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Research progress on the biosynthesis, activity and application of natural tetrapyrrole compounds

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ABSTRACT

Tetrapyrrole compounds play vital roles in the life processes of animals and plants, such as respiration and photosynthesis, due to their functions in light energy capture and transmission, signal transduction, binding and transport of oxygen, their research originated from the study of heme and chlorophyll chemistry. The special structure of tetrapyrrole determines its various properties, which contribute to its antioxidant, anti-inflammatory, antitumoral, antibacterial, neuroprotective and other biological activities. Although many functions of tetrapyrrole compounds have been excavated and utilized, there is a lack of a complete system to summarize them. This review summarizes the biosynthesis, functional evolution, biological activities and optical applications of tetrapyrrole compounds based on existing research on tetrapyrrole compounds.

1. Introduction

Tetrapyrrole chemistry has been developing for more than 200 years and has made significant contributions to various life activities. Tetrapyrrole compounds have the functions of adsorption and binding oxygen, electron transfer, light signal transduction, play important roles in the life processes of respiration and photosynthesis, tetrapyrrole compounds are widely applied in agriculture and the food, health, and cosmetics industries (Bryant et al., 2020). Tetrapyrrole compounds are widely distributed natural alkaloids in organisms, they are connected by four five-membered rings by single-carbon (such as methylene or hypomethyl) bridges and can be categorized into linear and cyclic types. In addition, tetrapyrrole compounds are divided into chlorophyll (Chl) and its derivatives, heme and its derivatives, and phycobilin (see Fig. 1).

Chl is widely found in green plants. Natural Chl is tetrapyrrole to form a porphyrin ring and binds to magnesium. Chl can capture solar energy in natural plants, synthesize organic matter from carbon dioxide and water in the air, release oxygen, and supply its own growth and reproduction. In addition, Chl has a wide range of biological activities, such as antioxidant, anti-inflammatory and antibacterial activities (Pucci et al., 2021). Phycocyanobilin (PCB) is a linear tetrapyrrole chromophore widely found in cyanobacteria, red algae and some cryptophytes. PCB is linked to the α and β subunits of apoproteins to form phycocyanin (PC). PC is currently used as a natural plant pigment in food and cosmetics industries. Modern pharmacological studies have confirmed that PCB and PC have the same anti-inflammatory and antioxidant effects (Li, 2022). Heme is an important component of hemoglobin in animals. Four heme molecules bind to globin to form hemoglobin. The structure of heme is a ring composed of four pyrrole subunits. A ferrous ion is connected to the middle of the ring. Ferrous ions can be combined with oxygen, which can be transported by blood to all parts of the body. In addition, heme and its derivatives bilirubin, biliverdin, etc. have been found to have strong anti-inflammatory effects (Takemoto et al., 2019).

Many plant-derived molecules, such as flavonoids (Tekin et al., 2022, Mohammed et al., 2023), chrysin (Mohammed et al., 2023) and polycyclic compounds such as γ-oryzanol (Jasim et al., 2024), have significant antioxidant and hepatoprotective effects and have become research hotspots. This paper systematically summarizes the biosynthesis, pharmacological effects and applications of natural tetrapyrrole compounds, in order to provide theoretical support for the development and application of tetrapyrrole compounds (see Fig. 1).

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2. Biosynthesis of tetrapyrrole compounds

The intracellular localization and function of tetrapyrrole compounds are different, and their intracellular synthesis pathways are divided into many branches with different functions. However, the preparation of tetrapyrrole compounds requires a common precursor, 5-aminolevulinic acid (5-ALA) (Pan et al., 2022), 5-ALA can be synthesized in plants, animals, and microorganisms (Jiang et al., 2022).

Glutamyl trna synthetase activates glutamic acid by connecting tRNA-Glu, and the activated glutamyl trna carboxyl group is reduced to formyl by glutamyl trna reductase (GluTR) to produce glutamyl trialdehyde (GSA). Subsequently, the intermolecular amino exchange reaction converts GSA into 5-ALA, which is catalyzed by GSA transaminase (GSA-at). Two ALA molecules are condensed to form a pyrrole molecule under the action of ALA dehydratase. Porphyrin choline (PBG), PBG deaminase can polymerize four PBG molecules to produce linear tetrapyrrole (Brzezowski et al., 2015). The biosynthesis of all tetrapyrroles in higher plants requires a process from glutamate to uroporphyrinogen III. Uroporphyrinogen III can synthesize several tetrapyrrole cofactors, uroporphyrinogen III decarboxylase converts the

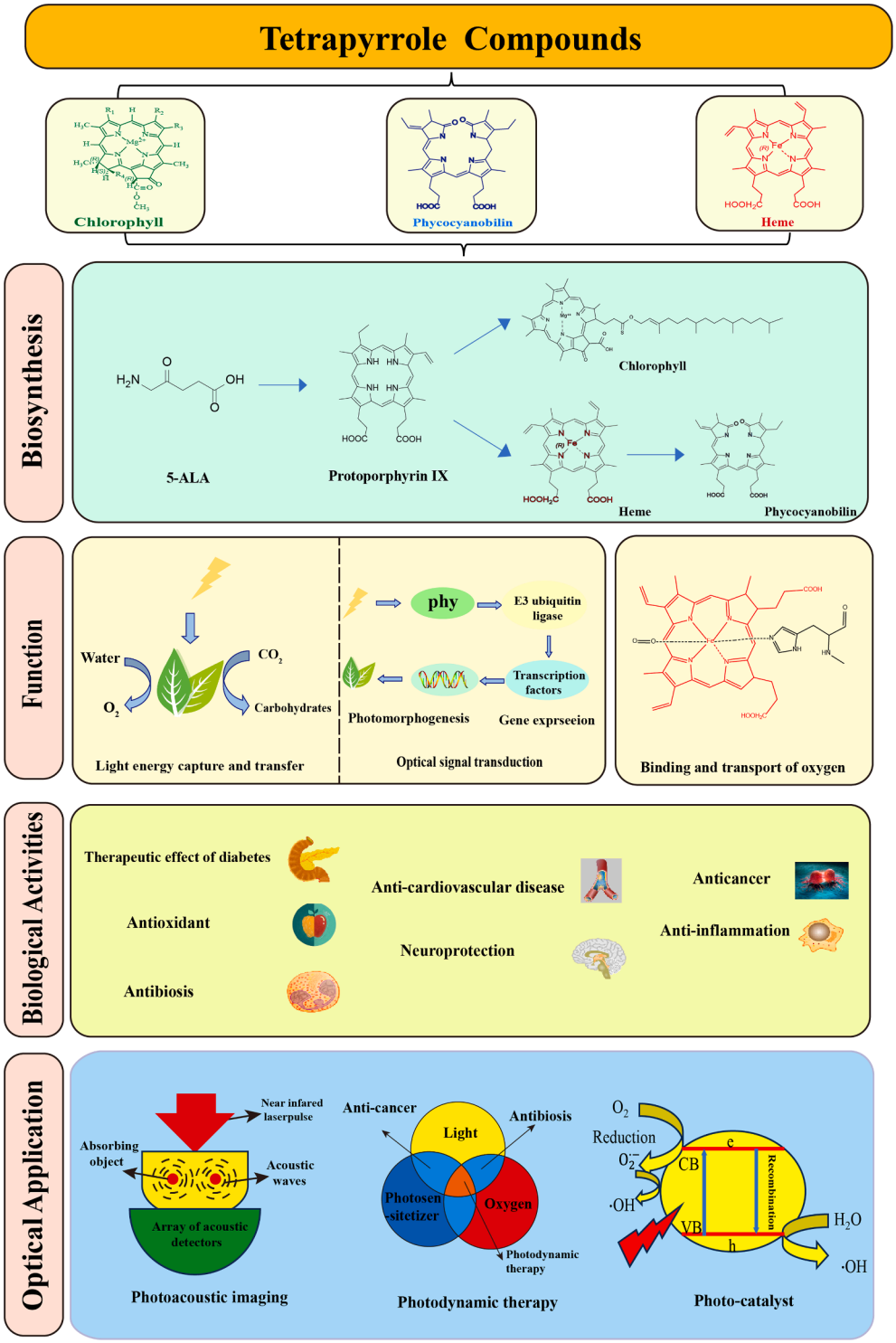

Fig. 1. Biosynthesis, functional evolution, biological activitives, and optical applications of tetrapyrrole compounds.

four acetate side chains into methyl groups to form coporphyrinogen III, and the two propionic acid groups of coporphyrinogen III are decarboxylated to form protoporphyrin IX, from which 6 electrons are extracted to form protoporphyrin IX (see Fig. 2) (Tanaka and Tanaka, 2007).

The initial catalytic step of the Chl branch is to chelate Mg^{2+} to the skeleton chain of protoporphyrin by magnesium chelatase catalysis. Then, through Mg-protoporphyrin IX methyltransferase, the methyl group of s-adenosyl-L-methionine was combined with the carboxyl group of Mg-protoporphyrin IX 13-propionate to form Mg-protoporphyrin IX. Monomethyl ester, in the next reaction, Mg-protoporphyrin IX. Monomethyl ester cyclase combines atomic oxygen with Mg-protoporphyrin IX. form 3,8-divinyl protoporphyrin IX. The D ring of the compound was reduced to 3,8-divinylprotochlorophyllolactone by protochlorophyllolactone oxidoreductase, and the 8-vinyl group of the B ring was reduced to 3-vinylchlorophyll acyl a by diacylchlorophyllolactone oxidoreductase. Finally, Chl synthase and phytol pyrophosphate esterified 17-propionic acid a on the D ring of monophyll green ester to form Chl *a*. (see Fig. 3) (Tanaka and Tanaka, 2007).

The primary site of tetrapyrrole biosynthesis in plants is the plastid (Tanaka and Tanaka, 2007), however, the exact site of heme biosynthesis is unknown. The last three enzymes of heme biosynthesis, porphyrinogen III oxidase (CPOX), protoporphyrinogen IX oxidase (PPOX), and iron chelating enzyme (Fech) have been proposed to co-locate in plastids and mitochondria. Protoporphyrin IX binds to Fe^{2+} form heme (Brzezowski et al., 2015).

There are two methods for the biological preparation of PCB: one is extraction and purification from cyanobacteria, red algae, and some cryptoalgae, and the other is recombination by a heterologous host, usually recombinant *Escherichia coli (E.coli)*, but with a low yield (Chen et al., 2022). Its biosynthesis follows the same pathway as the pre-Chl and heme biosynthesis pathways up to the protoporphyrin IX formation stage. PCB synthesis uses heme as a direct substrate, under the catalysis of HO-1, biliverdin IXa is generated and releases Fe^{2+} and carbon monoxide, subsequently, biliverdin Ixa is reduced to form PCB (see Fig. 3) (Mysliwa-Kurdziel and Solymosi, 2017).

3. Function evolution of tetrapyrrole compounds

3.1. Light energy capture

Photosynthetic organisms use light as an energy source for photosynthesis and a signal source for photomorphogenesis and have developed complex light perception, energy transfer, and signal transduction systems. The presence of chromophores in photoreceptors is critical for photobiological responses. Tetrapyrrole molecules, including Chl and PCB, are prosthetic groups of light-sensing proteins in plants and algae (Mukougawa et al., 2006). Plants and algae are good at capturing and transmitting light energy, and the center of algae photosynthesis is composed of pigment. When the difference in the energy levels of

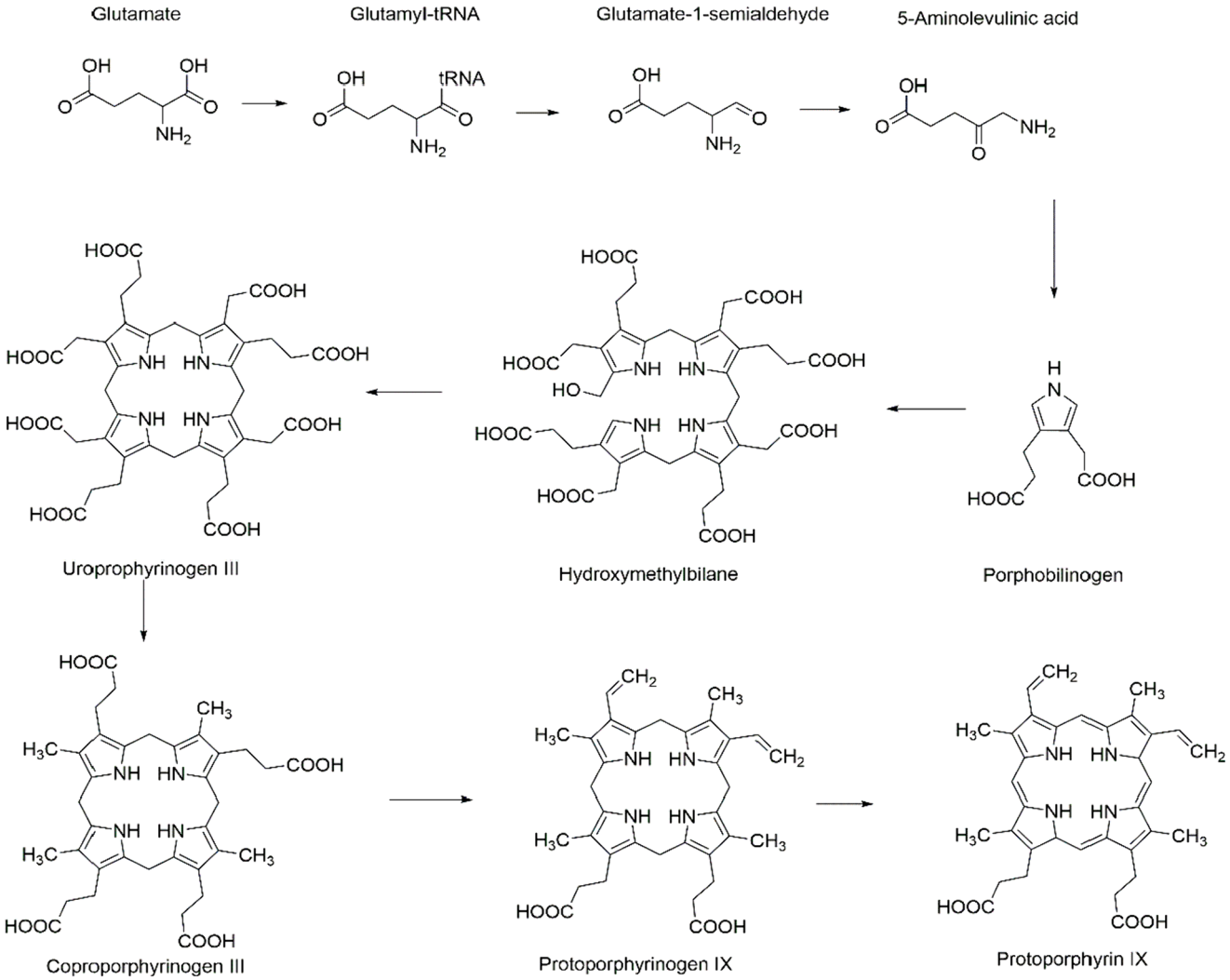

Fig. 2. Common pathways of Chl and heme biosynthesis.

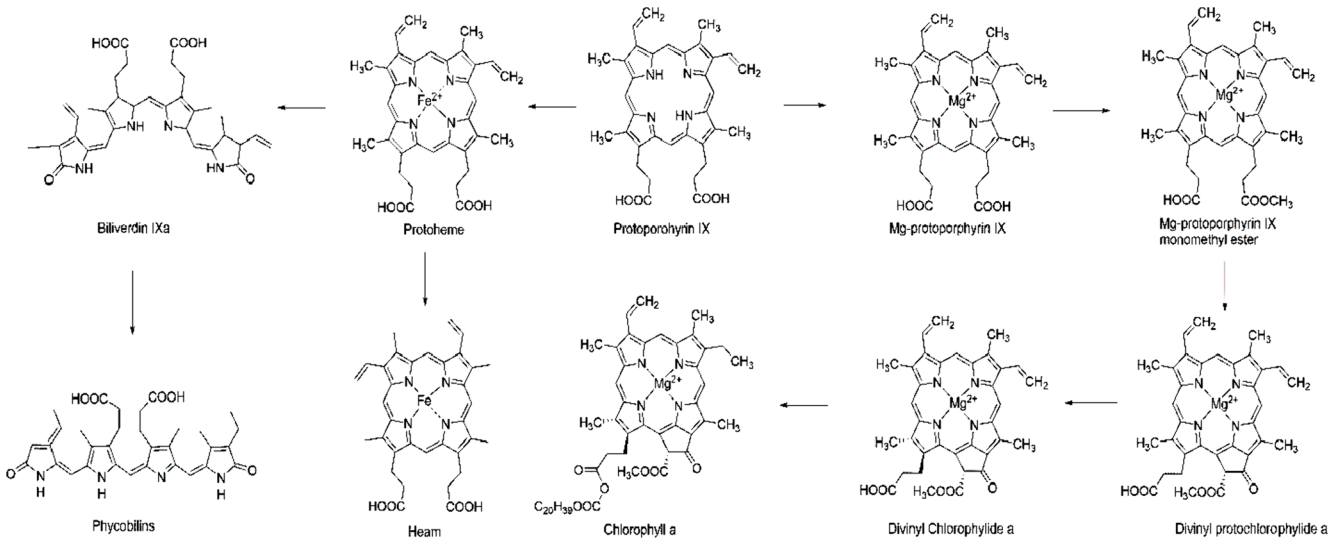

Fig. 3. Biosynthetic pathways of Chl *a*, phycobilin and heme.

electrons in pigment is equal to the light quantum energy, pigment absorb light energy. After excitation of Chl and PCB, these pigments enter a high-energy state, and the high-energy electrons are transported to an electron transport chain, producing a series of chemical reactions that eventually convert light energy into chemical energy.

Chl *a* mainly absorbs light with a wavelength of about 450 nm, that is, blue-violet light, and reflects light with a wavelength of 500~550 nm, that is, green light. The main structure of Chl is a Mg-centered cyclic porphyrin structure. As a metal ion, Mg is surrounded by a large number of electron clouds. Due to the resonance of the covalent bond between N atoms and Mg, the range of the electron cloud becomes larger. Chl can absorb light by this complex cyclic porphyrin structure (Emerson and Arnold, 1932). Plants have two different photoreaction centers. Each photoreaction center has a receptor molecule that accepts high-energy electrons from Chl. As a compensation, the Chl that loses electrons will obtain an electron from the water molecule and eventually produce oxygen molecules and hydrogen ions (H^+). According to research, for each molecule of oxygen produced, about 2500 Chls are involved (Hillier and Babcock, 2001).

Light capture is the process by which a series of photosynthetic pigment molecules absorb light energy and deliver it to the center of the photosynthetic reaction. Light capture systems play a vital role in the natural process of photosynthesis. The simulation of natural light capture systems is highly important for biological imaging, light-emitting device design, photocatalysis, and green energy development (Pangannaya et al., 2020).

3.2. Optical signal transduction

Tetrapyrrole compounds are the most common photoreceptors in biomedical applications. These compounds absorb light energy from the environment and convert it into other energy forms to fulfill certain functions in living organisms. At present, red/far-red light-mediated and miniaturized photosensitive pigment-based photoswitch systems are being studied based on plant photoreceptors and have shown many applications (Zhou et al., 2022). Phytochromes (Phys) exist in two forms and are converted to each other upon the absorption of red or far-red light, activated or passivated, functioned in the activated state (Bo and Yu-Hua, 2006).

Phys absorb mainly red light and far-red light in the wavelength range of 600 ~ 750 nm. Chemically, Phy are protein complex pigments, tetrapyrrole compounds and deprostoprotein are covalently linked, and chromophores are responsible for absorbing light. Phys can also enter the nucleus to transmit light signals through the regulation of several events in the nucleus, and it has been found that some photosensitive pigment factors play a role in the process of light signal transduction (Liao et al., 2004). These proteins are composed of dimers of complex proteins, and the relative molecular weight of monomeric proteins varies according to the plant species, generally ranging from 120 000 g/mol to 150 000 g/mol. The N-terminus generally forms a hydrophobic region of 70 000 and binds linear tetrapyrrole chromophores via a covalent bond, and the 52nd amino acid residue at the N-terminus participates in the stimulation of light. The molecular weight of the chromophore is very low, accounting for only 1 % of the total amount of photosensitive pigments. The two monomers are connected by C-terminal 680~840 amino acid residues to form dimers, and the C-terminus participates in signal transmission for functional nuclear localization to regulate physiological activities (Nagy and Schäfer, 2002).

3.3. Binding and transport of oxygen

Heme is a pigment that transports oxygen, oxidative catalysis, and respiratory electrons (Girvan and Munro, 2013), it can bind to oxygen, and in the hemoglobin molecule, there are four iron ions, each of which combines one molecule of oxygen to form hemoglobin oxygenation. In the presence of oxygen, oxygen molecules bind to the ions in hemoglobin to form stable hemoglobin oxygenation. When hemoglobin oxygenates reach the lungs, due to the high concentration of oxygen in the lungs, oxygen molecules will leave the hemoglobin and enter the alveoli, thereby completing the inhalation of oxygen. When oxyhemoglobin reaches tissues, the carbon dioxide produced by tissue metabolism causes the pH in the blood to drop so that oxygen binds loosely to the iron ions on the hemoglobin molecule, releasing oxygen for tissue use.

4. Biological activities of tetrapyrrole compounds

Tetrapyrrole is widely present in nature and is a natural pigment. Among them, Chl and PCB are rich in a variety of medicinal plants. Chl, as a kind of green pigment contained in higher plants and all other organisms capable of photosynthesis, is higher in green leaf plants, but is also rich in traditional Chinese medicines such as *Schisandra chinensis, Gnaphalium affine, Lycium barbarum leaves*, and Lophatherum gracile leaves. In addition, some algae also contain Chl, while PCB mainly exists in cyanobacteria, such as *Spirulina*, *Gexianmi*, etc. *Spirulina* has been proved to have anti-inflammatory and antioxidant effects, as well as against nerve damage and other effects (see Table 1). Tetrapyrrole

Table 1
Pharmacological effects of tetrapyrrole chemicals.

The main Natural tetrapyrrole compounds	Pharmacological action	Mechanism	Reference
Chlorophyll	Antioxidant	Scavenges different free radicals and blocks the formation and spread of nonradical substances.	(Fatahala et al., 2017, Ozcan et al., 2021)
	Anticancer	Affects the redox environment of cancer cells and reduces cancer cell viability	(Vanková et al., 2018, Yu et al., 2018, Ozcan et al., 2021, Rashed et al., 2023)
	Cardiovascular disease	Lowers blood lipids	(Freitas et al., 2019, Feldman et al., 2020)
	Anti-inflammation	Inhibits expression of inflammatory factors and inhibits iNOS protein expression to inhibit NO	(Islam et al., 2013, Nathan, 2022)
	Antibiosis	Promotes the body's metabolism and provides unfavorable conditions for pathogenic bacteria	(Fatahala et al., 2017, Ahmadi et al., 2022)
Bilirubin	Antioxidant	Scavenges free radicals	(Zahir et al., 2015, Bianco et al., 2020)
	Anticancer	Inhibits oxidative metabolism and glycolysis	(Keshavan et al., 2004, Kaur et al., 2021)
	Cardiovascular effect	An essential prosthetic group involved in many cardiovascular processes	(Nowis et al., 2006, Ben-Amotz et al., 2014, Bianco et al., 2020)
	Anti-inflammation	Inhibits VCAM-1-dependent leukocyte migration and inhibits the expression of inducible nitric oxide synthase (iNOS).	(Matheny et al., 2000, Zucker et al., 2015, Lee et al., 2016)
	Diabetes	Protect islets from hypoxia, oxidative stress and inflammation	(Dekker et al., 2011, Zhu et al., 2017, Yao et al., 2019b)
	Neuroprotection	Affects neuronal survival and differentiation biological processes	(Doré et al., 1999, Hartl et al., 2011, Barone et al., 2014)
PCB	Antioxidant	Scavenge, inhibiting NOX to reduce the accumulation of ROS	(Hirata et al., 2000, McCarty et al., 2021, Li, 2022)
	Anticancer	Regulates the expression of NME1 in colon cancer cells, downregulates the expression of COX-2, and can block the cell cycle in the G1 phase	(Konícková et al., 2014, Rashed et al., 2023)
	Anti-inflammation	Suppresses the inflammatory signal passage	(Li, 2022, Marín-Prida et al., 2022)
	Diabetes	Inhibits the production of proteinuria and mesangial expansion, and inhibits oxidative stress of kidneys	(Zheng et al., 2013a, McCarty, 2017)
	Neuroprotection	Inhibits NADPH oxidase activity and lipid peroxidation, and scavenges peroxy radicals	(Pentón-Rol et al., 2021)

compounds special structure determines its good biological activities through a series of effects on the body's wellbeing, greatly contributing to the treatment of human diseases.

4.1. Antioxidant activity

Chl can effectively scavenge different kinds of free radicals (such as ·OH and $\cdot O_2^-$) and block the formation and propagation of nonradical substances such as hydrogen peroxide and singlet oxygen(Fatahala et al., 2017). Chl is an antioxidant that interferes with Glutathione S-transferase P1–1 activity, Ozcan *et al.* (Ozcan et al., 2021) established a breast cancer model to evaluate its short- and long-term protection against DNA damage using Chl as an antioxidant. The results showed that the protective effect of Chl on related enzymes delayed the formation of breast tumors and improved the activity of glutathione reductase, which can act as an antioxidant molecule, enhance antioxidant enzyme activity, and regulate the balance of trace elements and minerals in tumor tissues and many organs.

Studies by Marín-Prida et al. (Marín-Prida et al., 2013) have confirmed that PCB can reduce the damage of PC12 cells by hydrogen peroxide and glutamic acid. In addition, PCB can regulate the expression of Mal, NADH dehydrogenase, Bcl-2a1, Gadd45g, Baiap2 and VEGFA genes, thereby reducing the brain injury caused by carotid artery occlusion in mice. PCB can reduce malondialdehyde content and induce superoxide dismutase to exert antioxidant effects. The study of Garcia-Pliego et al. (Garcia-Pliego et al., 2021) showed that PCB could treat renal oxidative stress caused by $HgCl_2$, and PCB had a recovery effect on the decrease of catalase, glutathione peroxidase and glutathione reductase activity caused by mercury. At the same time, PCB reduced the excessive activity of cysteine protease-3 and cysteine protease-9 caused by mercury, thus reducing the renal injury score. Zheng et al. (Zheng et al., 2013b) confirmed that PCB can prevent proteinuria and mesangial expansion in spontaneous type II diabetic mice, restore normal expression of tumor necrosis factor and fibronectin, and restore normal expression of renal oxidative stress markers and NADPH oxidase, thereby preventing renal dysfunction in spontaneous type II diabetic mice.

The antioxidant activity of bilirubin is mainly due to its capacity to neutralize free radicals (Zahir et al., 2015). It significantly increases the function of antioxidant enzymes (SOD and GSH-Px), reduces the levels of ROS and malondialdehyde. Zahir *et al.* (Zahir et al., 2015) studied the effect of bilirubin on cryopreserved islets and evaluated the antioxidant capacity of bilirubin by monitoring the vitality, insulin secretion function, oxidative stress level and transplantation performance of islets; the results showed that diabetic mice transplanted with bilirubin-preserved islets restored to normal blood glucose within 28 days, even surpassing diabetic mice transplanted with fresh islets, which confirmed that the protective effect of bilirubin is related to its antioxidant capacity (Yao et al., 2019a).

Oxidative reactions cause a series of types of damage to the body, accelerate the aging of the body, lead to diabetes, such as Alzheimer's disease, atherosclerosis, and other diseases. Although the antioxidant effect of tetrapyrrole compounds has made many contributions to human disease treatment, in the field of prevention and treatment of oxidative diseases, these compounds need to be further explored and

studied.

4.2. Anticancer activity

Chl exerts an anticancer effect by inhibiting HO-1 activity and mRNA expression, affecting the redox environment of cancer cells. Ozcan *et al.* (Ozcan et al., 2021) evaluated the anticancer activity of chlorogenic acid by injecting chlorophyllin and the carcinogen N-Methyl-N-Nitrosourea (MNU) into mice and establishing a control group. Their findings indicated that the cancer incidence in mice injected with MNU alone was 1.0 and that in mice injected with Chl was 0.4, which confirmed that Chl has a certain inhibitory effect on cancer. Vaňková *et al.* (Vaňková et al., 2018) performed experiments on the effect of Chl on the vitality of pancreatic cancer cells, identified and analyzed various indicators, and found that in the concentration range of 10~125 μmol/L, all the Chl *a/b*, and magnesium Chl *a* concentrations reduced cell viability in a dose-dependent manner, indicating that Chl could reduce the viability of cancer cells, displaying an anticancer effect. In addition, other studies confirmed the significant effect of Chl in the treatment of breast and colon cancer (Yu et al., 2018, Rashed et al., 2023).

PCB can upregulate the expression of the antimetastatic genes NME1 and COX-2 and arrest the cell cycle in the G1 phase, Rashed *et al.* (Rashed et al., 2023) used a metal ion (derived from zirconium chloride) carrier to load PCB, and detected free PCB and a highly stable organometallic backbone loaded with PCB in colon cancer cells (HT-29). Through analysis of the cell cycle distribution and apoptosis, they found that free PCB had a dose-dependent cytotoxic effect on HT-29 cells. Compared with that of free PCB, the IC50 of metal ion-supported PCB was 2 times greater. The results demonstrated that PCB has an anticancer effect and that metal ion loading enhances PCB anticancer activity. Koníčková *et al.* (Koníčková et al., 2014) established an experimental model of pancreatic cancer to assess the anticancer efficacy of PCB, studied the antiproliferative effect of PCB in human pancreatic cancer cell lines and xenograft nude mice, used PA-TU-8902, Mia PaCa-2 and BxPC-3 pancreatic cancer cells for in *vitro* research, used the MTT method to detect the viability of tumor cell lines, the results also showed that PCB could effectively reduce the viability of pancreatic cancer cells.

Since many cancers are characterized by high glycolysis rates, targeted glycolysis has become a potential therapeutic strategy that supplements the heme precursor ALA to promote heme synthesis, inhibit oxidative metabolism and glycolysis, thereby reduce the proliferation of ovarian and breast cancer cells (Kaur et al., 2021). Keshavan *et al.* (Keshavan et al., 2004) studied the impact of bilirubin on the growth and survival of colon adenocarcinoma cells by treating a monolayer of adenocarcinoma cells with bilirubin and reported that all therapeutic agents effectively decreased the survival rate of pancreatic cancer cells in a dose-dependent manner after detecting apoptosis.

Cancer is a major cause of death in the world, exploring its preventive methods and therapeutic drugs has always been a global problem. Natural tetrapyrrole compounds have good therapeutic effects on different cancers and can be used to develop related drugs to treat cancer.

4.3. Cardiovascular disease

Fat reduction can prevent various cardiovascular diseases and reduce the incidence of vascular lesions (Feldman et al., 2020). A new Chl derivative was discovered from marine cyanobacteria by Freitas *et al.* (Freitas et al., 2019) who isolated and structured the compound, to characterize the lipid-lowering activity of two isolated Chl derivatives, Freitas used the zebrafish Nile red fat metabolism assay. After zebrafish larvae were exposed to phyllins 1 and 2 (13^2-hydroxy-pheophytin A and 13^2-hydroxy-pheofarnesin A), a significant decrease in Nile red staining was observed for phyllins 1 at 10, 5, and 2.5 μg/mL, and for phyllins 2 at 10 and 5 μg/mL, slow staining with Nile red (a lipophilic fluorescent stain) was observed, indicating lipid-lowering functions of the compound.

Heme is involved in several cardiovascular processes, such as the regulation of blood pressure and the modulation of vascular tone, it can also act as an antioxidant against oxidative stress and prevent cardiovascular system damage (Bianco et al., 2020). Overall, heme is not only crucial for oxygen transport but also plays a vital role in the normal functioning of the myocardium and various cardiovascular processes. The cardioprotective effect of heme in angioproliferative diseases such as atherosclerosis has been successfully demonstrated in rats with hyperbilirubinemia and wild-type rats (Nowis et al., 2006). Ben-Amotz *et al.* (Ben-Amotz et al., 2014) established an experimental model of mouse coronary ischemia, injected coronary artery ischemia rats with heme peritoneally, and then perfused them one hour later. In addition, they established a control group and found that the myocardial infarction area in the control group was 25.5 %, while that in the experimental group was 13.34 %. According to the experimental results, heme supplementation can significantly reduce the infarct area, thereby helping to cure cardiovascular diseases.

Tetrapyrrole compounds can lower blood lipids, which can indirectly reduce the incidence of cardiovascular disease. Therefore, tetrapyrrole compounds can be used as potential compounds for the treatment of cardiovascular drugs.

4.4. Anti-inflammation

Inflammation is the dynamic response of the immune system to internal or external damage and infection (Nathan, 2022). Chl derivatives can inhibit lipopolysaccharide-induced NO production in mouse mononuclear macrophages to inhibit inflammation, Islam *et al.* (Islam et al., 2013) evaluated the anti-inflammatory effect of Chl in mouse foot edema experiments. The inflammatory mice were treated with Chl and diclofenac gel to the left and right forelimbs, respectively. The weights of the left and right paws were measured to assess the anti-inflammatory effect. The weights of the left and right paws of the mice were the same, suggesting that the anti-inflammatory effects of Chl and diclofenac gel were similar. In another set of experiments, the authors determined the effect of different concentrations of demagnesiumized Chl *a* on the anti-inflammatory effect, three levels of Chl (0.5 %, 1.0 %, and 2 %) were tested, and their influence on inflammation was assessed. The results of the experiment showed that the anti-inflammatory effect of Chl was dose dependent, which indicated that higher concentrations of Chl resulted in stronger anti-inflammatory effects. Chl has been shown to have comparable anti-inflammatory activity to diclofenac gel, and its effectiveness is dependent on the concentration applied. In addition, demagnesiumized Chl *a* can inhibit NO production by inhibiting inducible nitric oxide synthase (iNOS) protein expression for the treatment of various inflammatory diseases.

PCB has anti-inflammatory effects by inhibiting the inflammatory signaling pathway NF, reducing the proinflammatory factors interleukin-6 (IL-6) and interferon-γ (IFN-γ), and upregulating the production of the anti-inflammatory cytokine IL-10 (Li, 2022). Marín-Prida *et al* (Marín-Prida et al., 2022) evaluated the anti-inflammatory activity of PCB by establishing an autoimmune encephalomyelitis (EAE) mouse model. The authors divided the mice into a prevention group and a treatment group, administered PCB and IFN-β combination therapy at different times, and evaluated the anti-inflammatory activity of PCB by observing the clinical symptoms of the mice. The results showed that the alleviation of inflammation in mice in the prevention group was greater than that in the advanced treatment group, but the inflammation in the treatment group was also relieved. PCB apparently reduces clinical symptoms in EAE mice, demonstrating that PCB, in combination with IFN-β, has anti-inflammatory activity and can be employed as a therapeutic agent for inflammation.

Bilirubin exerts anti-inflammatory effects by inhibiting vascular cell adhesion molecule-1 (VCAM-1) dependent leukocyte migration and

inhibiting the expression of iNOS, which helps modulate the inflammatory response and protect against tissue damage (Matheny et al., 2000). Given that VCAM-1 and iNOS are important tissue damage mediators in mouse models of inflammatory colitis, Zucker *et al.* (Zucker et al., 2015) established a mouse model of dextran sodium sulfate (DSS)-induced inflammatory colitis to evaluate the anti-inflammatory activity of bilirubin in gavaged male C57BL/6 mice treated with 2.5 % DSS for 7 days via intraperitoneal injection of bilirubin (30 mg/kg). The control group was treated with potassium phosphate alone, and disease activity was monitored in a study involving DSS-treated mice. The results showed that compared with the vector-treated animals, DSS-treated mice received bilirubin treatment, serum nitrate levels were reduced, and disease severity was reduced. In addition, bilirubin can be covalently bound to polyethylene glycol compounds (PEG) to obtain polyethylene glycol bilirubin (PEG-BR). PEG-BR self-assembles into nanoparticles (BRNPs) with a size of about 110 nm. The nanoparticles significantly increase the water solubility of BR, and the BRNPs after intravenous injection will preferentially accumulate in the inflammatory site of colitis mice and inhibit the inflammatory process (Lee et al., 2016).

4.5. Diabetes

NADPH oxidase (NOX), uncoupled nitric oxide synthase, and NO can lead to diabetic complications (Inoguchi and Nawata, 2005, Youn et al., 2012, Thallas-Bonke et al., 2015). Zheng *et al.* (Zheng et al., 2013) established a db/db model of type 2 diabetic rodent mice to analyze the effect of oral PCB on oxidative stress and kidney abnormalities. The experimental group was fed a powdered PCB (15 mg/kg) for two weeks, and the control group was given the same drug-loaded diet for the detection of urine ALB. After 2 weeks of treatment with PCB (15 mg/kg, purity 89 %), the urinary and renal oxidative stress marker levels and urine albumin concentration of the db/db mice returned to normal, which indicated that PCB could inhibit proteinuria and mesangial expansion in db/db mice and normalize the expression of transforming growth factors and fibronectin by inhibiting renal oxidative stress, thereby exerting certain effects on diabetes and kidney disease. Therefore, identifying the root cause of oxidative stress and the associated loss of NO biological activity are critical for controlling diabetic complications (McCarty, 2017).

Mildly elevated bilirubin levels in diabetic patients are inversely associated with the development of diabetic complications (Zhu et al., 2017). Dekker *et al.* (Dekker et al., 2011) performed atazanavir treatment on subjects with type 2 diabetes mellitus, which induces moderate hyperbilirubinemia, and evaluated the effect of bilirubin on diabetes by observing and evaluating endothelial function and vasodilation. The authors found that the plasma antioxidant capacity and endothelial-dependent vasodilation of patients were significantly improved, the plasma von Willebrand factor was significantly reduced. The study showed that the improvement in a patient's symptoms was attributed to associated hyperbilirubinemia, and the higher the bilirubin level was, the less likely the patient was to develop diabetes and its complications. In addition, according to Yao *et al.* (Yao et al., 2019a), bilirubin protects islets from hypoxia, oxidative stress, and inflammation, and in combination with metformin and gliclazide, it enhances the treatment of diabetes and its complications and increases insulin sensitivity for long-term tolerability of islet transplantation.

4.6. Antibacterial effect

Bacteria are becoming increasingly resistant to antibiotics, and efforts are being made worldwide to find new treatments. Chl derivatives can be extracted from natural sources or simple extraction reactions, and metabolites can be quickly removed from the body after they are activated. Therefore, these materials are very suitable for the development of antimicrobial agents (Fatahala et al., 2017). The antibacterial effect of Chl can be achieved by promoting the metabolism of the body to create unfavorable living conditions for pathogenic bacteria, thereby hindering the internal respiration of pathogenic bacteria and ultimately killing them (Mowbray, 1957). Ahmadi *et al.* (Ahmadi et al., 2022) investigated the antibacterial effect of several bacteria under different concentrations of Chl (20, 40, 60, and 100 μM) by agar disc diffusion and the microdilution method, from which the bacterial activity was evaluated. The results showed that a Chl concentration of 40 μM had a significant inhibitory effect on *Listeria monocytogenes L.*, and a Chl concentration of 100 μM had the greatest inhibitory effect on bacteria. Different concentrations of the extract had significantly different inhibitory effects on *Listeria* and *Staphylococcus*. Wang et al also (Wang et al., 2019) the pathogen *Staphylococcus aureus* to study the effect of Chl on microorganisms, and the results proved that Chl and its derivatives can inhibit the multidrug resistance of bacteria. At the same time, Chl can play an antibacterial role as a photosensitizer. Ludačka et al. (Ludačka et al., 2021) prepared antibacterial polystyrene nanoparticles (ChlE @ NPs) using Chl as a raw material, and studied the antibacterial effect of the nanoparticles by co-culturing with *E. coli*. In the process of co-culture, the co-cultured bacterial solution was irradiated with 662 nm red light, and the irradiated bacterial solution was cultured on the plate to observe the growth of *E.coli*. The results showed that the irradiated ChlE @ NPs could significantly inhibit the growth of *E.coli* compared with the single *E.coli* suspension, and the colony formation unit ratio was significantly reduced.

4.7. Neuroprotection

In cultured neurons, heme accumulates intracellularly, after which neurotoxicity and HO-1 levels are elevated in the brains of patients with neurodegenerative diseases. Therefore, heme participates in pathological processes leading to abnormal mobilization of Fe^{2+}, mitochondrial isolation, increased oxidative stress, and ultimately mitochondrial dysfunction (Barone et al., 2014). Neurodegeneration is a complex process that leads to the progressive and selective loss of neurons. Heme is an essential cofactor involved in several biological processes, including neuronal survival and differentiation (Hartl et al., 2011). There are two HO-active isoenzymes that metabolize heme to bilirubin: the inducible heat shock protein HO-1 and high concentrations of constitutive HO-2 in neurons. Doré *et al.* (Doré et al., 1999) established a human embryonic kidney cell line containing HO-1 or HO-2 overexpressing human cytochrome P450 reductase and cultured rat primary hippocampal and cortical neurons, these authors tested the combination of these two cell lines to directly determine whether bilirubin has neuroprotective effects in H_2O_2-treated hippocampal neuronal cultures. The results showed that 10 μM bilirubin completely reversed the neurotoxic effects of H_2O_2. However, at concentrations less than 3 μM, the neuroprotective effect was significantly weakened. The results showed that bilirubin produced by HO-2 has physiological neuroprotective effects. However, heme can be toxic at a certain threshold concentration (Gozzelino, 2016).

PCB mainly exerts its effects by inhibiting NOX activity, limiting lipid peroxidation, and scavenging peroxy free radicals. which can further trigger the peroxidation of lipids. PCB has the potential to protect CNS tissues by inhibiting the chain reaction of lipid peroxidation. Research has suggested that PCB can interact with cellular membranes and modify their structure and function. By doing so, they may disrupt the chain reaction of lipid peroxidation by scavenging ROS or preventing the formation of lipid radicals. By quenching the chain reaction of lipid peroxidation, PCB can reduce oxidative stress and minimize damage to CNS tissues (Pentón-Rol et al., 2021).

5. Optical applications

5.1. Photoacoustic imaging (PAI)

PAI is a hybrid imaging technique used in biological and medical applications based on the photoacoustic effect, which is the generation of acoustic waves by the absorption of light in tissue (Ntziachristos and Razansky, 2010, Neprokin et al., 2022). Photoexcitation of chromophores converts absorbed light to heat, producing a sound pressure wave that can be captured by an ultrasound sensor, from which an image can be created (Banala et al., 2016). Overall, medical imaging has found extensive applications in various fields, providing valuable insights and aiding in the diagnosis, treatment planning, and monitoring of numerous medical conditions (Attia et al., 2019). Tetrapyrrole compounds have good photophysical properties, their triplet lifetime is long and yieldable, most of the tetrapyrrole triplet and oxygen molecules in the energy interval are low, and singlet oxygen production is also very high. Natural tetrapyrrole compounds such as Chl and bilirubin are modified which can be used as PA probes for disease monitoring.

Chl can be used as a photosensitizer for photodynamic therapy and a therapeutic diagnostic agent for PAI due to its spontaneous fluorescence activity and absorption peak at 680 nm, Zhong et al.(Zhong et al., 2020) proposed a micro-swimming system based on photosynthetic biological hybridization, using *Spirulina* as a brake and superparamagnetic Fe_3O_4 functionalized nanoparticles. The nanoparticles can not only release Chl as a photosensitizer to produce reactive oxygen species, inhibit tumor cell growth and achieve photodynamic therapy, but also monitor tumor treatment and tumor TME environment through PAI. Zhang et al.(Zhang et al., 2016) synthesized a liposome-encapsulated chlorophyll derivative, and used *pyropheophorbide* a as a photosensitizer to synthesize liposome / PPa nanoparticles. The nanoparticles were injected into tumor mice 12 h later and imaged with a PAI system. The results showed that the nanoparticles as a strong PA signal at the tumor site, which proved that the nanoparticles could be used as a multifunctional contrast agent for PAI.

5.2. Photodynamic therapy (PDT)

As an innovative and versatile phototherapy approach, PDT has received increasing attention from basic research into translational medicine (Kwiatkowski et al., 2018). Specifically, exogenous ALA enters the porphyrin-heme pathway and is converted into the photosensitizer Ppix; then, it is activated by an appropriate wavelength of light to produce singlet oxygen radicals, thereby destroying target cells (Rkein and Ozog, 2014). Compared to other destruction methods, PDT selectively and effectively treats lesions simultaneously over large surface areas with little scarring (Rkein and Ozog, 2014).

Photosensitizers (PSs) for PDT can be divided into first-, second-, and third-generation photosensitizers based on their history and conceptual synthesis methods (Kou et al., 2017, Zhang et al., 2018, Mfouo-Tynga et al., 2021). The first generation of tetrapyrrole PSs includes the porphyrin sodium and hemoporphyrin. Second-generation PSs were developed by modifying precursors to improve the ability of the long-wave spectral region to absorb light and increase ROS production, these PSs are chemical compounds, including porphyrin, chlorine, bacterial-chlorine, phthalocyanine, and other modified derivatives coupled with various target molecules. They have a strong absorption capacity in the visible light and near-infrared electromagnetic spectra and have a strong effect on tumors (Correia et al., 2021). Third-generation PSs are encapsulated in different carriers that bind to vectors to increase tumor selectivity, and nanoparticles (Chen et al., 2020, Chizenga and Abrahamse, 2020) and Chl derivatives containing Ce6 are effective novel tetrapyrrole-structured photosensitizers. Galliani *et al.* (Galliani and Signore, 2019) used nanotechnology to synthesize a phospholipid liposome that encapsulates iron Chl (Fe-Chl). Liposomal nanoparticles are absorbed by endocytosis and accumulate mainly in mitochondria and nuclei.

The main shortcomings of first- and second-generation PSs are poor water solubility and limited depth of light penetration, resulting in decreased treatment efficacy for tumors, while third-generation PSs lift various limitations. The bioconjugation and encapsulation of targeted precursor components are the main tactics for the development of third-generation photosensitizers, but trelated research is still in the early stage (Plekhova et al., 2022).

Compared to other oncological treatments, PDT is characterized by selectivity and the same treatment outcome. There is growing interest in treating tumors with optical techniques due to their noninvasive nature and high sensitivity. In addition, new methods to improve the effectiveness of PDT continue to be developed, and this method combined with other technologies can significantly improve treatment outcomes and reduce side effects.

5.3. Photochemical catalysis

Pharmaceutical wastewater accumulation has become a major problem, especially with the development of drug-resistant bacteria. There is an urgent need to develop drugs capable of destroying these pollutants for effective degradation through oxidative processes (Medforth et al., 2009). Among these drugs, tetrapyrrole macrocycles are of particular interest because they are among the most promising catalysts for degradation, and the use of tetrapyrrole-based catalysts produces byproducts that have lower toxicity and greater environmental persistence. Porphyrin complexes have been used as candidates for multifunctional catalysts for homogeneous or multiphase catalysis (Piccirillo et al., 2021).

In recent years, a number of photocatalysts based on tetrapyrrole macrocycles have been used for the degradation of antibiotics, among which the degradation of tetracycline-family antibiotics has been studied, and photocatalysts based on porphyrin derivatives have been investigated; e.g., *meso*-tetrakis(4-carboxyphenyl) porphyrin (TCPP) embedded in graphene oxide- Bi_2WO_6 to form the ternary catalyst TCPP@rGOBi_2WO_6 (Hu et al., 2019) and the incorporation of tetrapyrrole macrocycles into semiconductor mixtures have also been reported for the degradation of antibiotics, e.g., TCPP (FeTCPP) in iron (II) covalently attached to TiO_2 via a toluene diisocyanate (TDI) linker (FeTCPP@TDI -TiO_2) (Yao et al., 2016), moreover, these catalysts have shown high reusability, and all of them exhibit a high degree of reusability (Piccirillo et al., 2021).

6. Prospects

This article reviews the biosythesis, functional evolution, biological activities and optical applicayions of tetrapyrrole compounds. The biopreparation of tetrapyrrole compounds is relatively mature, and the tetrapyrrole biosynthesis pathway involves not only photosynthesis, respiration, nitrite and sulfite reduction but also various cellular processes, including gene expression, protein input and essential protein assembly. However, there are still certain problems in the biosynthesis of tetrapyrrole, such as a long synthesis pathway, low yield, and low conversion efficiency of key enzymes. The negative feedback inhibition of target products and intermediate products and their toxic effects on cells through accumulation need to be explored in the following directions: (1) screening of optimal key enzymes: using computational biology and structural biology, screening and establishing key enzyme libraries, and optimizing the combination of different enzymes in the pathway to obtain the best catalytic efficiency; (2) optimize the expression of heterologous pathways in chassis cells: use N-terminus and signal peptide engineering to locate the spatial location of key enzymes or reasonably regulate the expression levels of heterologous pathways and autometabolic pathways in prokaryotes to achieve reasonable allocation of cell resources; (3) enhancement of the extracellular crine pathway: Protein engineering technology is used to optimize the

screening of specific tetrapyrrole compound transporters to improve the efficiency of tetrapyrrole compound transport to the extracellular space and alleviate the toxicity of tetrapyrrole compound accumulation to cells. With the maturity of synthetic biology technology, the problems encountered in the process of microbial synthesis will be gradually solved, and finally, the construction of high-yield cell factories of tetrapyrrole compounds will be realized, however, chemical synthesis research on these plants is still limited, and additional methods need to be explored.

Tetrapyrrole compounds have been confirmed to have a variety of pharmacological activities, and researchers have proven that tetrapyrrole can participate in the treatment of a variety of diseases, including cancer and cardiovascular diseases. However, its development as an antioxidant, anti-inflammation, or anticancer drug is just the beginning of its vast application in the future. Our understanding of the mechanism of tetrapyrrole in treating diseases is incomplete. At present, there are many products in the global market that apply tetrapyrrole to health care, such as Swisse, chlorophyllin copper sodium capsules, Super chlorophyll powder, etc. In addition, tetrapyrrole compounds can be used as photosensitizers in cancer treatment. Therefore, natural tetrapyrrole compounds have great research significance. Hopefully, the underlying mechanisms will be elucidated in the foreseeable future, and tetrapyrrole could be explored as an effective drug for treating additional diseases. Tetrapyrrole is involved in light capture, light perception, and electron transfer reactions and has been widely used as a PA probe and photosensitizer. However, developing high-quality PA probes, creating novel PSs molecules with desirable drug properties, and applying them in clinical trials are the remaining challenges, which require continuous improvement of technology, and it is believed that tetrapyrrole will be more widely used in various fields. The potential of tetrapyrrole as a potential drug requires further research and verification. Scientists are working to gain insight into the mechanism of action, efficacy and safety of these agents, with a view to providing new options for future drug development and treatment.

Author contribution

Mengdie Hu and Xianwen Lu are responsible for article writing and picture drawing; Runze Liu, Qi Wang, Song Qin and Chenyang Lu are responsible for article review and revision; Wenjun Li is responsible for financial support.

CRediT authorship contribution statement

Mengdie Hu: Writing – original draft. **Xianwen Lu:** Writing – original draft. **Song Qin:** Writing – review & editing. **Runze Liu:** Writing – review & editing. **Qi Wang:** Writing – review & editing. **Chenyang Lu:** Writing – review & editing. **Wenjun Li:** Project administration, Writing – review & editing.

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