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Gonadotropin-Releasing Hormone (GnRH) - Its Approaches to Improve Reproduction in Fish

(Hormon Pelepas Gonadotropin (GnRH) - Pendekatannya untuk Meningkatkan Pembiakan Ikan)

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ABSTRACT

This review briefly highlights previous studies on the gonadotropin-releasing hormone (GnRH) and its approaches to improving fish reproduction in the aquaculture industry. Reproductive system dysfunction of the captive fish is the main problem that has to be treated depending on the compatibility of fish species. This problem is caused by the non-synchronized maturation of female and male broodstock, and the low quality of broodstock. As shown in previous studies, induced breeding with exogenous treatment from specialized hormones could be one of the best cures for this issue. Hormonal treatments have been used by farmers to overcome the reproductive system dysfunctions in establishing captive wild or hatchery-based breeding. Although the imitation in its natural condition has been set up, for broodstock to spawn naturally problems still occur, hence the need for hormonal therapy. This review aims to deliver the results and contributions of an established artificial hormone, gonadotropin-releasing hormone analogue (GnRHa), to treat fish reproductive system dysfunction, to improve the qualities of eggs, seedlings, and broodstock, mainly to help fish farmers and can be used in the aquaculture industry to improve the reproduction of cultured fishes for sustainable aquaculture production to achieve the market demand and consumption.

Keywords: Artificial breeding; fish reproduction; GnRH analogue; gonadotropin-releasing hormone; reproductive hormones

ABSTRAK

Kajian ini secara ringkas menyerlahkan kajian terdahulu mengenai hormon pelepas gonadotropin (GnRH) dan pendekatan untuk meningkatkan pembiakan ikan dalam industri akuakultur. Disfungsi reproduktif pada ikan tawanan merupakan masalah utama yang perlu dirawat bergantung kepada keserasian spesies ikan. Masalah ini berlaku disebabkan kematangan induk betina dan jantan yang tidak berlaku serentak, serta kualiti induk yang rendah. Kajian terdahulu telah menunjukkan bahawa pembiakan teraruh dengan rawatan luaran daripada hormon khusus boleh menjadi salah satu penawar terbaik untuk masalah ini. Rawatan hormon telah menjadi penyelesaian untuk mengatasi masalah berkaitan sistem pembiakan dalam mewujudkan kurungan liar atau berasaskan penetasan. Walaupun mimikan dalam habitat semula jadinya telah dilakukan, masalah untuk anak induk bertelur secara semula jadi masih berlaku, justeru memerlukan terapi hormon. Kajian ini bertujuan untuk menyampaikan hasil dan sumbangan hormon tiruan yang telah ditetapkan, analog hormon pelepas gonadotropin (GnRHa) untuk merawat pembiakan ikan yang gagal, untuk meningkatkan kualiti telur, anak benih dan stok induk, terutamanya untuk membantu petani dan boleh digunakan oleh industri untuk menambah baik pembiakan ikan ternakan untuk pengeluaran akuakultur yang mampan bagi mencapai permintaan pasaran.

Kata kunci: Analog GnRH; hormon pelepasan gonadotropin; hormon pembiakan; pembiakan buatan; pembiakan ikan

Introduction

Aquaculture is a well-known industry and expanding rapidly in supplying animal protein for human consumption (Ahmad et al. 2021). With an increasing global population, the demand for protein food supply also becomes greater (Rahman et al. 2019). The species seed collection from the wild was found to take a long time, undependable, and economically unreasonable for a huge amount of fish culture (Marimuthu 2019). Fortunately, the production of aquaculture these days has exceeded the wild catch. In recent years, it helps supply the demand worldwide and will keep the sustainability of wild fish populations to be continuously available (Roser & Ritchie 2019).

The demand for aquaculture production was reported to be 46% of the total production in 2018 and was estimated to increase to 52% of the value for human consumption (FAO 2020). By the year 2030, aquaculture reproduction is estimated to reach up to 62% of the total production worldwide. As for now, China is on top of the list in aquaculture production with a 35% contribution to the global fish production in 2018 (FAO 2020), however, Southeast Asia is expected to uplift their aquaculture production in the future (Mayerle et al. 2020).

One of the problems encountered in aquaculture production is the seeds' insufficient supply accompanied by low-quality broodstock caused by the species' hatchery problems related to induced breeding, coordinated maturation of male and female broodstock, and low supply of high-quality broodstock (Ina-Salwany et al. 2019). In addition, the broodstock caught from the wild and nurtured in a captive environment might be incompatible with the conditions for reproduction and can cause dysfunction in the development of their reproductive system (Marimuthu 2019).

Thus, to solve these reproductive dysfunctions, induced breeding is the most acceptable method for sustainable seed production and supply (Marimuthu 2019). This method has been used in fish hatcheries production for almost 60 years (Rahman et al. 2019; Zidan et al. 2020). The important hormones necessitate in the reproductive system of fish are the gonadotropin-releasing hormone (GnRH), which triggers the secretion of the pituitary gonadotropin hormones (GTH); follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and later act on the gonads to produce sex steroid (Nyuji et al. 2020).

There are plenty of artificial breedings that use hormonal treatment in treating the fish reproductive system dysfunction in captivity, and until today, a lot of research has proved their success in fish reproduction (Sukendi et al. 2019). Gonadotropin-releasing hormone analogue (GnRHa), is an implanted GnRH that has been proven to induce the maturation of oocytes and ovulation, improving the productivity of eggs, and synchronising the spawning period in captive fishes (Superio et al. 2021). To analyse the effects of GnRHa in fish, plenty of studies have been carried out, and such attempts are still in progress with various developments in the reproductive system of fish species in the aquaculture industry. This paper will review the GnRHa in fish and its approaches to improving the reproduction of fish in captivity.

Brain-Pituitary-Gonadal Axis and Reproductive System Dysfunction in a Cultured Fish

The brain-pituitary-gonadal (BPG) axis, also known as the hypothalamic-pituitary-gonadal (HPG) axis, is crucial for the reproductive system of the fish by stimulating maturation through hormonal and neurological feedbacks in teleosts as well as other vertebrates (Borella et al. 2020). Two factors influence the gene expression in the BPG axis; the exterior factors such as feeding time and dosage and water temperature, and the interior factors such as fish growth and age (Nyuji et al. 2020). These indicators stimulate the BPG axis and GnRH release, and changes in photoperiod which were sensed in the saccus vasculosus and hypothalamus with a seasonal change sensor in the brain of the fish (Nyuji et al. 2020). The BPG axis enables vertebrates to have neuroendocrine control in complex chores such as fish reproduction, growth, metabolism, and osmoregulation (Jeffries et al. 2019; Zohar et al. 2010).

Gonadotropin-releasing hormone (GnRH) neurons usually produce GnRH-1 located in the preoptic and hypothalamic areas, which stimulates gonadotropin hormones (GTH); follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the pituitary gland (Fallah & Habibi 2020). The FSH involves in the initiation of gametogenesis, whereas the LH involves in the final maturation process (Levavi-Sivan et al. 2004). The FSH and LH are released into the bloodstream of the fish and control all features of the gonadal activities by steroidogenesis; development of the gonad, spermatogenesis, and oogenesis, gonadal sexual hormones production, spermiation, ovulation, and broodstock spawning (Muñoz-Cueto et al. 2020).

GnRH and GTH (FSH and LH) play crucial roles in the regulation of gonads in both mammals and teleosts. In teleosts, GnRH neurons directly project to the pituitary gland, and mainly control the LH release, meanwhile, in mammals, FSH and LH are released in the same gonadotroph, and obtain GnRH peptides through the vessel of the hypophyseal portal. The LH pulse is important for folliculogenesis in addition to FSH (Kanda 2019). When the fishes are cultured in captivity, most of them will show dysfunction in reproduction (Mylonas et al. 2013; Zohar & Mylonas 2001). Female fishes are common to undergo failure of final oocyte maturation (FOM), ovulation, and spawning, however, there is less dysfunction in the sperm produced by male fishes. These problems may occur from a few aspects such as the captivity-induced stress, the lack of suitable natural imitation of broodstock spawning conditions, and the lack of necessary components of nutrition. A study shows a trend that plasma such as vitellogenin and LH indicates a weak hormone response in captivated female fishes that possibly inhibit the maturity (Akhtar et al. 2017).

GONADOTROPIN-RELEASING HORMONE (GnRH) IN FISH REPRODUCTION

A key hormone that regulates reproduction in fish is GnRH. GnRH stimulates the synthesis and the release of gonadotropin hormones (GTH) from the anterior pituitary for oogenesis and spermatogenesis by stimulating the production of sex hormones in the gonads (Honji et al. 2019). Recently, there are 14 forms of GnRHs identified in invertebrates and are classified into three forms GnRH; GnRH-1, GnRH-2, and GnRH-3 (Whitlock et al. 2019). The GnRH is a decapeptide in the teleost fish and usually, the brain consist of two or three forms that is species-specific-type GnRH or seabream GnRH (GnRH-1), chicken GnRH (GnRH-2), and salmon GnRH (GnRH-3) (Nyuji et al. 2020).

A more comprehensive study of juvenile development of adult striped bass (*Morone saxatilis*) showed that the GnRH-1 was ten times more plentiful than the GnRH-2 in the pituitary gland of a sexually mature fish (Muñoz-Cueto et al. 2020). GnRH-1 is the main site that releases neurons in the hypothalamus and controls the release of gonadotropic cells from the pituitary gland, whereas, GnRH-2 is located in neurons of the midbrain tegmentum, and functions as the regulator of reproductive behaviour, meanwhile, GnRH-3 is located in the terminal nerve and in the ventral telencephalon involving in neuromodulatory system which is directly related to social behaviour for fish reproduction (Whitelock et al. 2019). In addition, to control the GTH secretion in the pituitary gland, GnRH-3 also acts as a neuromodulator in the brain (Amano 2010). GnRH-3 and GnRH-2 are also suggested to act as neuromodulators in the brain because of their immunoreactive fibres that were located in the brain and not in the part of the pituitary gland (Amano et al. 2002). There is proof suggesting GnRH-2 is involved in the regulation of feeding behaviour and has a likely mediatory role between food intake and reproduction (Somoza, Mechaly & Trudeau 2020). GnRH-2 induces anorexigenic activity in both females and male goldfishes, suggesting that GnRH-2 also acts as an appetite inhibitor in this species (Matsuda et al. 2008).

Different forms of GnRH have distinct reproductive functions, as reproduction-related changes in GnRH expression differ among GnRH forms. For example, in the female red seabream's brain and pituitary gland, GnRH-1 level increases during the breeding phase however, GnRH-2 and GnRH-3 levels in the brain are higher in the regressed phase and remain low during the breeding phase. GnRH-1 levels are higher in the sexually mature red seabream than in recrudescent fish, meanwhile, the level of GnRH-2 content remains consistent (Volkoff & Peter 1999).

Different fish species possess two or three GnRH systems depending on their lineage. Neurons belonging to these systems are all decapeptides with a conserved structure (Somoza et al. 2002). Several species of teleost have only two GnRH forms, for example, the salmon and zebrafish express GnRH-2 and GnRH-3 forms, meanwhile in catfish and eel express GnRH-1 and GnRH-2. These absent forms are compensated by the axonal projections of the remaining forms (Zohar et al. 2010). The various forms of GnRH distribution in a few fishes in a distinct area of their brain were inspected by radioimmunoassay (RIA) to examine their different functions in the brain (Amano 2010). Although within the same species, there are two or three forms of GnRH (Okubo & Nagahama 2008). Thus, to recognising the multiple forms of GnRH in the brain is required to understand fish biology and their reproductive system. The existence of GnRH-1 and GnRH-2 for the teleost brain was first found in goldfish through reversed-phase high-performance liquid chromatography (rpHPLC) in conjunction with RIA (Amano 2010). The GnRH-2 occurs in neurons within the midbrain tegmentum, whereas the GnRH-3 is present in the terminal nerve. Salmon (*Oncorhynchus masou*) has two forms of GnRH (Amano et al. 2003) meanwhile, the fishes that have three forms of GnRH are gilthead seabream (*Sparus aurata)*, African cichlid (*Haplochromis burtoni*), Mozambique tilapia *(Oreochromis mossambicus)*, European sea bass (*Dicentrarchus labrax*), and striped bass (*Morone saxatilis*) (Amano et al. 2003).

DEVELOPMENT OF GnRH AS HORMONAL THERAPIES IN CULTURED FISH

Hormonal treatments have been used to treat the reproductive system problems that occurred a long time ago in wild captured or hatchery-produced broodstock. To have a sufficient supply of the juveniles, the mass aquaculture production must increase to reach the market requirements and consumers' demands, new methods of reproduction without waiting for the spawning season are urgently needed (Mylonas et al. 2011). The efficacy of hormones is often influenced by various aspects such as species, physiological status, and amount of the hormone dosage administered (Rottmann et al. 2001). To secure sustainable fish supplies, hormones are utilized through artificial reproduction and sex reversal if one of the sexes in the same species has the capabilities to enlarge faster than the other. The differences among genders, particularly during puberty, frequently occur in teleost fish (Hoga et al. 2018).

The examples used in finfish reproduction are hormones such as human chorionic gonadotropin (hCG), pituitary extract, GTH, gonadotropin-releasing hormone analogue (GnRHa), and dopamine antagonist (e.g., domperidone, DOM) (Mohammadzadeh et al. 2020; Zohar & Mylonas 2001) that have been endorsed for commercial application in the aquaculture market worldwide (Song et al. 2020). GnRH is a neuropeptide and dopamine is a neurotransmitter released by the hypothalamus that reaches the pituitary gland of some teleost fish.

These neurons function as stimulatory and inhibitory factors for fish reproduction and are considered to be the primary modulators of gonadotropin hormone release in fish (Abdel-Latif et al. 2021; Zohar et al. 2010). Hence, an efficient method to induce ovulation in various types of fish is the usage of dopamine receptor antagonists combined with GnRHa (Abdel-Latif et al. 2021). Dopamine neurons responsible for the inhibitory control of reproduction originate in a specific nucleus of the preoptic area and directly project to the location of the pituitary gland consisting of gonadotrophic cells as shown in numerous neuroanatomical investigations (Dufour et al. 2010).

Commercial hormone including carp pituitary extracts (CPE), hCG, GTH, GnRH, GnRHa, Ovatide, Ovaryprim, Ovaprim, Ovopel, Ovupin-L, Ovulin, and Aquaspawn becomes the best method when used for captive African catfish induced spawning through injection to overcome reproduction problems by improving fertilization, hatching, and survival rate, with the possibility to produce sustainable fish supply all year round (Sukendi et al. 2019).

Ovopel is composed of mammalian GnRHa and dopamine antagonists (metoclopramide) (Souza et al. 2018). It has been used to trigger the reproduction of the wild mature asp fish (*Aspius aspius*), induce spermiation of the Amazon catfish (*Leiarius marmoratus*), and trigger the ovulation of pacu fish (*Piaractus mesopotamicu*s). Ovopel is effective in the reproductive of male tambaqui (*Colossoma macropomum*) and resulted in greater fertility and hatching rate in European Perch (*Perca fluviatilis*), when being treated with Ovopel (Souza et al. 2018).

Ovaprim is an artificially made hormone with a combination of salmon GnRHa (sGnRHa) and domperidone (Zadmajid et al. 2017). One successful injection of Ovaprim for the *longspine scraper* (*Capoeta trutta*) is likely correlated to the instigation of LH endogenous, which can only be effective at certain stages of the growth development of the fish (Zadmajid et al. 2017). Meanwhile, Ovaplant, is an artificial hormone of salmon GnRHa (sGnRHa), as the name implies, it is given to the fish by intramuscular pellet implantation, showed as a matrix of cholesterol-based spawning inducer. Previously, a dose of 150 µg of Ovaplant was correlated with a higher density of Pacu, *Piaractus mesopotamicus* fitted for induction of hormone at 35 days after implantation (DAI), when three out of five (60%) are in the maturation stage which already advanced in maturation compared to one out of five (20%) control groups. Hence, this study proved that implantation can potentially improve ovarian maturation of female fishes between DAI 0 and 35 (Kuradomi et al. 2017).

The human chorionic gonadotropin (hCG) hormone stimulates in the induction of gonadal maturation and ovulation until breeding (Putra & Mulah 2019) given the composition of LH which takes place in the ovulation process to spawn, and FSH that responsible in the process of gonad maturation. This hCG hormone in freshwater finfish is only effective in multi spawning cyprinids, such as goldfish (*Carassius auratus*) (Targońska et al. 2011), crucian carp (*C. carassius*) (Targońska et al. 2011), and barbel (*Barbus barbus*) (Targońska et al. 2011). The hCG treatment can also be effective in single-spawning cyprinids to fishes such as common dace (*Leuciscus leuciscus)* (Kucharczyk et al. 2019), and ide (*L. idus)* (L.) (Kucharczyk et al. 2020). Meanwhile, for clariid fish species, particularly catfish species, hCG treatment is effective to induce breeding (Abdel-Latif et al. 2021).

Carp pituitary extracts (CPE) are the most frequently used hormonal treatment for fish reproduction and induction (Souza et al. 2018). The CPE treatment enhances hormonal actions hence it directly gives effect the final ovaries' maturation and oocytes release. The high variable of hatching rates recorded in tambaqui (*Colossoma macropomum*), a large species of freshwater fish by using CPE treatment was mostly caused by various environmental aspects (Souza et al. 2018).

For final sexual maturation induction in fish spawning, various attempts of endocrine techniques have been applied in fish (Aizen et al. 2017; Mohammadzadeh et al. 2020). There is important usage using GnRHa compared with the other gonadotropin-based treatment such as artificial gonadotropins or pituitary of fish. The artificial GnRH eliminates the possibility of contagious disease transmission and allows the chance to apply exact doses of GnRH. In addition, it has a high frequency of similarity among species between GnRH peptides which is useful for various fish species (Gothilf & Zohar 1991; Mohammadzadeh et al. 2020).

DEVELOPMENT GONADOTROPIN-RELEASING HORMONE AGONIST

GnRH agonist is used as a fish reproduction inducer (Souza et al. 2018). Developing more dynamic GnRH analogues (agonist and antagonist) mainly depends on the improvements made during peptide synthesis (Padula 2005). GnRH analogues (GnRHa) in combination with dopamine antagonist (DA) or dopamine inhibitors have been proven to increase the efficiency in fish reproduction, mainly in species with high gonadotropin release-inhibitory hormones (Souza et al. 2018). Some of the species are common carp (*Cyprinus carpio*), catfish (*Heteropneustes fossilis*), rohu (*Labeo rohita)* and mrigal (*Cirrhinus mrigala*), nase (*Chondrostoma nasus*), pearl mullet (*Chalcalburnus tarichi*), rainbow trout (*Oncorhynchus mykiss*), lake trout (*Salvelinus namaycush*), and sockeye salmon (*Oncorhynchus nerka*) (Heyrati et al. 2007).

Dopamine functions as an inhibitor of gonadotropin hormone release hence, directly suppressing the gonadotropin hormone release and regulating the function of GnRH (Abdel-Latif et al. 2021). The neuroendocrine systems are needed to control the release of gonadotropin hormones in teleost fish. The neuroendocrine systems are needed to control the release of gonadotropin hormones in teleost fish. To control the reproduction of commercially important finfish.

VARIOUS TYPES OF GnRHa DELIVERY SYSTEM FOR A SUSTAINABLE HORMONE RELEASE IN FISH

Reproductive system control is crucial to sustaining the commercial production of hormones in the aquaculture industry (Mehdi & Ehsan 2011). The cause of dysfunction for broodstock spawning and ovulation is the failure of the pituitary gland to release gonadotropin hormones. There are two actions in the release of the gonadotropin hormones and these are by GnRH and by inhibition of dopamine of GnRH. It is important to administer the dopamine antagonist or inhibitor such as domperidone (DOM) in several fishes, which results in the release of huge amounts of luteinizing hormones (LH) (previously known as GTH-II). Excessive GnRHa dose alone is efficient in a few other injections. In some marine species, LH release is not the control of dopaminergic inhibitory, however, it is a reaction to exogenous agonist hormones (e.g., GnRHa). In various types of fishes, GnRHa is broadly useful to induce broodstock spawning. While in various marines and tropical freshwater finfishes, hormonal therapies such as pituitary homogenate, hCG, and semi-purified fish gonadotropin are used. Recently, natural GnRH is replaced and consequently, resulting in multiple increments in the secretion of LH (Mehdi & Ehsan 2011).

In previous studies, the GnRHa sustainability from the treatment by sustained-release of hormonal delivery is recommended to be more efficient for the continuous maturation of spermatogenesis and oogenesis, by the release of FSH, than with multiple injections. For example, in previous research on greater amberjack (*Seriola dumerili*), the implantation of GnRHa was proven to be more efficient to induce breeding than with multiple injections of GnRHa because the fish continuous to respond every after the implantation, breeding at 2.2 ± 1.9 average spawns per implantation (Fakriadis et al. 2019; Sarih et al. 2018).

Cholesterol pellet is made by combining cholesterol, cellulose, and GnRHa in a powder form and compressed in a pellet presser, with an occasional addition of cocoa butter (Zohar & Mylonas 2001). The cylindrical pellets (3 mm diameter × 3 mm long, 30 mg) are loaded with 25-250 µg of GnRHa and applied to the fish intraperitoneally or intramuscularly, via a small incision or using a syringe-type applicator. In the numerous batch spawner Senegalese sole (*Solea senegalensis*), in comparison between a single (Guzmán et al. 2009) and multiple GnRHa injections, two different GnRHa sustained-release delivery systems have shown remarkable results to be the most effective method to induce breeding (Agulleiro et al. 2006).

The GnRHa regulated by cholesterol-based pellet or injection has effectively induced maturation of oocytes, ovulation, and spawning in Atlantic salmon, *Salmo salar*, sea bass, *Lates calcarifer,* and gilthead seabream *Sparus aurata* (Kumakura et al. 2003). In these studies, the fish with oocytes that almost fully matured and induce the FOM, also the ovulation in the ovaries (Kumakura et al. 2003). When GnRHa was implanted alone, the induction of ovulation in the late vitellogenic females increased, whereas the fish fertility was approximately below 10% compared to when the dopamine antagonist was administered, the fertility went up to 85% caused by impairment of dopamine with final gamete maturation under convenient aquaculture environment (Saillant et al. 2021).

The ethylene-vinyl acetate copolymer (EVAc) is another GnRHa delivery system, a non-degradable copolymer of ethylene and vinyl acetate monomers in the form of microspheres or solid implants (Mylonas & Zohar 2000). The EVAc delivery system is prepared by adding the solvent-dissolved polymer to a mixture of inulin and bovine serum albumin (i/bsa) and GnRHa in powder form. A solidified sponge-like matrix consisting of polymer and i/bsa with GnRHa is a result of an evaporated solvent. The use of rubbery 2 mm-long cylindrical implants of 2 or 3 mm diameter (5 or 15 mg), usually loaded with 25-250 µg of GnRHa, and are given intramuscularly using a syringe-type applicator are the GnRHa-loaded EVAc systems applied in fish (Mylonas & Zohar 2000). GnRHa-delivery systems using EVAc are easy to imitate with 200-500 batches of implants that can be reproduced in a single preparation, therefore minimizing the production cost and GnRHa-content variation among individual implants. The application is very manageable and is not harmful to the fish, and if stored under -20 °C, the implants can sustain their efficiency for at least 3 years (Mylonas & Zohar 2000).

COMPARATIVE STUDY OF GnRHa TO IMPROVE FAST AND VAST REPRODUCTIONS IN FISH

Cholesterol pellet implantation with a combination of GnRHa and domperidone, and its effects in premature female red seabream on sexual maturation were studied (Kumakura et al. 2003). A 16-month-old sexually immature fish was intramuscularly implanted and reared for 10-20 days. Fish samples were divided into three groups for treatment: (1) control group (no implantation of GnRHa), (2) GnRHa implantation with cholesterol pellet, and (3) GnRHa implantation with cholesterol pellet + domperidone. On Day 10 post-treatment, their vitellogenesis was observed, on Day 20 post-treatment, the treated fish of groups 2 and 3, their ovulation was observed. On Day 10 post-treatment, the mean gonadosomatic index (GSI) in both groups 2 and 3 had significantly increased (1:49 ± 0:47 and 1:93 ± 0:74, respectively), meanwhile, the result of the control group is only (0:41 ± 0:03, $p < 0{:}05$). On Day 20 post-treatment, the GnRHa implanted groups had increased in the mean GSI (5:72 ± 0:94% in GnRHa while in GnRHa + domperidone is 3:71 ± 0:99%, $p < 0{:}05$), almost all fishes in both treatment groups had to go through ovulation process. This study proved that the GnRHa alone could trigger advanced maturation in red sea bream, with additionally the efficiency increases when the GnRHa is combined with DOM.

Mylonas et al. (2004) examined in their study the probability of maturing Mediterranean greater amberjack (*Seriola dumerili*) using GnRHa implants. Both female and male fishes were implanted with ethylene-vinyl acetate (EVAc) GnRHa (Zohar & Mylonas 2001) with a dose of 500 µg GnRHa. To allow the fish to undergo re-maturation, they were being implanted twice with a few day gaps in the same season of reproduction to induce additional cycles of final oocytes maturation (FOM). In the first GnRHa implantation, a group of oocytes had started FOM with the germinal vesicle at different stages of vitellogenesis, whereas several of the biggest oocytes had started FOM. For the second GnRHa implantation (15 days after the first implantation), the oocytes in the ovary almost completed their lipid droplet development while their yolk globules continued to develop. After 36 h of post-treatment, implantation with the GnRHa-delivery system induced the first broodstock spawn. The second GnRHa implantation resulted in eggs that have been fertilized at 36 h and 5 days post-treatment. Hence, after the second implantation of GnRHa, the female fish breeds twice. That gives this study a total of three broodstock spawning. Therefore, GnRHa implants can be used to induce multiple broodstock spawns of viable eggs, however, it is recommended to re-implant 15 days after the first implantation, hence, the number of spawning increases.

To identify the time course effect of FOM and ovulation, another study was conducted on the chub mackerel *Scomber japonicus* (Shiraishi et al. 2008). The GnRHa was injected at two different times, 14:00 (2:00 PM) and 02:00 (2:00 AM) h, then the FOM and the ovulation were compared. Forty fish with same species were injected with GnRHa, a dosage of 400 mg/kg body weight, suspended in coconut oil (Scott et al. 1999; Shiraishi et al. 2008) injected intramuscularly at 14:00

and 02:00 h. The time course of FOM and ovulation in fish with GnRHa injection at 02:00 h and the fish injected at 14:00 h were similar. When GnRHa was injected regardless of the timing, the ovulation began at 36 h post-injection of GnRHa (Shiraishi et al. 2008). Thus, GnRHa is proven to be effective and the FOM and the ovulation in chub mackerel follow the natural time course induced by endogenous pituitary LH, regardless of the timing of the hormonal treatments.

The river catfish, *Hemibagrus nemurus* (Adebiyi et al. 2013) also record the effect of GnRHa. The enzyme-linked immunosorbent assay (ELISA) was used to ensure the hormonal readings. Saline was used as a treatment for control and GnRHa at different dosages per body weight (BW); 5, 20, and 50 in unit µg/kg. The plasma sex steroid hormone is high even at the lowest dosage of 5 µg/kg. There was a significant increase ($p<0.05$) in GnRHa treatments in plasma sex steroid levels with 20 µg/kg and 50 µg/kg BW. The best result is with a dose of 50 µg/kg BW GnRHa, therefore, results of 5 µg/kg BW GnRHa produced slow progress in the production of steroids. To compare the three treatments of GnRHa, the dosage of 20 µg/kg and 50 µg/kg showed quicker progress than 5 µg/kg. In conclusion, steroid production of *H. nemurus* and the response towards GnRHa treatment is dependent on the dosage given. Hence, it is suggested to use a dose of 20 µg/kg BW GnRHa, to increase the sustainability in the economic aspect because there was no significant difference found between the dosage of 20 µg/kg BW GnRHa and 50 µg/kg BW GnRHa (Adebiyi et al. 2013).

Two methods were examined by another study to induce the spawning and oocyte maturation in greater amberjack (*Seriola dumerili*) through GnRHa using injections or sustained-release delivery systems (Fakriadis et al. 2019). The fish were captured in the wild and injected with GnRHa, administered thrice a week. Implantation of GnRHa is another method used, administered twice every two weeks. Mean daily relative fecundity in the implanted fish (15,170 ± 2,738 eggs kg^{-1} female day^{-1}) was significantly higher ($t1.3 = -5.24$, $P = 0.012$) in comparison with fish that was injected (6,119 ± 2,790 eggs kg^{-1} female day^{-1}). Total relative fecundity was also significantly greater in the fish that was implanted (102,402 ± 20,337 eggs kg^{-1} female) than in the injected fish (26,517 ± 9,938 eggs kg^{-1} female), however, no differences were found in the eggs' quality, embryo survival in 24 h, hatching, and larval survival in 5 days. The fully vitellogenic oocytes females suitable for broodstock spawning reduced from seven to six for the implant treatment and seven to three females for the injection treatment. Therefore, GnRHa implant is a more suitable method than abundance injections for the greater amberjack because it stimulates vitellogenesis besides involves less contact with the fish (Fakriadis et al. 2019).

A study has been performed on voluntary spawning after the injection of oxytocin along with the Ovatide, a mixture of sGnRHa (salmon GnRHa) and domperidone (dopamine antagonists) into the walking catfish (*Clarias magur)* brooders (Priyadarshi et al. 2021). A dose of 40 mIU/kg BW administration of oxytocin after 12 h injection of Ovatide showed a result in voluntary breeding of the fish (81.5% i.e., 31/38 trials), with a hatching rate of more than 70% in plain and low-cost facilities for broodstock spawning. Histology of male gonads showed a sustained sperm maturation and the gonads were ripe in both male fishes that received artificial hormones. In comparison, gamete maturation is reduced after 10 h post-injection in the control fish, and in the fish injected with Ovatide without domperidone. This showed that oxytocin act an important role in sustaining maturation in males induced by Ovatide and activating the mating behaviour which can lead to natural spawning within the catfish family (Priyadarshi et al. 2021). In this study, the results showed that oxytocin with Ovatide treatment has commercial potential in the seed production of catfish technology.

GnRH studies on the reproduction of fish that have been done successfully for decades. To conclude all of the studies above, GnRHa is proven to be effective for inducing breeding in various species of teleost fish, however, the efficiency increases when the GnRHa is combined with domperidone. For the administration of the artificial hormone, a slow-release delivery system is a more effective method in increasing the sustainability of fish in releasing oocytes and spermatocytes than with the multiple injections as it involves less contact with the fish hence reducing stress. The studies above indicated that, the dosage of 20 µg/kg BW GnRHa is effective enough to induce broodstock spawning for *H. nemurus,* however, it might not suffice for other species because of their compatibility. Nevertheless, this can be a new idea for new studies among other species.

FUTURE PROSPECT AND CONCLUSION

The GnRH has been proven to give huge effects on fish reproduction based on the research stated above (summarized in Table 1). This hormonal treatment has opened up new ideas for scientists in the related field to further explore and innovate the existing production, particularly the GnRH products for sustainable fish breeding. Artificial hormones such as Ovaprim, Ovaplant, and Ovopel are some of the hormones commercialized in the market that use GnRH with the combination of dopamine antagonists to double up the effectiveness of the artificially induced breeding. Further studies should be conducted on the possible contributions of GnRHa in fish to improve fish reproduction, the qualities of eggs, seedlings, and broodstock spawning that mainly help the aquaculture farmers, and increase the production of fish to achieve worldwide market demand. In conclusion, numerous studies showed the importance of GnRHa to improve fish reproduction. Apart from that, more research should be done on the optimization of the GnRHa treatment to synchronize more females to spawn by using alternative hormonal therapies and allow them to complete vitellogenesis and undergo spawning to achieve sustainability of the species.

TABLE 1. Summarized table of comparative studies in GnRHa used for fish reproductive system

AIM OF STUDY	METHODS	RESULTS	DISCUSSIONS	REFERENCES
To determine the outcome of cholesterol pellet implantation (GnRHa+domperidone) in pre-matured female red seabream on the sexual maturation	Implantation of cholesterol pellets with GnRHa or GnRHa+domperidone by intramuscularly	This study proved that implantation of cholesterol pellet containing GnRHa could induced vitellogenesis and ovulation in female juvenile red seabream	GnRHa combine with domperidone is much more effective as it induce and release huge number of LH and ovulation	Kumakura et al. (2003)
To determine the effects of hCG and GnRHa that were administered at two different times, 14:00 and 02:00 h	The hCG and GnRHa were administered at two different times, 14:00 and 02:00 h	Ovulation began at 36 h post-injection of GnRHa, regardless of the timing of injection	These results indicate that the time course of FOM and ovulation in the chub mackerel followed a similar pattern whether stimulated by hCG injection or spontaneous LH surge because GnRHa induce to release LH from the fish pituitary	Shiraishi et al. (2008)
To study the effect of GnRHa in river catfish (*Hemibagrus nemurus*) on sex hormones	4 treatments: 1) saline (control), 2) GnRHa at doses of (i) 5 µg/kg, (ii) 20 µg/kg, (ii) and 50 µg/kg	High doses of 20 µg/kg BW GnRHa and 50 µg/kg BW GnRHa resulted in quick response compared with the low dose of 5 µg/kg BW GnRHa	The results indicated that GnRHa increased steroid production in the plasma of river catfish. The results of this study showed that response of *H. nemurus* to GnRHa treatment and steroid production was dose dependent	Adebiyi et al. (2013)
To study the suitable methods to induce the maturation of oocyte and breeding in greater amberjack (*Seriola dumerili*), through GnRHa either using implantation or injections	GnRHa through implantation and injections. The samples were wild-captured Fish were given a GnRHa injection once a week (three injections), or a GnRHa implant every 2 weeks (two implantations)	Mean daily relative fecundity was significantly higher in the implanted fish compared to the injected fish Total relative fecundity was also significantly higher in the implanted fish compared to the injected ones	Hence, GnRHa implantation is the best method in greater amberjack compared with multiple injections of GnRHa because it triggers vitellogenesis besides less handling with the fish which can reduce stress	Fakriadis et al. (2019)
To observe the effects of oxytocin injection to lead voluntary spawning in *C. magur*	Oxytocin injected with Ovatidealong with Ovatide which consists of salmon GnRHa and domperidone	Voluntary spawning of the fish (81.5%, i.e., 31 out of 38 trials), with more than 70% hatching rate in simple and low-cost spawning facilities	Oxytocin plays a significant role in sustaining the male gamete maturation induced by Ovatide and trigger the behavioural mating response, leading to voluntary spawning in C. magur oxytocin works both by sustaining the gamete maturation process in Male catfish after inducing GnRHa-domperidone and stimulate behavioural responses needed for mating	Priyadarshi et al. (2021)

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