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Bioactives From Marine Animals: Potential Benefits for Human Reproductive Health

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Reproductive and sexual health issues, including infertility and sexual dysfunctions (SD), are common concerns affecting millions of reproductive age worldwide. Scattered literature reports that marine animals such as oysters, sea cucumbers, seahorses and spoon worms have unique bioactive compounds like saponins, steroids, seahorse-derived hydrolysates, polypeptide, oligopeptides and essential trace elements that significantly improve infertility, hormonal imbalance, SD, and impotence. In addition, these compounds have exhibited pharmacological properties against reproductive problems due to diabetes and exposure to electromagnetic fields, cyclophosphamide, or a high exercise load. This review presents the first critical assessment of the advances in understanding and applying bioactives from marine organisms to support human reproductive health. Key knowledge and technical gaps have been identified for future research to improve the lack of in-depth understanding of the mechanism and action of these bioactives in human clinical studies. There is a need to develop simple, selective, low-cost, and scalable processes to isolate and purify individual bioactive compounds for industrial applications. The optimizing culturing and farming conditions for specific bioactive compounds from targeted species are suggested for sustainable production. The review indicates a promising future of extracts and marine-derived bioactives as functional foods in preventing and managing human reproductive health issues, but mechanistic studies and further clinical trials are urgently required to evaluate their efficacy and safety.

Keywords: bioactive compounds, reproductive health, sea cucumber, oyster, seahorse, sea worm, marine, sexual health

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INTRODUCTION

Reproductive and sexual health problems have troubled a significant proportion of the world population (McCool-Myers et al., 2018; Sun et al., 2019; Szamatowicz and Szamatowicz, 2020). Notably, a comprehensive assessment from 195 nations and regions between 1990 and 2017 indicates that infertility has increased globally over the observational period, and this increasing

trend exists in all countries regardless of the socio-demographic index (Sun et al., 2019). According to Szamatowicz and Szamatowicz (2020), around 100 - 140 million people (50 -70 million couples) in the world are suffered infertility, and the decrease in semen quality is accounted for nearly a quarter of cases (Salas-Huetos et al., 2017). Levine et al. (2017) reported a significant decline in sperm concentration (52.4%, 1.4%/year) or total sperm count (59.3%; 1.6%/year) in men across North America, Europe, Australia, and New Zealand between 1973 and 2011. Additionally, SD such as impotence, an essential indicator of sexual health, has affected 52% of Massachusetts men of 40-70 years old (Feldman et al., 1994). Furthermore, about 26 cases per 1,000 Massachusetts men of 40 - 69 years old suffered erectile dysfunction (ED), which is significantly associated with aging, education, or diseases such as diabetes, heart disease, and hypertension (Johannes et al., 2000). Regarding women in the reproductive stage, 12.7% of the USA females need helps for fertility (Carson and Kallen, 2021), while 41% of the females in the world were affected by SD (McCool-Myers et al., 2018). Since sexual and reproductive health is closely linked to general health and wellbeing, infertility and other diseases, more efforts should be made to improve reproductive health.

Growing attention has been focused on discovering natural health products and derivatives of natural products from marine organisms due to their safety, high nutrition contents of trace elements and unique bioactive compounds that exhibit health beneficial effects. For example, some scientific evidence indicates the pharmacological properties of sea cucumbers, oysters, spoon/sea worms, and sea horses can benefit human sexual and reproductive health (Matsuda and Walanabe, 2003; D'Aniello et al., 2012; Moghadam et al., 2016; Sudirman et al., 2021). These functions are summarized in **Figure 1** and **Table 1**. Notably, sea cucumber and oyster extracts exhibit the protecting function against damages caused by methotrexate, electromagnetic field, and cyclophosphamide (Vasei et al., 2015; Saad et al., 2018; Li et al., 2020). In addition, seahorse hydrolysate improves reproductive hormone levels (Kim et al., 2016b), and oyster oligopeptides and polypeptide and sea/spoon worm peptides can enhance sexual function (Kim et al., 2016a; Zhang et al., 2018; Chen et al., 2019b). Furthermore, sea slug exhibits aphrodisiac properties (Hashim et al., 2014). Importantly, the bioactive compounds and extracts from these organisms can support fertility by enhancing sperm or oocyte maturation (Haryanto et al., 2016; Riani et al., 2017; Sudirman et al., 2021). Marine-derived bioactive substances have continuously gained considerable attention for reproductive health, but there is a lack of a systematic review of the scientific advances and applications. This review, therefore, aims to critically assess published literature to understand the scientific evidence for the efficacy and benefits of using bioactives from marine organisms to support human sexual function and reproductive health. In addition, we highlight the need to understand pharmacological properties and potential compounds and identify knowledge gaps, technical needs and directions for future research in developing functional foods, nutraceuticals, and therapeutics against human reproductive and sexual health issues. Scientific studies published between 2010 and 2021 in PubMed, Scopus and Web of Science were included in this review using keywords "marine", "reproductive health" and "sexual health". Publications that do not specifically address the changes in reproductive functions were excluded, resulting in 35 articles selected in this review.

HUMAN REPRODUCTIVE HEALTH BENEFITS FROM MARINE ANIMALS

Protecting Effects and Antioxidant Activities

Numerous factors have been identified as possible causes of SD and reproductive issues. For example, male infertility is caused by oxidative stress (OS) associated with environmental and lifestyle factors, including pollution, radiation, smoking and drugs, and systematic pathologies such as diabetes and cancer (Agarwal et al., 2018). In addition, the excessive amount of reactive oxygen species (ROS) can significantly damage the sperm antioxidant system, and sub-fertile and infertile males significantly have high ROS in the reproductive tract to impair reproductive cells (Martin-Hidalgo et al., 2019). Regarding female infertility, OS negatively affects fertility by causing reproductive cell membrane lipid peroxidation, cellular protein oxidation, and DNA damage (Smits et al., 2018; Noh et al., 2020).

Antioxidants can be a promising solution against OS since it plays a vital role to protect the reproductive system at the cellular response level against OS (Agarwal et al., 2018; Martin-Hidalgo et al., 2019; Noh et al., 2020). The intake of antioxidants can improve semen quality and prevent DNA damage (Lloyd and Hornsby, 2009; Moghadam et al., 2016; Martin-Hidalgo et al., 2019). For example, the polysaccharides such as antihypercholesterolemic found in sea cucumber, *Holothurian nobilis* could inhibit lipid peroxidation and improve the healing process of interstitial cells in hypercholesterolemia rats (Ulhusna et al., 2020). Saad et al. (2018) reported that the extract of sea cucumber, *H. atra* could protect testicular cytotoxicity and dysfunction induced by methotrexate in a rat model. Moghadam et al. (2016) suggested that the extracted saponin from sea cucumber *H. leucospilota* could enhance the maturation of pre-antral follicles in mice through limiting OS and TNF-α expression to induce antioxidant enzyme activity.

Intensive exercises can negatively impact the reproductive tissues in the rat by enhancing ROS generation, resulting in testicular spermatogenic and steroidogenic disorders. Oyster peptide supplement could significantly support the function of the hypothalamus-pituitary gonad axis in male rates during heavy load training. This supplement can considerably reduce OS in testis by up-regulating steroidogenic enzyme expression to promote steroidogenesis and spermatogenesis (Jin et al., 2021b). In another study, oyster peptides and oyster powder were used to feed rats with reproductive dysfunction induced by cyclophosphamide. The results indicate that oyster peptides

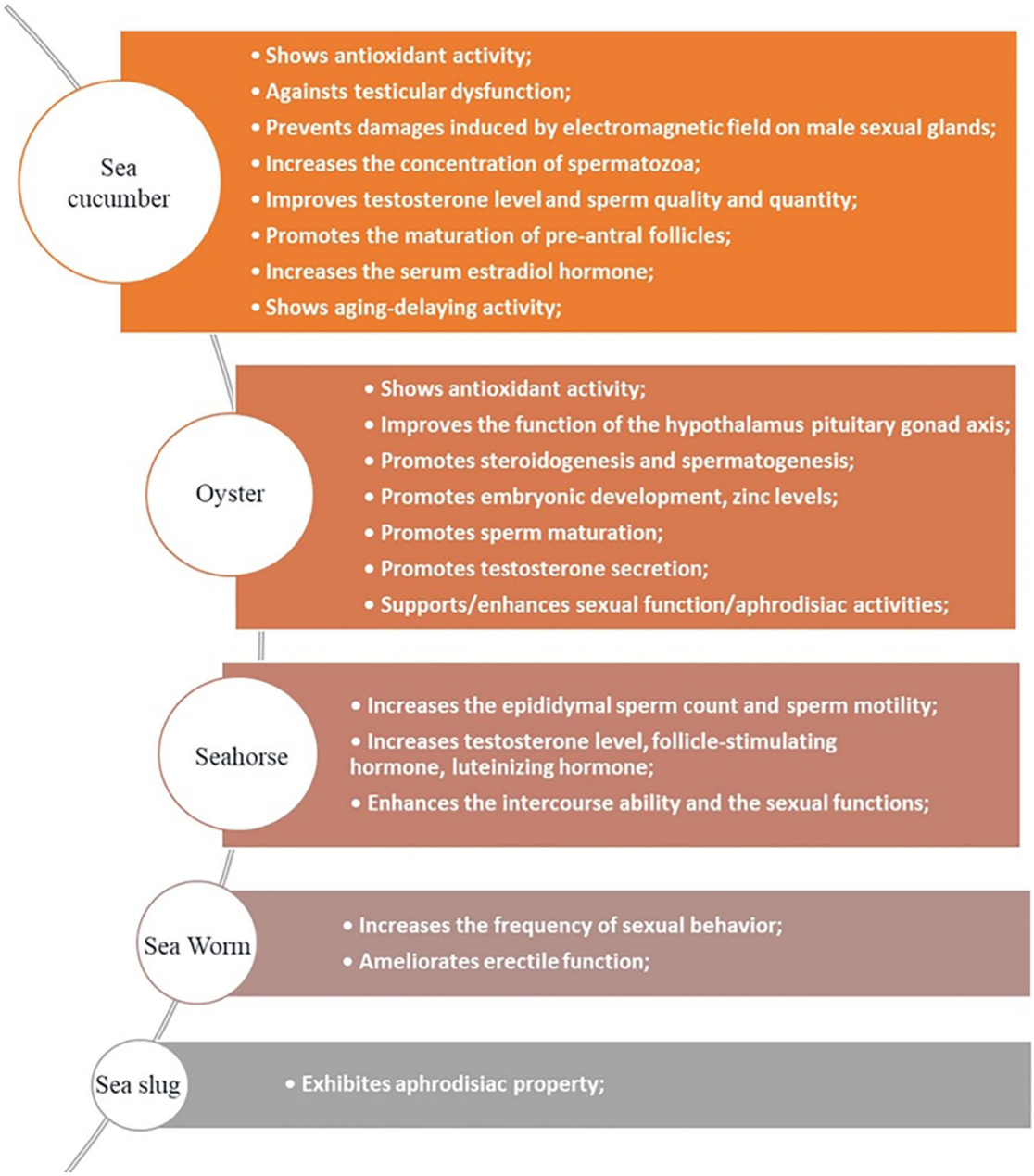

FIGURE 1 | A schematic summary of a range of marine animals reported with various functions to improve human reproductive health. These animals include sea cucumber, oyster, seahorse, sea worm and sea slug.

exhibit a beneficial effect on reproductive injury by positively influencing the biochemical parameters of blood, the pathological state of the testes and kidneys, and reducing OS responses (Li et al., 2020). According to Zhang et al. (2021b), peptides from oyster hydrolysate can be used to prevent reproductive injury and spermatogenesis disorders induced by triptolide. Although the role of antioxidants from marine organisms has been explored as a possible treatment option for reproductive issues, few bioactive compounds have been identified, characterized and purified to elucidate their unique functions. Additionally, some mechanisms of action have remained unknown and limited numbers of marine species have been investigated for those benefits.

Fertility Improvement

Infertility is defined as being unable to become pregnant after at least one year of unprotected sex (Vander Borght and Wyns, 2018). It affects approximately 8-12% of global couples during

TABLE 1 | Summary of marine animals and their potential bioactive compounds reported to exhibit benefit to human sexual function and reproduction health.

General functions	Species	Extracts/ fractions	Tested doses	Cell/ Animal model	Efficacy and mechanisms	References
Protective effects and antioxidant activity	Sea cucumber	polysaccharides	400 mg/kg of bw	rat	prevented lipid peroxidation, supported interstitial cells during the healing process	(Ulhusna et al., 2020)
		body wall extract	300 mg/kg bw	rat	protected against testicular cytotoxicity and dysfunction	(Saad et al., 2018)
		Saponin (triterpenoid glycosides)	0, 1, 2, 4 and 8 μg/ml saponin	mice oocytes, granulosa cells	improved of maturation rate; enhanced egg follicle growth; decreased oxidative stress and TNF-α expression	(Moghadam et al., 2016)
		aqua extract	N/A	mice	prevented damages on male sexual glands	
	Oysters	oyster peptide	intragastric administrated with 1.2 g/kg bw/day	rat	improved function of HPG axis; reduced oxidative stress in the testis; up-regulated expression of steroidogenic enzymes; promoted steroidogenesis and spermatogenesis	(Jin et al., 2021b)
		oyster peptides	0.2 and 0.3 g/kg bw/day	rat	improved reproductive function; increased androgen level in blood; improved pathological state and oxidative stress state	(Li et al., 2020)
Fertility improvement	Sea cucumber	saponin (triterpenoid glycosides)	1 & 2 μg/ml saponin	mice	promoted maturation of oocytes	(Moghadam et al., 2016)
		body wall methanol extract	5, 10, 20, 30 μg/mL (immersion)	mice	improved oocyte maturation	(Khalilzadeh et al., 2016)
		powder steroid content	10, 30, and 50μg of steroid/ 100g bw	mice	increased the concentration of spermatozoa	(Riani et al., 2017)
		aqua extract	N/A	mice	prevented damages on male sexual glands	(Vasei et al., 2015)
	Oyster	soft-body sites extraction	N/A	rat	improved concentrations and motility function of sperm	(Miki et al., 2011)
		oyster extract	Trial 1: 20, 40, 80 g/kg diet Trial 2: 109 g/kg diet	mice	reduced the rate of reproductive failure and embryonic defects; increased sperm motility	(Matsuda and Walanabe, 2003)
	Seahorse	acetic ether extracts	0.9 g dry seahorse/kg bw	mice	increased epididymal sperm count and sperm motility	(Xu et al., 2014)
		Peptide/enzymatic hydrolysate	4, 8, and 20 mg/kg	rat	improved reproductive; increased the level of testosterone, follicle-stimulating hormone, luteinizing hormone, sperm count, and motility	(Sudirman et al., 2021)
Improving reproductive hormone	Sea cucumber	head and body powder	diets of 12% sea cucumber powder	rat	increased testes weight, testosterone level, concentration, and mobility of spermatozoa	(Ikram et al., 2018)
		alcoholic extract or non-polar extract	injection of 100 and 200 mg/ kg	Molly fish	stimulated body testosterone and cholesterol levels	(Golestani et al., 2016)
		dry/frozen sandfish steroid	0,5 ml of sandfish steroid 0,4 g/ml	rooters	improved testosterone and cholesterol concentration	(Riani et al., 2013)
		meat powder (30 μg steroid/100 g)		rats	increased estradiol hormone	(Riani et al., 2016)
	Oyster	oyster peptide	The peptide-rich preparation of >95% peptides, <3000 Da	Mouse, Leydig-derived TM3 cells	enhanced the contents of serum testosterone, NO and cAMP in male mice; up-regulated the expression of Areg and Acvr2b	(Zhang et al., 2021a)
		oyster oligopeptide	0.5, 1.2, 2.0 g/kg bw/day	rat	promoted the synthesis of testosterone; reduced oxidative stress in testis	(Jin et al., 2021a)
	Seahorse	hydrolysates	rondo cells were treated at 0.05, 0.2, 0.5 and 1 mg/mL, while mice were orally administered 25 mg/kg hydrolysates	mice	increased sperm motility and testosterone level; stimulated the proliferation of TM3 cells	(Kim et al., 2016b)
		water extract	100, 500, 1000mg/kg	mice	increased testes weight, sperm count, sperm motility and serum testosterone level	(Park et al., 2015)
Enhancing sexual function	Oyster	small molecule polypeptide	N/A	mice	enhanced sexual function; improved mating ability, weight and organ coefficient of gonad and sperm qualities; increased content of cholesterol and sex hormones in serum and NO in the penis; improved expression of sexual function-related genes	(Chen et al., 2019b)

(Continued)

TABLE 1 | Continued

General functions	Species	Extracts/ fractions	Tested doses	Cell/ Animal model	Efficacy and mechanisms	References
		oyster oligopeptides	640 oyster oligopeptides + 110 walnut oligopeptides + 220 yam polysaccharide mg/ kg bw	mice	improved the sexual function	(Zhang et al., 2018)
		oyster oligopeptides	62.5 mg/kg ginger oligopeptides + 160.0 mg/kg oyster oligopeptides	rat	improved male sexual function; elevated serum nitric oxide, testosterone, and cGMP contents; decreased corpus cavernosum phosphodiesterase-5 content	(Li et al., 2021)
		Enzymatic hydrolysate of oyster	0.103, 0.308 and 0.617 g/kg bw/day	rat	promote the synthesis of testosterone; stimulate the synthesis of luteinizing hormone; increase serum NO content	(Wang et al., 2020)
	Sea worm/ spoon worm	isolated peptide (DDL, 361.15 Da)	N/A		enhance erectile function; increase the levels of NO and cGMP	(Ryu et al., 2014)
		active peptide	100 or 500mg/kg/d sea worm peptide.	Rat	improved erectile function; improved intracavernosal pressure; increased NO and cGMP activities; supported eNOS and nNOS expression and smooth muscle distribution in corpus cavernosum	(Kim et al., 2016a)
		hydrolysate powder	20, 100, 500 mg/kg	rat	enhance sexual function	(Paick et al., 2016)
Aphrodisiac properties	Oyster	the alcalase-treated oyster meat	250 mg/kg bw	mice	induced aphrodisiac activities; enhance sexual behavior	(Zhang et al., 2019)
		ethanol extract and aqueous extract	50, 100, 200 mg/kg	mice	increased the number of mating behavior	(Ridzwan et al., 2013)
	Sea slugs	aqueous extract and lipid extract	50, 100, 200 mg/kg	rat	improved frequency of mating behavior	(Hashim et al., 2014)
	Seahorse	*Hippocampus* capsule	0.095, 0.135 and 0.405 g/kg	rat	enhance intercourse ability; shorten the latency of males catching females and ejaculation after their combination	(Xu et al., 2003)
		Haima Zhuangyang capsule	0.54, 0.70 and 1.40 g/kg	rat	increased the mating ability	(Lu et al., 2001)

N/A, indicates as not available.

the reproductive period. Recently, Thoma et al. (2021) reported that infertility had been overlooked in sexual and reproductive health, even though 10 - 25% of couples (from 48 to 180 million people) have suffered. According to Deyhoul et al. (2017), infertility is commonly associated with reproductive system disorders or diseases, hormonal issues, aging, drinking and smoking, stress, and other unknown causes. Additionally, exposure to environmental pollutants and toxins can negatively affect reproductive cells, leading to infertility (Thoma et al., 2021). Infertility treatments vary, including conventional solutions such as hormone therapy or *in vitro* fertilization. However, marine natural alternatives have gained more interest since they are safe and effective solutions and provide various pharmaceutically significant bioactivities to benefit human health, including protections against reproductive health disorders.

Recent studies have confirmed the potential application of marine animal-derived bioactive compounds in supporting human fertility. Particularly, at a given dose, saponin as triterpenoid glycosides of sea cucumber, *H. leucospilota* can positively affect *in vitro* maturation of oocytes. The extracted saponin at a 1 or 2 μg/ml concentration increased follicle growth and superoxide dismutase SOD activity and inhibited ROS formation and TNF-α expression in granulosa cells. However, the mechanisms of saponin action on oocyte and granulosa cells need further investigations (Moghadam et al., 2016). Similar research has been performed to evaluate the effect of Persian Gulf Sea cucumber, *H. leucospilota* Brandt, body wall methanol extract on *in vitro* maturation of immature mouse oocytes. The results show that the extraction can enhance the maturation level of oocytes. Furthermore, the treated oocytes at 20 μg/mL of this sea cucumber extract have the highest percentage of Metaphase II stage (Khalilzadeh et al., 2016). According to Riani et al. (2017), sea cucumber also exhibits the pharmaceutical potential for enhancing the quality of male reproduction. Male mice were given the sea cucumber (*Holothuria scabra*) powder at 10, 30, and 50 μg of steroid/100g body weight during 12 days. The results indicate that the powders significantly improved semen concentration at a given dose of 10 μg of steroid/100 g body weight.

Zinc is an essential element for regular reproductive activity and semen quality. Zn deficiency impedes spermatogenesis, associated with sperm abnormalities and depression of sperm motility. Additionally, the serum testosterone level, seminal plasma, and total seminal zinc loss per ejaculate in young males are negatively influenced by zinc depletion in a short period (Hunt et al., 1992; Matsuda and Walanabe, 2003; Fallah et al., 2018). The oyster extract, containing significant amounts

of zinc, exhibited supportive functions to reproductive health through improving embryonic development, concentrations of zinc serum and semen maturation (Matsuda and Walanabe, 2003; Miki et al., 2011). For example, Miki et al. (2011) evaluated the effects of the oyster extract on animals with low semen concentration of 1.3 x 10^7/ml (the standard level of sperm concentration was >2 x 10^7/ml) or low concentration of motile sperm of 1 x 10^6/ml (the standard level of progressively motile sperm was > 5 x 10^6/ml). The results show a significant increase in the semen concentrations that reached the standard levels after administration for 8 weeks in both treatments. Therefore, the oyster extract has pharmacological activities to address semen concerns, including dysfunction and low concentrations. According to Matsuda and Walanabe (2003), a significant decrease in body weight, testis weight and semen quality were found in male mice with zinc deficiency for 12 weeks, whereas feeding oyster extract (20, 40 or 80 g/kg of dried oyster extract) could prevent reproductive failure, embryonic defects and declined semen motility. However, those authors also suggested that other nutrients found in oyster extracts, such as taurine and glycogen, may be associated with the recovery of reproductive function.

Seahorses have been commonly used as a traditional remedy in some Asian cultures for centuries, as seahorses have the potential to cure some diseases such as infertility (Xu et al., 2014; Zhang et al., 2017; Sudirman et al., 2021). Notably, seahorse extracts showed protective effects against oligospermatism by impairing benign prostatic hyperplasia symptoms and reversing oligospermatism (Xu et al., 2014). The cyclophosphamide (CP)-induced mice fed 1.0 g/kg body weight of seahorses acetic extracts for 30 days had significantly higher epididymal sperm count and sperm motility than the control group (Xu et al., 2014). According to Sudirman et al. (2021), seahorse, *H. kuda*, peptide hydrolysate could prevent reproductive dysfunction in diabetic rats by improving testosterone level, follicle-stimulating hormone, luteinizing hormone and semen functions. Particularly, diabetic rats fed on seahorse hydrolysate (20 mg/kg) exhibited inhibiting lipid peroxidation, elevating antioxidant enzyme activity and restoring seminiferous tubule morphology in testes.

Bivalves such as blood clam *(Scapharca broughtonii)* are rich in D-aspartate and *N*-Methyl-D-aspartic acid (NMDA) that are found in the neuroendocrine systems and associate with hormone production (Tsesarskaia et al., 2009). D-aspartate is involved in luteinizing hormone and testosterone release, and supplementation of D-aspartate has positive effects on sperm motility (Topo et al., 2009; D'Aniello et al., 2012). According to D'Aniello et al. (2012), taking D-aspartate for two to three months can significantly improve spermatozoa count and mobility in humans. The commercial form of D-aspartate was used in humans by D'Aniello et al. (2012). However, by now, limited research has been conducted regarding the extraction, purification and uses of bivalve-derived D-aspartate and N-Methyl-D-aspartic acid (NMDA) as bioactive compounds or food supplements to support men's fertility. Furthermore, research into identifying new bivalve species containing D-aspartate and NMDA is strongly encouraged since limited blood clam populations have been studied.

Reproductive and Sex Hormone Production

Testosterone, one of three important steroids, is produced by steroidogenesis that is essential for general wellbeing and the development of the male reproductive system (Andersen et al., 2011). Testosterone generally affects almost every organ in the body, including reproductive functions such as promoting and supporting spermatogenesis, sperm maturation, accessory organs, sexual desire and secondary sexual characteristic development (Andersen et al., 2011; Chen et al., 2019a). However, the imbalanced testosterone level has been associated with a wide range of commonly clinical diseases, including SD and a decline in male reproductive capacity (Petak et al., 2002; Chen et al., 2019a). According to statistics, low testosterone level or low sperm count occur in 35% of infertile couples (Odisho et al., 2014) and lower total serum testosterone was observed as 20%, 30% and 50% in male groups of 60, 70 and 80 years old, respectively in the Baltimore Longitudinal Study on Aging (Harman et al., 2001). In contrast, the lower total serum testosterone was found in 12.3% of men aged 40 to 70 with three or more symptoms of hypogonadism in the Massachusetts Aging Male Study report (Araujo et al., 2004) and 5.6% of men aged 30 to 70 being hypogonadal from the Boston Area Community Health Study (Araujo et al., 2007). Approximately 6.5 million American males between 30 and 79 years old will have symptomatic androgen deficiency by 2025 (Araujo et al., 2007). Various treatments, including hormone replacement therapy, have been explored to address reproductive and sexual issues caused by low hormone levels (Chen et al., 2019a).

Sea cucumber has a bioactive potency that could improve testosterone level and sperm quality and quantity (Golestanin et al., 2016; Ikram et al., 2018). The extracts of sea cucumber positively influenced the production of steroid hormones in rats, fish, and roosters. For example, Ikram et al. (2018) investigated the effects of sea cucumber, *Scincus scincus* extract on testosterone secretion and abundance, and semen quality of rats. The animals were fed with experimental diets containing 12% of either body (SB) or head (SH) of sea cucumber. The body weight, the relative weight of the testes and testosterone level in experimental rats were significantly improved in comparison with control groups. Furthermore, a significant increase in semen concentration (235.37x10^6/ml) and motility (62%) were observed in those sea cucumber treatments. In other animal studies, injection of alcoholic extract (200 mg/kg) or non-polar extract (100 and 200 mg/kg) of Persian Gulf Sea cucumber significantly dismissed body testosterone and cholesterol levels in the molly fish (Golestani et al., 2016). The rooters fed 0.5 ml of dry/frozen sandfish steroid 0.4g/ml were able to elevate testosterone and cholesterol levels in blood serum, fastening secondary reproduction characteristics and promoting growth (Riani et al., 2013).

Oysters contain various bioactive compounds, a great source of protein and trace elements such as zinc, taurine, which may

support sexual development, sexual function, hormone production, and reproductive cells (Jin et al., 2021a; Hao et al., 2022). In recent years, research using animal models has confirmed that oyster peptides have a strong antioxidant effect and can stimulate testosterone secretion and enhance sexual function (Zhang et al., 2018; Chen et al., 2019b; Jin et al., 2021a). Remarkably, the treatment with a medium (1.2 g/kg bw) dose of oyster oligopeptide had positive effects on testosterone production by reducing OS in testis and preventing the formation of cyclophosphamide-induced partial androgen deficiency of ageing males (Jin et al., 2021a). According to Zhang et al. (2021a), oyster peptide (in which >95% peptides were <3000 Da) from *Crassostrea gigas* can improve the serum testosterone and cyclic adenosine monophosphate (cAMP) in male mice.

Seahorse-derived hydrolysates have positive effects on male reproductive health due to improving the serum testosterone level (Kim et al., 2016b). Male mice with a daily intake of hydrolysates from seahorse, *H. abdominalis* for 12 weeks showed increased sperm motility and testosterone level. It was suggested that the hydrolysates stimulate the proliferation of TM3 cells *via* the AKT, ERK, and JNK pathways (Kim et al., 2016b). In another research, Park et al. (2015) reported that water extract of seahorse *Hippocampus* significantly increased the absolute and relative testes weight, semen parameters, and testosterone concentration in cyclophosphamide (CP) treated animals compared to the control group.

Enhancing Sexual Function

Sexuality is one of the critical indicators for human health and wellbeing that significantly contributes to the quality of life. Good health is commonly linked to normal or healthy sexual function, whereas poor life quality, significant psychological distress and many diseases are associated with sexual issues (Balon, 2017; Soldati et al., 2020). SD is recognized as incapacity to sexually respond or experience sexual pleasure despite adequate stimulation (Soldati et al., 2020). It is generally related to disorders in desire, arousal, orgasm, and pain in women, while ED, premature/delayed ejaculation, hypoactive sexual desire disorder were commonly found in men (Krakowsky and Grober, 2018; Chen et al., 2019a; Soldati et al., 2020). Between 20 and 30% of adult men worldwide experienced at least one type of sexual disorder, and the number was higher with an increase in age (Lewis et al., 2010; Berger et al., 2016). Importantly, males at the reproductive stage frequently suffer SD, which causes infertility in some instances (Lotti and Maggi, 2018). ED, one of the most common SD, were observed in 31.7%, 179 out of 810 Australian men from 35 to 80-year-old residing in northern and western Adelaide, Australia (Martin et al., 2014). Regarding women's sexual health, SD was reported to negatively influence up to 41% of women at the reproductive stage worldwide (McCool-Myers et al., 2018). According to certain studies, 5.8% of women reported symptoms of SD, while 15.5% of females experienced lifelong SD in the United Kingdom (Burri and Spector, 2011). Australian research indicates that 36% of females suffered at least one type of sexual difficulty a year (Smith et al., 2012). Among the women age group of 19-40 years old, more than haft of females (53%) had at least one symptom of SD; while it was 31% for males in Sweden (Ljungman et al., 2020). Furthermore, Ambler et al. (2012) reported that the prevalence of SD was between 25% and 63%, and the figures were even higher in postmenopausal women with rates between 68% and 86.5%. The solutions for addressing sexual problems have been investigated, including synthesized compounds such as sildenafil, tadalafil, and phosphodiesterase-5 (PDE5) inhibitors (Balon, 2017; Hess and Boehmer, 2020). However, the side effects of taking synthesised compounds, including anxiety, headaches, high blood pressure or increased heart rate, have been recently reported (Hess and Boehmer, 2020). Therefore, the use of natural alternatives and their bioactive components is a promising solution and is highly recommended in the future study.

Oysters are rich in nutritional and medicinal value that are believed to have significant effects on nourishing kidneys and remitting fatigue in traditional Chinese medicine (Luo et al., 2021; Zhang et al., 2019). They are also traditionally used as an aphrodisiac in Western countries (Ridzwan et al., 2013). Recent studies have reported its medical applications in improving male sexual function. For example, Chen et al. (2019b) reported that small-molecule polypeptide of Pacific oysters could enhance the sexual function of male mice by improving the mating ability, weight and organ coefficient of gonad and sperm qualities, increasing the content of cholesterol and sex hormones in serum and nitric oxide (NO) in the penis, and improving the expression of sexual function-related genes in mice. Moreover, the degree of sexual function enhancement could have dose-dependency within a certain range. Zhang et al. (2018) suggested that feeding male mice with oyster oligopeptides, together with walnut oligopeptides and yam polysaccharides (640 + 110 + 220 mg/kg bw) could improve the sexual function in male mice. In a similar study, the combination oligopeptides isolated from ginseng (GOPs) and oyster (OOPs) at the level of 62.5 mg kg^{-1} GOPs or 60.0 mg kg^{-1} OOPs had the best effects in improving male sexual behavior, serum NO, testosterone, and cyclic guanosine monophosphate (cGMP) contents and decreasing PDE5 content. These oligopeptides could be considered a natural alternative for enhancing male sexual function (Li et al., 2021). Feeding oyster hydrolysate supplementation (0.617, 0.308, 0.103 g/kg bw per day) had significant effects on alleviating ED and promoted the synthesis of testosterone by stimulating the synthesis of luteinizing hormone, which then increased the serum NO content through the NO-cyclic guanosine monophosphate (NO-cGMP) signaling pathway (Wang et al., 2020). Interestingly, the research results indicate that fresh oyster extract can also promote and support healthy sexual function and endurance by inhibiting the activity of PDE5 (Li et al., 2021). PDE5 inhibitors are a group of medications commonly used to treat ED or SD in men (Ahmed et al., 2021).

Seahorse, *Hippocampus* species, have been widely used as a traditional folk medicine for ED treatment, enhancing the intercourse ability and sexual functions, which have a long history in some Asian cultures (Chen et al., 2015; Cui et al., 2021). Those pharmacology effects lead to some available commercial products on the markets (Chen et al., 2015).

Notably, the hormone-like activity of *Hippocampus* was investigated for treating ED during the past years. The significant enhancement in the intercourse ability and the sexual functions were observed in male rats fed on *Hippocampus* capsule twice a day for 12 days at doses of 0.095, 0.135 and 0.405 g/kg (Xu et al., 2003). Similarly, rats given doses of 0.54, 0.70 and 1.40 g/kg of the Haima Zhuangyang capsule for 20 days significantly had more mating activities but reduced the incubation period for the erection and supported kidney function (Lu et al., 2001). In another report, the *Hippocampus* capsule increased the sexual activities in mature male rats and reduced males' latency catching females and ejaculation (Xu et al., 2003).

Echiurans, known as sea worms, commonly found in North China, Korea, and Japan, are also known to have positive effects on ED (Ryu et al., 2014; Kim et al., 2016a). Kim et al. (2016a) evaluated the effects of the active peptide from spoon worm, *Urechis unicinctus* by high temperature/pressure and ultra-wave assisted lysis on ED in streptozotocin-induced diabetic rats. The results indicate that active peptides of spoon worm could prevent ED in a streptozotocin-induced diabetic rat by improving levels of NO and cGMP, while reducing activity and expression eNOS and nNOS. The *in vitro* study by Ryu et al. (2014) also confirms that the isolated peptide from spoon worm may enhance erectile function by increasing the levels of NO and cGMP.

Aphrodisiac Properties

Low sexual desire/pleasure, loss of libido or sexual attraction are usual sexual concerns that may occur in many men and women at some stages of their life. According to Parish and Hahn (2016), quality of life, general happiness and satisfaction with partners, positive emotion are negatively affected by the loss of sexual desire. Poor relationships, aging, stress, anxiety, and exhaustion are the major causes. Besides, it is also linked to other health issues (Parish and Hahn, 2016). The aphrodisiacs are substances that have generally been used to increase libido, potency, sexual attraction, sexual pleasure and sexual performance in both males and females (Sandroni, 2001; Bella and Shamloul., 2014; Hess and Boehmer, 2020). Synthesized compounds such as Phosphodiesterase V inhibitors (sildenafil, tadalafil, and vardenafil), Yohimbine, Steroid hormones (dehydroepiandrosterone – DHEA), Flibanserin, Arginine, Phenethylamines, Gamma-hydroxybutyric acid (GHB) and its precursors have been increasingly popular in recent years to enhance erectile function, sexual arousal and desire (Hess and Boehmer, 2020). However, intensive side effects and intoxications have been recently reported by Hess and Boehmer (2020) for some synthetic products that cause an increasing demand for safe and effective sources such as ginko, ashwaganda, maca root, panax ginseng and seafood.

There is growing scientific evidence to confirm the aphrodisiac values of sea animals. Marine organisms such as oysters, sea horses, spoon worms and sea slugs have been reported to possess aphrodisiac values (Ridzwan et al., 2013; Rosa et al., 2013; Hashim et al., 2014; Kim et al., 2016a). Oysters have been taken to enhance sexual desire and performance since ancient times and there are available scientific evidence to confirm the supporting functions of this bivalve species. For example, Ridzwan et al. (2013) experimented with screening the aphrodisiac property in the local oyster of *Crassostrea iredalei*. Mice treated with oyster ethanol extract exhibited mating behavior at the dose levels of 50, 100 and 200 mg/kg compared to aqueous extract. According to Zhang et al. (2019), oyster meat and its hydrolysates showed antioxidant and aphrodisiac activities and significantly improved sexual performance both *in vitro* and *in vivo*. The enhancement of sexual behavior in experimental animals occurred at a dose of 250 mg/kg. Sea slug, *Aplysia dactylomela*, which shares the same phylum Mollusca with oyster, also exhibited the aphrodisiac function in the rat model due to a high level of steroids. The lipid extracts (50 mg/kg) exhibit aphrodisiac properties due to increasing mating behavior frequency (Hashim et al., 2014). According to Paick et al. (2016), rats offered dried sea worm, *Urechis unicinctus*, hydrolysate power significantly increased the frequency of sexual behavior such as mount and ejaculation. Similarly, seahorse species also exhibit the function of aphrodisiac activity. According to Rosa et al. (2013), other medicinal uses and properties of seahorses include promoting sexual desire, aiding in ED treatment, improving the sexual potency of older men and increasing sexual potency. Those evidence promote interests in using the marine-derived aphrodisiac property as an alternative therapy to improve male sexual performance.

PATENTS REVIEW ON HUMAN REPRODUCTIVE SUPPORTING FUNCTIONS FROM MARINE ANIMALS

As excellent sources of bioactive compounds and pharmacological benefits, the number of published patents has continuously increased toward marine derive over time. A range of unique bioactivities from marine organisms has been identified for pharmacological functions of anticancer, antimicrobial, anti-inflammatory, and neuroprotection (Shinde et al., 2019). However, limited patents or patent applications are associated with the potential of marine organisms as a source of natural therapeutics for human reproductive health (**Table 2**). For example, the extraction of the sea cucumber viscera could improve the motility of human and animal spermatozoids and libido and stimulate spermatogenesis number and mobility of sperm (Slutskaja et al., 2003; Timchishina et al., 2003). Kim and Ryu (2014) submitted a patent application that high temperature-high pressure and ultrasonic waves were used to extract the unique compound for spoon worm for managing the sexual dysfunction. Another published patent was reported on enhancing sexual function by antioxidants from oysters (Xiao et al., 2017).

CURRENT KNOWLEDGE AND TECHNICAL GAPS AND FUTURE PERSPECTIVES

The marine environment is an exceptional source of novel bioactive natural products that have been explored for treating

TABLE 2 | A summary of patents on marine animals to support human reproductive health.

Species	Patent number/application number	Description of function	References
Spoon worms	US-20140065235A1	improved sexual function; being an erection dysfunction therapy agent; a health function food for a sexual function improvement	(Kim and Ryu, 2014)
Oyster	US-2017362629-A1	enhanced sexual function/antioxidants	(Xiao et al., 2017)
Sea cucumber	RU 2215532	improved motility of human and animal spermatozoids	(Slutskaja et al., 2003)
	RU 2210377	increased libido; stimulated spermatogenesis; improved numbers and mobility of sperms	(Timchishina et al., 2003)

a wide range of ailments (Jha and Zi-Rong, 2004; Pavão, 2014; Carson and Clarke, 2018; Hossain et al., 2020; Catanesi et al., 2021; Huang et al., 2021; Macedo et al., 2021; Wei et al., 2021). However, their pharmacological functions to support human sexual and reproductive health have underexplored to the best of our knowledge. As discussed in the previous sections, only a few species and a handful of bioactive compounds have been identified mostly *in vitro* or *in vivo* animal tests by now. Most of the studies have used the parts of marine organisms and their extracts without purifying and identifying exact active compounds; hence the reported health benefits could not be elucidated by the mechanism of action to improve sexual function, hormone production, and fertility.

The bioactives including crude extracts and compounds from marine organisms can support human reproductive health through several mechanisms of action reported in the literature. These mechanisms are generally summarized in Column 6 of **Table 1**, primarily including antioxidant mechanism of reducing ROS, and elevating SOD activity; stimulating testosterone production *via* elevating production of cAMP and NO; preventing ED through improving intracavernosal pressure (ICP) and ration of ICP/MAP (mean arterial pressure), NO, cGMP, endothelial nitric oxide synthase (eNOS), and neuronal NOS (nNOS) level. For example, sea cucumber saponins enhance egg production, ovarian follicle growth, and SOD activity; limit ROS formation while decreasing oxidative stress and TNF-α expression (Moghadam et al., 2016). According to Zhang et al. (2021a), *Crassostrea* oyster peptides can stimulate testosterone and NO production in mice by enhancing the level of cAMP and NO, and up-regulating the *Areg* genes, *Acvr2b* and *Hsd17b/let767*. However, the mechanisms of actions of many marine bioactives for reproductive health benefits are remained unknown and are required for future research to elucidate the underlying cellular and molecular mechanisms (Hashim et al., 2014; Riani et al., 2017).

Some widely available commercial synthesised products such as testosterone replacement and phosphodiesterase-5 inhibitor therapy have generally been described to treat sexual and reproductive health issues (Elizur and Tulandi, 2008; Hess and Boehmer, 2020; Li et al., 2021). However, varying degrees of side effects, treatment limitations and risks of taking those substances lead to an increasing public demand toward the discovery of novel products from marine organisms that pose less risk to health but show significant potency, bioavailability with negligible side effects and affordable cost (Hess and Boehmer, 2020; Li et al., 2021). In this regard, a higher concentration of bioactives in targeted marine animals is desired, but these naturally derived compounds are often low in these animals.

The concentration of the bioactive compound and their biosynthetic pathway generally differ depending on species, body parts, animals' life cycles, including spawning period, seasonal variations, geographical location, food availability and feeding regimes (Van Dyck et al., 2010; Hurtado et al., 2012; Feng et al., 2021). For example, saponin contents were compared between five tropical sea cucumber species and between two body parts by (Van Dyck et al., 2010). The lowest saponin diversity was observed in *Holothuria atra*, while the highest was in *Bohadschia subrubra*. The saponin congeners also significantly varied between the body wall and the Cuvieran tubule. For example, the saponins are higher in Cuvieran tubules of *H. leucospilota*, but less in *A. echinites* or similar in *B. subrubra* and *P. graeffei* compared with body wall (Van Dyck et al., 2010). Isono et al. (2020) reported that the oyster glycogen content from Hiroshima during March was significantly lower than those from Okayama and Hyogo regions in Japan. In contrast, the highest level of zinc was observed in Hiroshima oysters during December, January, February, and April. Seasonal and biological variations in the concentration of bioactive compounds from marine animals have been well documented. However, how their contents are significantly affected by environmental and biological factors have been poorly investigated. Higher contents of these bioactives in these marine organisms are desired from both efficacy and commercial perspectives. Therefore, breeding and optimizing cultivation conditions in manipulating animal biosynthetic capacity to improve the yield and production of these bioactive compounds are highly recommended. Importantly, some commercial species, such as sea cucumbers, have been reported as depletion due to overfishing (Ramírez-González et al., 2020). Meanwhile, seahorses have been globally considered flagship species regarding overexploitation, illegal trade, incidental bycatch and habitat loss (Koldewey and Martin-Smith, 2010; Pierri et al., 2021). Thus, aquaculture plays an important role in the sustainable production of bioactive compounds for supporting human health as functional foods, supplements or traditional medicines.

The effective and clean methods for extracting and purifying marine bioactive compounds are crucial for advanced product development and application, particularly for quality and efficacy control. The current review highlights the limitations in this research area. In addition, the current processes for the preparation of bioactive extracts and purified compounds

are mainly at the lab scale, which will need to be optimized toward cost-efficient, clean, and scalable production for industry application.

CONCLUSION

Marine organisms can be a potentially excellent source of unique bioactive compounds as health supplements or even pharmaceuticals to support human sexual and reproductive health. The scientific evidence has been limited among a few groups of marine animals, including oysters, sea cucumbers, sea horses, spoon worms when tested with animal parts, their extracts, and hydrolysates. Several pharmacological activities of these marine organisms-derived bioactives have been recognized as antioxidant effects and aphrodisiac properties to support treatments of hormone deficiency, infertility, SD, and other reproductive issues. However, the precise mechanisms of actions are largely undetermined as most of the studies used crude extracts. Most of these studies have failed to purify and identify the pure bioactive compounds but implicated that saponin, steroids, polysaccharides, proteins, polypeptides, oligopeptides, and essential elements are likely the bioactive compounds. The commercial potential cannot be realized without addressing key knowledge and technical gaps to substantiate the reproductive health benefits in rigorous human clinical studies, understand the mechanisms of actions, and establish cost-effective, scalable, and sustainable production methods.

AUTHOR CONTRIBUTIONS

TH reviewed the literature, designed the structure and wrote the manuscript. QL, YT, JQ, and XL contributed to the development of the concept, provided valuable comments on the manuscript, wrote the draft and addressed comments from editors and reviewers. WZ proposed the review concept early framework and provided critical comments on the manuscript. All authors contributed to the article and approved the submitted version.

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