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Glyceroglycolipids in marine algae: A review of their pharmacological activity

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Glyceroglycolipids are major metabolites of marine algae and have a wide range of applications in medicine, cosmetics, and chemistry research fields. They are located on the cell surface membranes. Together with glycoproteins and glycosaminoglycans, known as the glycocalyx, they play critical roles in multiple cellular functions and signal transduction and have several biological properties such as anti-oxidant and anti-inflammatory properties, anti-viral activity, and anti-tumor immunity. This article focused on the sources and pharmacological effects of glyceroglycolipids, which are naturally present in various marine algae, including planktonic algae and benthic algae, with the aim to highlight the promising potential of glyceroglycolipids in clinical treatment.

KEYWORDS

glyceroglycolipids, source, structure, pharmacological, marine algae

1 Introduction

Marine algae are photosynthetic plants with energy and nutritional value in the marine ecosystem. Although they are at the bottom of the food chain, they account for more than half of the biodiversity of the aquatic environment. In addition, marine algae represent a rich source of bioactive compounds and secondary metabolites (Saadaoui et al., 2020; Cepas et al., 2021). Based on differences in pigmentation, cell structure, reproductive method, and reproductive organ structure, there are about 27,000 species of marine algae and can be divided into planktonic algae, including Cyanobacteria, Chlamydomonas, Dinophyta, prochlorophytes, Euglena, xanthophyll, Cryptophyta, and diatoms, and benthic algae, including Chlorophyta, pheophytin, and Rhodophyta (Lordan et al., 2011; Guiry et al., 2021; Mandalka et al., 2022). Over the past decades, marine algae have been considered a major constituent for drug discovery. The massive diversification of marine algae in the marine ecosystem serves as a reservoir for a wide range of natural compounds (Agatonovic-Kustrin et al., 2018; Bharadwaj et al., 2022). Presently, marine algae are being researched as sources of food, medicine, cosmetics, fertilizer, fodder, and bioenergy (Zhang et al., 2022). However, the development and utilization of glyceroglycolipids in marine algae have been limited due to their low natural abundance.

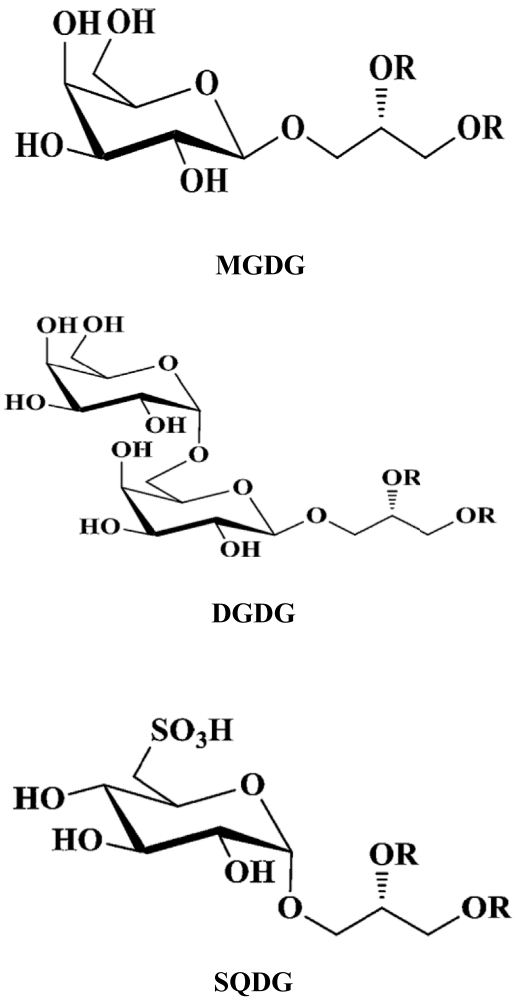

FIGURE 1
Basic structures of glyceroglycolipids.

Glyceroglycolipids have recently received increasing attention due to their anti-bacterial, anti-viral, anti-tumor, and anti-inflammatory activities (Hölzl and Dörmann, 2007; Michaud et al., 2017; Cepas et al., 2021). They are especially abundant in marine algae (Domingues and Calado, 2022) and can be divided into the following three main categories according to their chemical structures and types of glycosyl and acyl structures: monogalactosyl-diacylglycerols (MGDG), digalactosyl-diacylglycerol (DGDG), and sulfoquinovosyl-diacylglycerol (SQDG) (Marcolongo et al., 2006; Zhang et al., 2014) (Figure 1). Glyceroglycolipids constitute more than half of the total lipids (including fatty acids, glycerolipids, glycerophospholipids, sphingolipids, sterol lipids, saccharolipids, and polyketides). Glyceroglycolipids have several beneficial health effects, including their anti-tumor immunity, anti-oxidant and anti-inflammatory properties, and anti-viral activity (Morimoto et al., 1995; Loya et al., 1998). However, due to the low natural abundance of glyceroglycolipids in marine algae and the difficulty of separation, their development and utilization are subjected to certain restrictions.

In the past few years, there has been increasing interest in researching the benefits of natural pharmacological products in treating various diseases. This review provides a comprehensive overview of glyceroglycolipid libraries obtained from Web of Science, SciFinder, Medline, and other databases. To have an in-depth understanding of the glyceroglycolipids derived from marine algae and highlight their potential and prospects in biology, we summarized the literature on the source, structure, and pharmacology of glyceroglycolipids in marine organisms.

2 Methods and summary

2.1 Quality appraisal

The quality appraisal of articles was performed in phase three of the PRISMA flowchart (eligibility check) to ensure the quality of the included articles. Relevant information on the marine algae was obtained from scientific online databases such as Google Scholar, PubMed, and Web of Science. Additional information was derived from other literature sources (e.g., Chinese Pharmacopoeia 2020 edition, Chinese herbal classic books, PhD and MSc thesis, etc.). The search process was mainly based on keyword search, with the main keywords being marine algae, glyceroglycolipids, antitumor, antibacterial, and antiviral, etc., for which they were searched individually or in combination. The scope of the literature search was focused on literature reports between 2012 and 2022. Some of these studies were not reported in the last decade, and we extended the search to earlier literature.

The initial search resulted in 2,351 articles. Then, those identified as duplicate articles, editorials, letters, or basic science studies were excluded, and 99 full-text articles were identified. With detailed analysis, we excluded 12 full-text articles (5 non-English; 7 could not be found). A total of 87 full-text articles were found to be relevant for the systematic review (Figure 2).

2.2 Source and structure of glyceroglycolipids in marine algae

Glyceroglycolipids are especially abundant in marine algae and exhibit a glycerol backbone that anchors one or two acyl chains esterified at the sn-1 and sn-2 positions and a sugar group attached at the sn-3 position in a β-anomeric linkage (Demé et al., 2014; Hoyo et al., 2016). MGDG, DGDG, and SQDG are the most

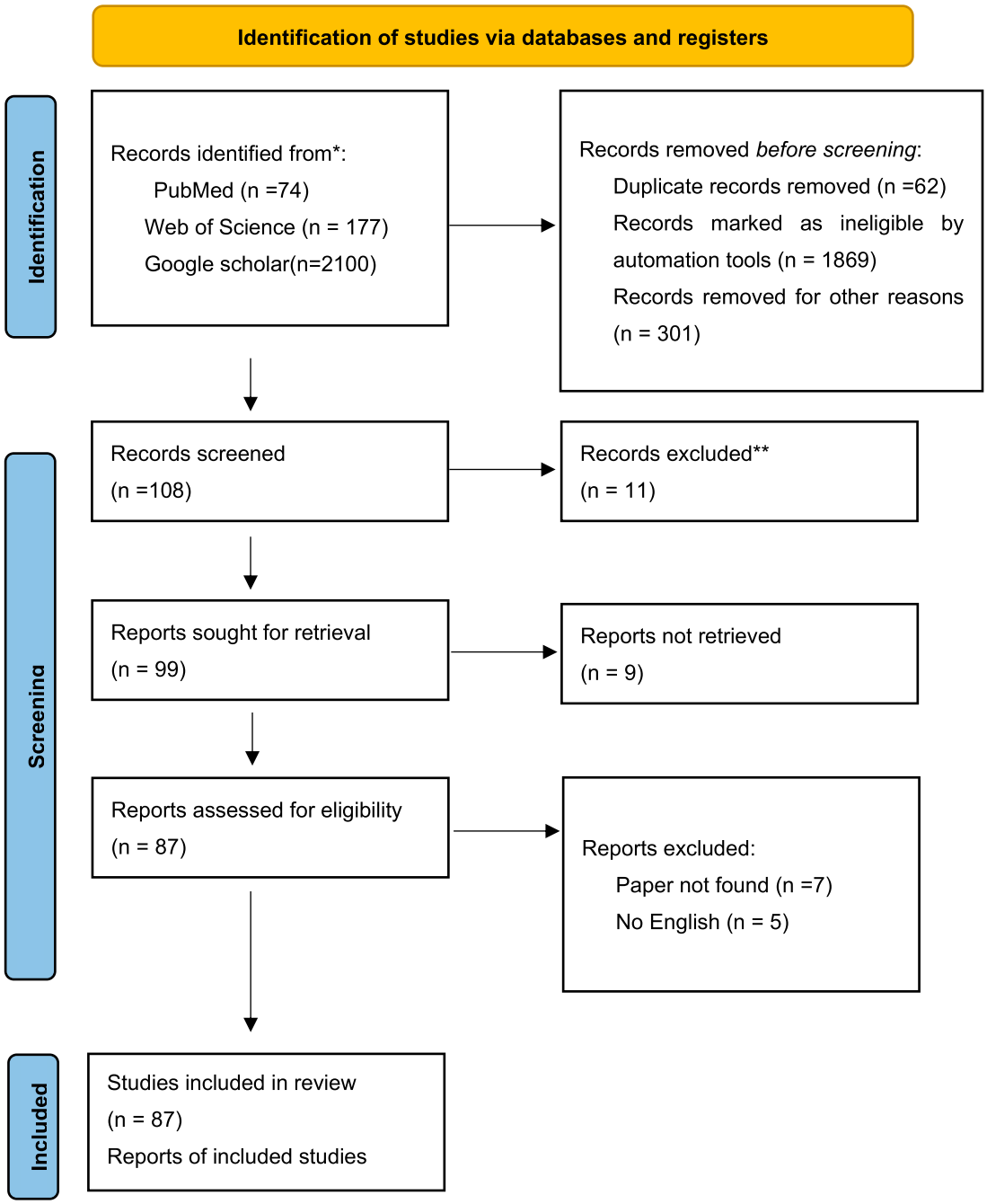

FIGURE 2
Flow diagram for synergy model review.

common glyceroglycolipids, which differ mainly in their fatty acid chain. The saturation and chain length of the fatty acid chains influence the biological activity of glyceroglycolipids. The former two glyceroglycolipids are neutral glycolipids, and the latter one is anionic sulfolipids (Alves et al., 2020; Chen and Wang, 2021). For the broad application of marine algae lipids, it is crucial to identify marine algae materials rich in glyceroglycolipids. Table 1 summarizes the form of fatty acids derived from glycerol in diverse marine algae sources, from which C16 and C18 can be seen as the main acyl fatty acid chains of glycerol glycolipids.

TABLE 1 Fatty acids of glyceroglycolipids in several marine algae species.

Species name	FA of the acyl part of glyceroglycolipids (sn-1/sn-2) or (total FA)	Ref
Chlorophyta		
Caulerpa taxifolia	**MGDG**: (C16:3/C18:3, C18:3/C16:3)	Mancini et al. (1998)
Chlorella sorokiniana	**MGDG, DGDG, SQDG:** (C16:0, C16:1n-7, C16:3n-3, C18:0, C18:1n-9, C18:2n-6, C18:3n-3)	Guschina et al. (2020)
Ulva armoricana	**MGDG:** C14:0/C16:1n-5; **DGDG:** C14:0/C18:3n-3	Kendel et al. (2015)
Klebsormidium flaccidum var. zivo	**MGDG: (C16:4/C18:3, C16:3/C18:3)** **DGDG: (C16:4/C18:3, C16:3/C18:3)**	Qiu et al. (2020)
Ulvella lens	**MGDG** (16:0/16:1n-9/16:1n-7/16:2n-6/16:4n-3/18:2n-6/18:3n-3) **DGDG** (14:0/16:0/16:2n-6/16:4n-3/18:2n-6/18:3n-3) **SQDG** (14:0/16:0/18:1n-7/18:2n-6/18:3n-3/20:1n-7)	Takahashi et al. (2002)
Pheophytin		
Saccharina japonica	**MGDG, DGDG, SQDG:** (C14:0, C16:0, C16:1, C18:0, C18; 1n-9, C18:2n-6, C18:3n-3, C18:4n-3, C20:4n-6, C20:5n-3)	Lee et al. (2004)
Sargassum vulgare	**MGDG:** (C16:0/C19:1), **DGDG:** (C16:0/C16:1), and **SQDG:** (C19:0/C16:0)	Plouguerné et al. (2020)
Cladosiphon okamuranus	**MGDG:** (18:3n-3/16:3n-3)	Terasaki and Itabashi (2003)
Sargassum thunbergii	**MGDG: 20:5/18:4, 18:3/18:4**	Kim et al. (2007)
Saccharina cichorioides	**MGDG, DGDG, SQDG:** (C16:0, C16:1n-7, C18:1n-9, C18:3n-6, C18:4n-3, C20:5n-3)	Logvinov et al. (2015)
Sargassum pallidum	**MGDG, DGDG, SQDG:** (C16:0, C16:1n-7, C18:1n-9, C18:2n-6, C18:3n-3, C18:4n-3, C20:4n-6)	Logvinov et al. (2015)
Fucus spiralis	**MGDG:** C20:5/C18:1, C20:5/C18:3	Lopes et al. (2014)
Fucus vesiculosus	**MGDG:** (18:1/14:0, 16:1/16:0; 18:4/16:0, 18:3/16:1; 18:3/16:0; 18:2/16:0, 18:1/16:1; 18:1/16:018:4/18:4; 18:3/18:4; 18:3/18:3; 18:2/18:3, 20:5/16:0; 20:4/16:0, 18:2/18:2; 20:5/18:4; 20:5/18:3, 20:4/18:4; 20:5/18:2, 20:4/18:3; 20:5/18:1, 20:4/18:2; 20:4/18:1; 20:4/18:0; 20:5/20:4; 20:4/20:4) **DGDG:** (14:0/18:2; 14:0/18:1, 16:0/16:1; 18:3/16:0; 18:2/16:0, 18:1/16:1; 18:1/16:0; 18:0/16:0; 18:3/18:4; 18:3/18:3; 20:5/16:0, 18:2/18:3; 20:4/16:0, 18:2/18:2; 18:1/18:2; 18:1/18:1; 18:1/18:0; 20:5/18:4; 20:5/18:3, 20:4/18:4; 20:4/18:3, 20:5/18:2; 20:4/18:2, 20:5/18:1; 20:4/18:1; 20:4/18:0) **SQDG:** 14:0/14:0; 16:0/14:1; 16:0/14:0; 18:3/14:0; 18:2/14:0; 18:1/14:0; 18:0/14:0; 18:3/16:1; 18:3/16:0; 18:2/16:0; 18:1/16:0; 20:5/16:0; 20:4/16:0	da Costa et al. (2019)
Rhodophyta		
Solieria chordalis	**MGDG:** (14:0/16:1)	Kendel et al. (2015)
Exophyllum wentii	MGDG (20:4n-6/16:0) DGDG (20:4n-6/16:0) SQDG (16:0 and 20:4n-6 acids)	Honda et al. (2016)
Gracilaria vermiculophylla	**MGDG:**C20:4n-6/C20:4n-6, C20:4n-6/C16:0 **DGDG:**C20:4n-6/C16:0, C20:4n-6/C16:0 **SQDG:** C20:4n-6/C16:0, C14:0/C16:0, C20:4n-6/C16:0	Muhammad et al. (2008)
Tichocarpus crinitus	**MGDG, DGDG, SQDG:** C16:0, C18:1n-9, C20:5n-3	Logvinov et al. (2015)
Chondria armata	**MGDG:**C20:5/C16:0 **SQDG:** (C16:0/C16:0)	Al-Fadhli et al. (2006)

According to some research, glycoglycerolipid biosynthesis mainly occurs via two routes: the prokaryotic pathway, which generates glyceroglycolipids with an sn-2 C16 acyl group, and the eukaryotic pathway, which generates glyceroglycolipids with an sn-2 C18 acyl group (Heinz and Roughan, 1983). Several studies have shown that glyceroglycolipids from marine algae have significant roles in connecting structural characteristics and pharmacological activities.

2.3 Pharmacological effects and mechanisms of glyceroglycolipids

Unlike polysaccharides and fatty acids in marine algae, the therapeutic benefits of glyceroglycolipids remain poorly understood in the current literature because of their limited natural abundance and absorption. Nevertheless, glyceroglycolipids can be digested and absorbed by the

gastrointestinal tract (Bajwa and Sastry, 1974). Andersson et al. (1995) showed that pancreatic lipase-related proteins could hydrolyze galactosylglycerides into galactosylmonoglycerides (MGMGs) and diglycerides (DGMGs), then into galactosylglycerol (MGG) and diglycerides (DGG), and finally into galactosylglycerol and glycerol. Andersson et al. (1996) also reported that although the hydrolysis and cleavage of thioisorhamnosylglycerol- and galactosylglycerol-based skeleton structure might not occur in the colon, they could be further hydrolyzed into sugar and glycerin in the cecum, indicating that glyceroglycolipids are absorbed and transformed at different degrees in the intestine and that their biological activity could be determined by the absorption and transformation of their glycosyl structure and unsaturated fatty acid *in vivo*. Hence, this review investigates the pharmacology of different structural types of glyceroglycolipids in marine algae by mainly focusing on their anti-oxidant and anti-inflammatory properties, anti-viral activity, and anti-tumor immunity.

2.3 1 Anti-oxidant activities

Excessive oxygen free radicals have been associated with cardiovascular disease, aging, skin damage, and cancer (Block et al., 1983; Hassan and Abdel-Aziz, 2010). Cells and tissues have a complex anti-oxidant system to selectively scavenge excess free radicals and avoid damage to cellular structures. Therefore, supplementing exogenous anti-oxidants into diet and plant derivatives might have potential health benefits. In particular, although it is known that glycerolipids from marine algae have significant anti-oxidant activities, these roles have not been fully explored.

Genetic evidence suggests that membranes rich in polyunsaturated fatty acids (PUFAs) act as supramolecular anti-oxidants that capture reactive oxygen species, thereby limiting damage to proteins. This process generates lipid-fragmentation products, including malondialdehyde (MDA), an archetypal marker of PUFA oxidation. MGDG accelerates the rate at which MDA is metabolized (Schmid-Siegert et al., 2016). Another study showed that SQDG significantly inhibited LPS-induced NO production in RAW264.7 cells without affecting cell viability (Gao et al., 2014). Scavenging free radicals were shown to play important roles in human health, and marine algae-derived glyceroglycolipids were shown to possess significant anti-oxidant activities.

Overall, we found that the anti-oxidant mechanism of glyceroglycolipids could be explained by the fact that its unsaturated fatty acids play an important role in metabolites produced by lysis in the body, inhibiting the production of oxidizing substances such as NO in cells. As a result, the study of unsaturated fatty acid chains of glyceroglycolipids might become a hot topic in the future.

2.3.2 Anti-inflammatory activities

Glyceroglycolipids of natural origins have immunomodulatory properties (Cheng et al., 2016). Marine algae-derived glyceroglycolipids are immunosuppressive and can reduce inflammation by activating cells with immunosuppressive functions, such as regulatory T cells (Treg) (Mueller et al., 2010; Du et al., 2015). MGDG, DGDG, and SQDG have been found to exert anti-inflammatory effects by inducing superoxide anion production in leukocytes and chemotaxis of human peripheral neutrophils to inhibit croton oil-induced ear edema in mice (Bruno et al., 2005). In addition, MGDG and DGDG showed significant activity in lipopolysaccharide-stimulated human THP-1 macrophages to inhibit TNF-α production and activate anti-inflammatory mechanisms in the organism (De Los Reyes et al., 2016). Another study demonstrated that MGDG activated the cyclooxygenase-2 (COX-2) pathway and had anti-inflammatory activities on human articular cartilage (Ulivi et al., 2011). Furthermore, glyceroglycolipids of marine algae extracts were found to inhibit TNF-α-induced IL-8 production in the HT-29 cell line (Kiem et al., 2012). These studies suggest that glyceroglycolipids from marine algae might have anti-inflammatory effects.

Inflammatory mediators such as PGE2 and NO play key roles in every step of inflammation and have been implicated in the pathogenesis of various inflammatory diseases. Glycerol glycolipids were reported to inhibit LPS-induced protein and mRNA expression of iNOS and COX-2 in RAW264.7 macrophages and strongly inhibit NO and PGE2 production. At the same time, it also regulated the response of macrophages, as shown in Figure 3.

2.3.3 Anti-viral activities

Anti-viral chemotherapy is important in preventing and treating many important viral infections (De Clercq and Field, 2006; Plouguerné et al., 2013). However, the acceptance of anti-viral chemotherapy has been challenging mainly because clinicians were made to believe that viral inhibitors can have toxic effects on the host (Hayashi et al., 2019; Cénat et al., 2020; Sun et al., 2020). Currently, novel sources of anti-viral drugs are being actively researched. In the last few years, marine algae compounds have been examined for potential use in anti-viral drugs, of which glyceroglycolipids represent an emerging anti-viral secondary metabolite (Zhang X. et al., 2020). MGDG and DGDG are resistant to herpes simplex virus 2 (HSV-2) and can make the virus lose its ability to bind to cells and inhibit its replication *in vivo* (Hayashi et al., 2019; Wang et al., 2020). In addition, MGDG has anti-viral activity and can also combine with other substances to form immune complexes, which can stimulate the production of specific antibodies *in vivo* to inhibit influenza virus hemagglutinin (HA), thereby demonstrating its anti-viral effects (Nina et al., 2017). One study found that isolating SQDG from brown algae of Brazil also had inhibitory effects on herpes virus (HSV-1 and HSV-2) (Nina et al., 2017). In addition, a previous study reported that SQDG could inhibit HIV replication with the same effects as HIV

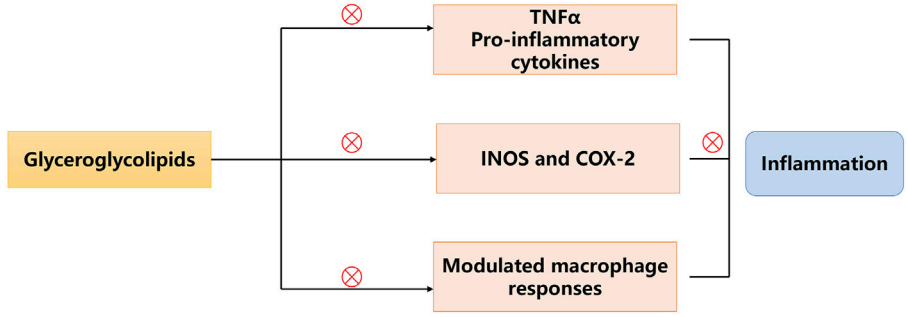

FIGURE 3
Anti-inflammatory mechanism of glyceroglycolipids.

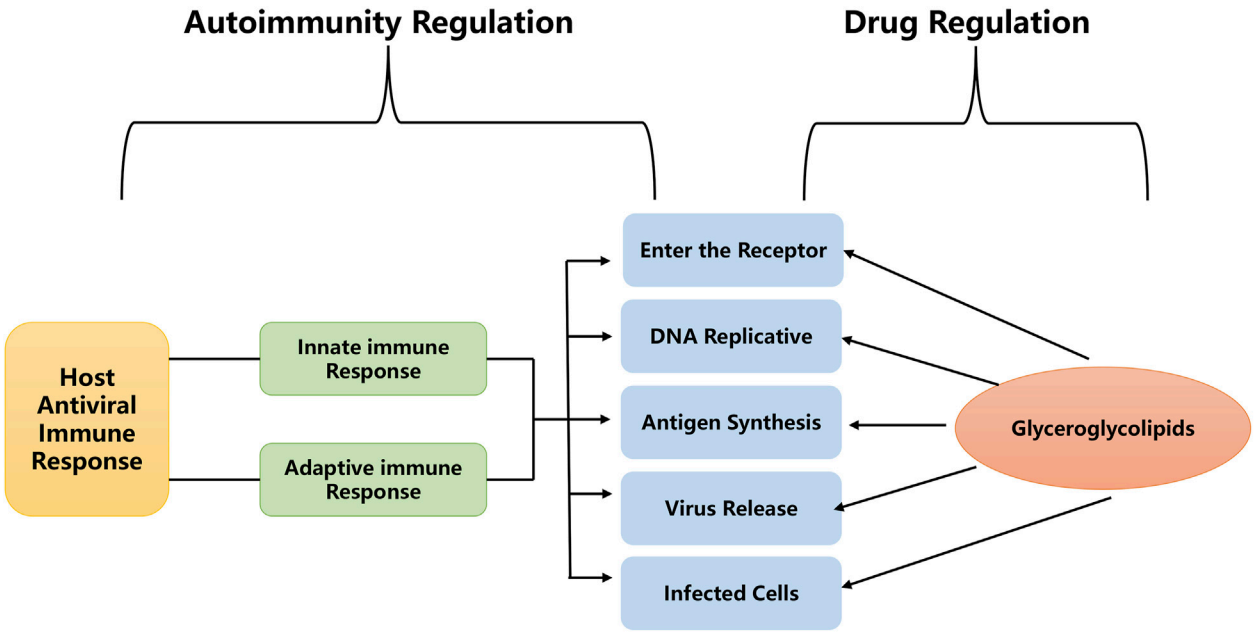

FIGURE 4
Potential anti-viral mechanism of glyceroglycolipids.

reverse transcriptase through cell experiments (Gustafson et al., 1989). Ash et al. (2017) also studied the anti-viral activity of SQDG and found that the anti-viral mechanism of SQDG was mainly through the combination with DNA to induce apoptosis.

Based on the existing literature, we can conclude that there are three main anti-viral mechanisms of glycerol glycolipids: 1) preventing viral infection from entering the host cell by directly inhibiting the binding of the virus to the cell surface; 2) preventing the virus from exfoliating in the host cell by binding at the variable configuration site of the viral capsid; and 3) inhibiting the transcriptional replication process of the virus from the host cell by interfering with replication enzymes such as reverse transcriptase or preventing the formation of reverse transcriptase proteins of cellular messenger RNAs (Figure 4). Thus, marine algae glyceroglycolipids might be a primary candidate for the future anti-viral drug discovery work.

2.3.4 Anti-bacterial activities

Many highly effective antibiotics against bacteria and fungi are already in widespread use. However, due to the poor membrane permeability of many hydrophilic antibiotics, the choice of antimicrobial drugs for intracellular use is limited (Jiang et al., 2020). Recent studies have found glyceroglycolipids to have anti-bacterial activities. Dai et al.

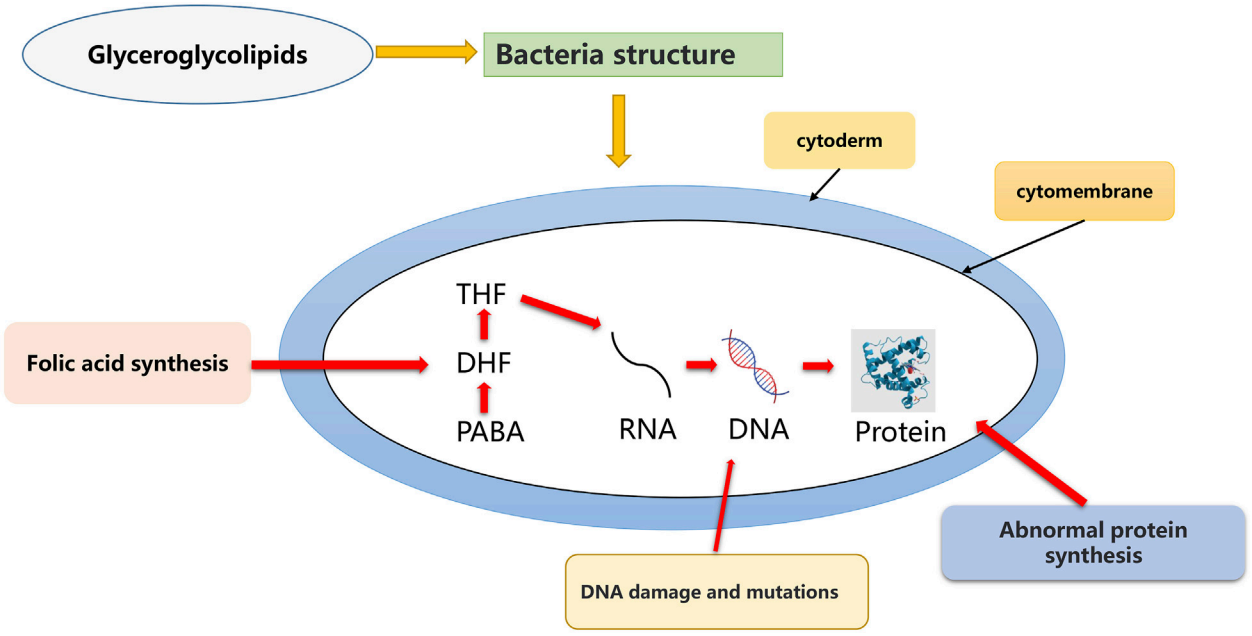

FIGURE 5
Potential mechanism of anti-bacterial activity of glyceroglycolipids.

(2001) found that glycoglycerolipid could inactivate *Bacillus*. Plouguerné et al. (2014) reported that MGDG had strong anti-bacterial activity against *Haemophilus influenzae*, *Legionella pneumophila*, *Propionibacterium acnes*, *Streptococcus pyogenes*, *Clostridium difficile*, and *Staphylococcus aureus*. In addition, Parveez Ahamed et al. (2017) found that the acyl structure of glycerol glycolipid was related to its anti-bacterial activity. In addition, Furukawa et al. (2006) found that SQDG inhibited the proliferation of *E. coli* JM190 cells, while MGDG and DGDG did not show similar activities. These studies show the differences in the anti-bacterial activities of different structural types of glycoglycerolipids. However, there are few studies on the antimicrobial activity of glycolipids, of which most of the experiments have focused on their mechanism of action *in vitro*. Figure 5 summarizes the mechanism of action of various antimicrobial agents. Glyceroglycolipids were shown to disrupt mitochondrial functions in fungal cells in MTT assay (Lopes et al., 2013). Many dehydrogenases, such as lactate dehydrogenase and succinate, are involved in the mitochondrial respiratory chain. Glyceroglycolipids exert their anti-microbial effects by increasing the mitochondrial respiration rate and interaction with these enzymes, leading to higher ROS production.

2.3.5 Anti-tumor activities

Cancer is a major disease that reduces life expectancy. Currently, the main methods to treat tumors are surgery, radiotherapy, chemotherapy, and hormone therapy (Zhang W. et al., 2020). Although these methods can have certain therapeutic effects, in many cases, they also have serious adverse events (Rath et al., 2019; Yan et al., 2019). Therefore, research on more effective oncology drugs with lesser toxicity is of great significance and has become a research hotspot. Numerous studies have attempted to explain the strong anti-tumor activities of glyceroglycolipids. Shirahashi et al. (1993) reported that galactoglyceride significantly inhibited the growth of tumors. One study showed that DGDG had inhibitory effects on dermal papilloma in mice (Tokuda et al., 1996). Colombo et al. (2005) found that galactosylglycerides with more branched and unsaturated acyl chains had strong inhibitory effects on mouse skin tumors and proved that the acyl structure of glycerosylglycerides had a great influence on the activity of the glyceroglycolipids. In addition, they also found that the presence of aliphatic or aromatic rings in glycerol glycolipids had a negative effect on their anti-tumor activity (Colombo et al., 2006) and revealed that galactosylglycerides played a therapeutic role in cancer prevention and treatment by inhibiting the growth of tumor cells and blocking the expression of protein kinase C (Colombo et al., 2011). In addition, Akasaka et al. (2013) found that MGDG, a DNA polymerase inhibitor, can enhance the anti-proliferation effects of gemcitabine on human pancreatic cancer cells. However, Maeda et al. (2005) reported that glycerol glycolipid was not only an inhibitor of DNA polymerase but also a growth inhibitor of human gastric cancer cells, and its activity was stronger when it was hydrolyzed by lipase. Maeda

TABLE 2 Anti-tumor activities and mechanism of glyceroglycolipids.

Structure type	Anti-tumor activities	Mechanism	Ref
MGDG	Breast cancer	Inhibition of DNA polymerases and growth inhibition of tumor cells	Akasaka et al. (2013)
MGDG	Prostatic cancer	Inhibition of DNA polymerases and growth inhibition of tumor cells	Akasaka et al. (2013)
MGDG	Lymphocytic leukemia	Inhibition of DNA polymerases and growth inhibition of tumor cells	Akasaka et al. (2013)
MGDG	Tumors of epithelial origin	Induce apoptosis upstream of Bax and Bak	Andrianasolo et al. (2008)
DGDG	Skin papilloma	Decrease protein kinase C protein translocation to membranes	Colombo et al. (2005)
DGDG	Stomach adenocarcinoma	Inhibition of DNA polymerases and growth inhibition of tumor cells	Ramm et al. (2004)
DGDG	Hepatocellular carcinoma	Inhibition of DNA polymerases and growth inhibition of tumor cells	Ramm et al. (2004)
SQDG	Skin papilloma	Inhibiting the Epstein–Barr virus activation	Dangate et al. (2009)
MGDG and DGDG	Melanoma	Inhibition of DNA polymerases and growth inhibition of tumor cells	Maeda et al. (2005)
MGDG and DGDG	Pancreatic cancer	Inhibition of DNA polymerases and growth inhibition of tumor cells; cytotoxicity	Maeda et al. (2005); Akasaka et al. (2016)
MGDG and DGDG	Lung adenocarcinoma	Moderately cytotoxic toward tumor cell	Perez Gutierrez and Lule, (2005)
MGDG and DGDG	Human oral epidermoid carcinoma	Moderately cytotoxic toward tumor cell	Perez Gutierrez and Lule, (2005)
MGDG, DGDG, and SQDG	Colon tumor	The protein expression level of proliferating cell nuclear antigen (PCNA) was decreased	Maeda et al. (2009)

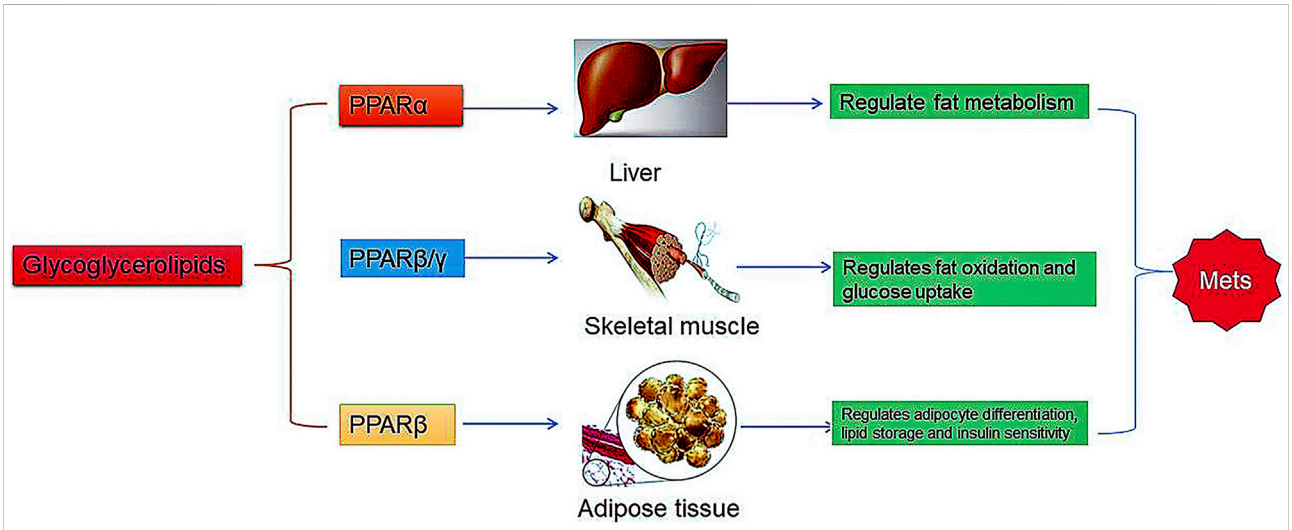

FIGURE 6
Effects of glyceroglycolipids on PPARs.

et al. (2009) also reported that glycerol glycolipid had an inhibitory effect on the growth of transplanted tumor sarcoma and colon tumors in mice. Dangate et al. (2009) found that SQDG had anti-tumor effects and inhibited tumor promoters. Ogunsina et al. (2013) suggested that the glycosyl structure of glycerols was related to the activity of anti-tumor glycerides, and the anti-tumor activity of galactosyls was greatly lost when they were replaced. Andrianasolo et al. (2008) found that galactoglyceride induced apoptosis at micromolecular concentration and played an important role in the anti-tumor mechanism of glyceroglycolipids.

In summary, the three functions of glyceroglycolipids are crucial for tumor invasiveness and occur through different mechanisms at different sites (Table 2). Many studies have reported that glyceroglycolipids have unique advantages in immune regulation and anti-tumor activity. The anti-tumor effects of glyceroglycolipids are an active focus of research in pharmacology.

2.3.6 Treatment of metabolic diseases

Obesity and obesity-initiated metabolic syndrome are characterized by high levels of cholesterol and lipids in blood

and intracellular fat accumulation in adipose tissues. Some researchers showed that glyceroglycolipids significantly reduced adipogenic PPAR-γ protein expression in differentiated 3T3-L1 cells (Chen et al., 2022; Prabhakar et al., 2022). Peroxisome proliferator-activated receptors (PPARs) are a family of ligand-regulated nuclear receptors that include PPAR-α, PPAR-β/δ, and PPAR-γ (Lee et al., 2022). These receptors play a significant role in the regulation of transcription, energy and lipid metabolism, and thermogenesis (Lee et al., 2020). One study identified a specific type of MGDG in which the acyl groups acted as a potent PPAR-γ (peroxisome proliferator-activated receptor γ) ligand (Figure 6) (Pinto et al., 2021). These studies suggest that algal-derived glycerolipids might be considered potential activation targets of the PPAR family, indicating the need for further in-depth analysis of marine algae and their natural products.

4 Conclusion

Glyceroglycolipids represent a broad class of biologically active natural products with a wide variety of molecular structures and biological functions, many of which are essential for life. They are naturally found in marine algae and appear to possess pharmacological activities such as anti-cancer, anti-bacterial, anti-viral, and anti-oxidant properties. There are various mechanisms underlying the activities of glyceroglycolipids, including the combination of cell signaling pathways at various stages of diseases.

In terms of anti-oxidants, the polyunsaturated fatty acids in glycerol glycolipids can reduce free peroxidation and rapidly scavenge malondialdehyde and are considered the main mechanisms of action. Meanwhile, glycerol glycolipids inhibited LPS-induced protein and mRNA expression of iNOS and COX-2 in RAW264.7 macrophages and strongly inhibited NO and PGE2 production. This mechanism indicates that glycerol glycolipids possess strong anti-inflammatory activities. In addition, glycerol glycolipids are also highly active against pathogenic microorganisms. Glyceroglycolipids prevent viral infection from entering the host cell by directly inhibiting the binding of the virus to the cell surface membrane. At the same time, polyunsaturated fatty acids bind to the variable conformation site of the viral shell and prevent viral shedding in host cells. Glycerolipids also exert anti-viral effects by interfering with replication enzymes (e.g., reverse transcriptase) or by preventing the formation of reverse transcriptase proteins of cellular messenger RNA, which inhibit the transcriptional replication process of viruses from host cells. In addition, the interaction of polyunsaturated fatty acids in glyceroglycolipids with various dehydrogenases increases the mitochondrial respiration rate, leading to higher ROS production, thus promoting anti-microbial effects. Glyceroglycolipids also have anti-cancer activities. Its main mechanisms of action include the inhibition of DNA polymerase and inhibition of tumor cell growth by inducing apoptosis upstream of Bax and Bak, reducing the transfer of protein kinase C protein to the membrane. The biological activity is closely related to the glycosyl and acyl chains of glyceroglycolipids. Consequently, it could be used in drugs for treating various diseases. However, due to the low natural abundance and difficult separation, research on the application of glycerolipids is limited. Meanwhile, the current research on glyceroglycolipids in marine algae remains under-investigated, urging the need for greater consideration due to their promising benefits.

Author contributions

S-SG conceived and designed the original manuscript and classified the pharmacological literature; and Z-GW proposed amendments and modified the manuscript. All authors contributed to the manuscript and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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