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Natural products in the discovery of novel sonosensitizers

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ABSTRACT

Sonodynamic therapy (SDT), which involves a combination of low-intensity ultrasound and chemotherapeutic agents called sonosensitizers, has been developed for its promising, distinct advantages, such as its noninvasive nature relative to traditional surgery and radiotherapy, greater accessibility to treat deeply located diseases than photodynamic therapy, and low systemic toxicity. Sonosensitizers derived from natural products play an important role in SDT, exerting potent sonodynamic activity for the treatment of various diseases including cancer, infections, and inflammation. In this review, the mechanism of SDT is systematically discussed and the recent advancements in the discovery and development of novel natural sonosensitizers for SDT are summarized. Furthermore, potential limitations and future perspectives are also presented.

Contents

1. Introduction

For challenging diseases such as cancer, traditional treatments including surgery, radiotherapy, and chemotherapy are still preferred. However, the emergence of drug resistance and treatment-associated toxicities has significantly limited the therapeutic profiles of such traditional treatment modalities. Although combination therapy is occasionally preferred for its synergic benefits, its increasing complexity is often challenging for patients. Sonodynamic therapy (SDT), a minimally invasive treatment, is being considered an excellent, promising alternative to conventional treatment modalities.

SDT is an innovative form of treating diseases, which depends on the preferential uptake and/or retention of chemotherapeutic agents termed as sonosensitizers in pathological cells and their subsequent activation via ultrasonic irradiation (Kuroki et al., 2007). As shown in Fig. 1, the following three elements are crucial to SDT: low-intensity ultrasound, a sonosensitizer, and molecular oxygen. The generation of reactive oxygen species (ROS) is the mechanism underlying SDT (Shibaguchi et al., 2011). When the sonosensitizer is exposed to a specific intensity and frequency of ultrasound, it is activated from a ground to an excited state. On returning to the ground state, it releases energy, which is transferred to oxygen to produce ROS, such as singlet oxygen and free radicals. These ROS can mediate apoptosis, thereby inhibiting the growth of pathological cells (Trendowski, 2014). It is worth noting that these sonosensitizers show low toxicity and no inhibitory effect, and they are bioactive only after being exposed to ultrasonic irradiation. Therefore, the risk of any systemic effects is greatly reduced. Although SDT is conceptually similar to the well-established photodynamic therapy (PDT), which uses light instead of ultrasound to activate the sensitizer (Dougherty et al., 1998), the former still exhibits several distinct advantages. Ultrasonic irradiation is superior to light irradiation in that the applied energy can be focused precisely on the specific

Abbreviations: B. cereus, *Bacillus cereus*; Ce6, chlorin e6; CFU, colony-forming unit; Chl–M, chlorophyllin–metal; Cur, curcumin; ER, endoplasmic reticulum; *E. coli*, *Escherichia coli*; GSH, glutathione; H22, hepatoma 22; HB, hypocrellin B; HMME, hematoporphyrin monomethyl ether; HP, hematoporphyrin; HPDs, hematoporphyrin derivatives; LPO, lipid peroxidation; MPPa, pyropheophorbide-a methyl ester; MRSA, methicillin-resistant *Staphylococcus aureus*; NPe6, mono-L-aspartyl chlorin e6; Pa, pheophorbide a; PDT, photodynamic therapy; PpIX, protoporphyrin IX; ROS, reactive oxygen species; SDT, sonodynamic therapy; SF1, Sonoflora 1™.

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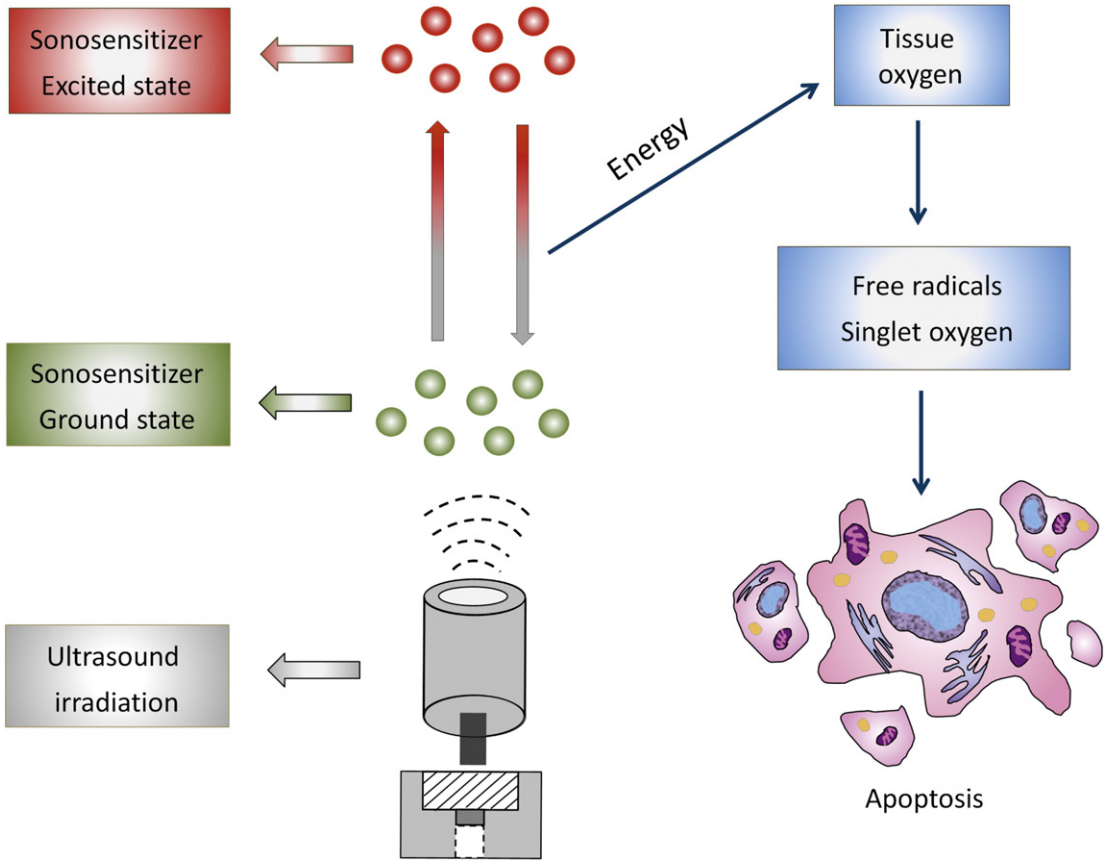

Fig. 1. Mechanism of action of SDT.

pathological location requiring treatment. Therefore, it is expected to locally activate the sonosensitizers around the pathological sites with minimal effect on the surrounding healthy cells. In addition, ultrasound is a type of mechanical wave that can penetrate tissues to a greater extent than light. As a result, SDT can be used to treat deeply located diseases (Tachibana et al., 2008). Moreover, studies have shown that low-intensity ultrasound can alter the cell membrane, thus increasing its permeability to sonosensitizers (Harrison & Balcer-Kubiczek, 1991).

For many years, natural products have been essential to drug discovery and development. At present, naturally occurring compounds and their analogues are being increasingly used not only in chemotherapy but also in modern SDT. Sonosensitizers derived from natural products play a significant role as highly potent anti-cancer, anti-infective, and anti-inflammatory agents. Compared with artificial sources, natural sonosensitizers are of great interest in drug development due to their complexity and molecular diversity. More importantly, natural compounds often exhibit high selectivity and specific biological activities based on their ability to modulate multiple signaling pathways (Cragg & Newman, 2013; Turrini et al., 2014).

In this review, the mechanism of SDT is systematically discussed and the recent advancements in the discovery and development of novel natural sonosensitizers are summarized. Some important classes of natural sonosensitizers that are being developed for SDT are presented by combining selected examples from the literature. In addition, the potential limitations and the promising prospects for natural sonosensitizers are also presented.

2. The mechanism of sonodynamic therapy (SDT)

Although a variety of studies have specifically investigated the mechanism underlying SDT, the exact mechanism remains to be elucidated. The application of SDT in clinical settings would ultimately depend on the type of sonosensitizer being administered. Moreover, different biological systems and ultrasound parameters including frequency and intensity also have a significant impact on the mechanism of SDT (Chen et al., 2014). Therefore, a universal mechanism for a synergism between ultrasound and drugs cannot be easily proposed. Essentially, the mechanisms possible for SDT can be classified into three common types: ultrasound-induced apoptosis, ultrasonic cavitation, and sonochemical effects.

2.1. Ultrasound-induced apoptosis

Apoptosis is a distinct mode of programmed cell death occurring either in unwanted cells or in severely mutated normal cells to prevent the passage of abnormal characteristics to the subsequent generations. As an ordered process of cell death, apoptosis is often stimulated by various triggers such as increased intracellular calcium concentration or oxidant concentrations, activation of Bax proteins, and increased production of ceramides (Feng et al., 2008; Hassan et al., 2010; Honda et al., 2004).

Several studies have investigated the mechanisms by which ultrasound can induce apoptosis. Ultrasound-induced cell death has been confirmed in human leukemia cell lines, including K562, U937, Nalm-6, L1210, and HL-60 (Feril et al., 2002; Honda et al., 2002; Lagneaux et al., 2002; Su et al., 2013; Wang et al., 2013c). These studies have demonstrated several characteristic features of ultrasound-induced apoptosis: disturbances in mitochondrial transmembrane potential, loss of phosphatidylserine asymmetry, morphological changes such as membrane damage, and eventual DNA fragmentation. Thereto, the mitochondria–caspase pathway is a fundamental mechanism that induces apoptosis (Lagneaux et al., 2002; Su et al., 2013; Wang et al., 2013c). Moreover, the significant decrease in the intracellular levels of glutathione (GSH) after SDT indicated the role of oxidative damage in