• Given profiles summarized in Table 1, are ATM therapies similarly effective in treating other complex CNS disorders beyond anxiety and pain (*e.g.*, autism, schizophrenia, epilepsy) clinically and in zebrafish models?
• Are there robust differences in ATM CNS effects between adult and larval zebrafish?
• Are there specific overlapping and/or distinct targets in zebrafish for acute and chronic ATMs effects?
• Does the administration route (*e.g.*, water immersion vs. injection) impact ATMs' effects in zebrafish models?
• Can zebrafish models be used for repurposing potential ATMs and/or informing the search for novel ATMs?
• Can zebrafish models assess other complex clinical CNS phenomena (*e.g.*, withdrawal, addiction) related to ATMs' action?
• Can zebrafish models be used to study the interactions between different ATMs, as well as between ATMs and traditional CNS drugs?
• How can we increase the translatability of ATMs effects found in zebrafish to humans?
• To what extent are the effects of zebrafish ATMs *in vitro* studies translatable to live fish and mammals?

zebrafish strains may offer reproducible/reliable systems for neurogenetics research, modeling CNS disorders involves mimicking 'real' human conditions that exist in genetically heterogeneous clinical populations. Thus, using outbred populations of zebrafish can represent a more populationally valid and translationally relevant approach to address these model limitations. This would also alleviate the impact of strain-specific peculiarities of zebrafish behaviors in different tests [105], and is in line with recent rodent data that outbred strains may be better subjects for most biomedical experiments [106].

A related common problem is the translatability of ATM-related effects between species. For example, while hog plum extracts are traditionally used as an anti-inflammatory, antiseptic, analgesic, and antispasmodic ATM, the use of this plant to treat behavioral deficits clinically is not widely accepted. However, its similar anxiolytic-like effects in both rodents and zebrafish, likely due to GABA-ergic modulation [51, 52], raises the possibility of repurposing this ATM and, therefore, exploring its clinical anxiolytic potential as well. Thus, zebrafish screens for various therapeutic compounds may eventually help reveal novel, previously unrecognized neurotropic properties of some traditional ATMs.

CONCLUSION

Overall, there are many open questions regarding ATM effects and mechanisms involved in their neuropharmacological profiles (Table **2**). Here, we argue that zebrafish-based experimental models and screens can provide valuable information on molecular mechanisms of ATM effects on the brain and behavior *in vivo*. Recognizing problems with low efficacy, treatment resistance, and multiple side-effects of conventional pharmacotherapies for brain disorders [107-109], ATMs and other folk medicines may provide valuable alternative treatment for these patients. Indeed, mounting evidence shows beneficial effects of herbal remedies in various CNS disorders, including anxiety, depression, insomnia, and dementia [110-112, 119-121]. Thus, experimental animal studies, including zebrafish, can increase the safety of ATM drugs [103], as well as offer templates and models for synthesizing analogous synthetic drugs based on ATMs, but with higher efficacy and lesser adverse CNS effects. While the growing use of zebrafish in this field is unlikely to replace or reduce the need for more conventional animal (*e.g.*, rodent) studies [122], the former can offer a promising complementary or alternative model organism to probe a wide range of CNS effects of various ATMs.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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