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The Chemotherapeutic Effects of Lapacho Tree Extract: β-Lapachone

Hsiu-Ni Kung*[1], Kuo-Shyan Lu[1] and Yat-Pang Chau[2]

[1]*Department of Anatomy and Cell Biology, College of Medicine, National Taiwan University, Taipei, Taiwan*

[2]*Department of Medicine, Mackay Medical College, New Taipei City, Taiwan*

***Corresponding author:** Hsiu-Ni Kung, Department of Anatomy and Cell Biology, College of Medicine, National Taiwan University, Taipei, Taiwan, Tel: 886-911750616; E-mail: kunghsiuni@gmail.com

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Abstract

Cancer, a serious problem throughout the world, needs more efficient drugs for clinical applications. One potential chemotherapeutic drug is β-lapachone. The study of β-lapachone begins from 1977. This commentary is going to discuss the current understanding for the therapeutic uses of β-lapachone.

Keywords: β-lapachone; Chemotherapy; Apoptosis; Necroptosis; Anti-tumorL; NQO1

The Introduction of β-lapachone

β-lapachone, (3,4-dihydro-2,2-dimethyl-2H-naphtho[1,2-b]pyran-5,6-dione), is a natural extract from lapacho tree (Handroanthus impetiginosus, (Mart. ex DC.) Mattos; Synonym: Tabebuia avellanedae). It has been reported to have many physiological effects, including anti-fungal [1,2], anti-bacterial [3,4], anti-parasitic [5,6], anti-inflammation [7], and anti-cancer [8,9] effects. Among all these effects, the most attention-grabbing effect of β-lapachone is the anticancer effect. β-lapachone has been demonstrated to elicit significant anti-tumor activity against many cancer cells, including leukemia [10,11], prostate cancer [12], osteosarcoma [13], breast cancer [14], bladder cancer [15], lung cancer [16], hepatoma [9], and even the worst pancreatic cancer [17-19]. There are at least three phase I and three phase II clinical trials of β-lapachone, as the name of ARQ 501, on treating patients with various cancers (National Cancer Institute) [20-22].

The *in vitro* Effect of β-lapachone on Tumor Cells

Many experiments showed that β-lapachone undergoes a redox cycle by NAD(P)H:quinine oxidoreductase (NQO1) [23], which reduces β-lapachone to an unstable semiquinone. Semiquinone then rapidly undergoes a two-step oxidation back to the parent stable compound, perpetuating a futile redox cycle (Figure 1). While NQO1 is highly expressed in cancer cells, futile cycle leads to the unbalance of intracellular reactive oxygen species (ROS) [24] and subsequently induces the cell death in cancer cells, and thus be considered as a potential chemotherapeutic drug.

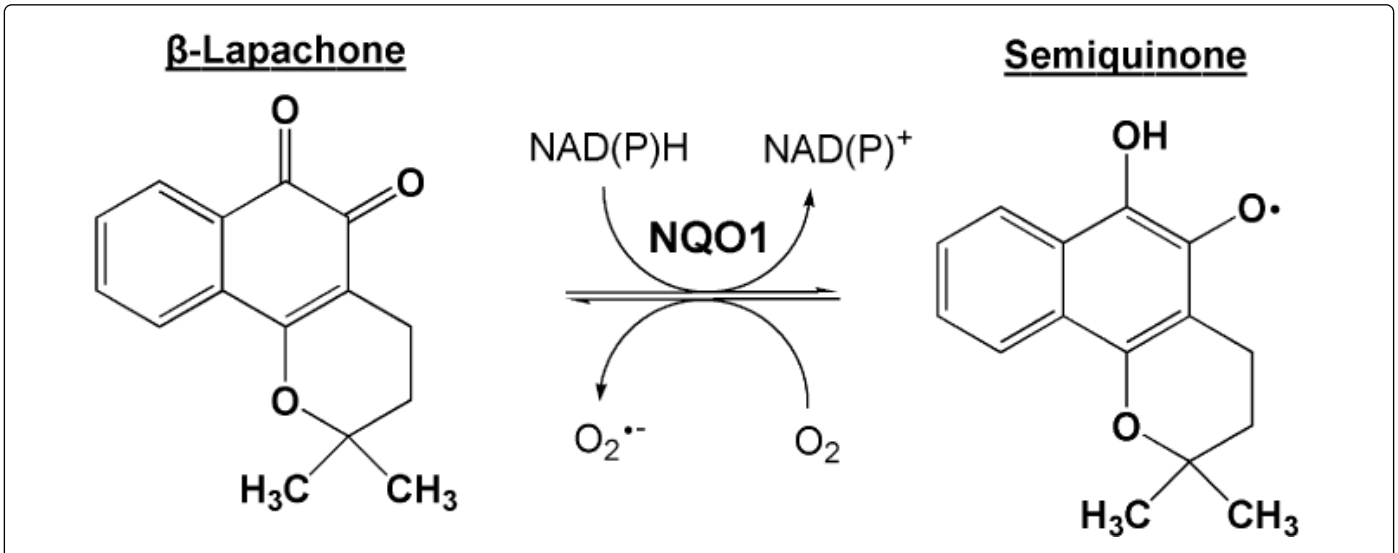

Figure 1: Futile cycle of β-lapachone. β-lapachone was reduced to an unstable semiquinone by NQO1. Semiquinone then rapidly undergoes a two-step oxidation back to the parent stable compound, perpetuating a futile redox cycle.

Does β-lapachone really induce apoptosis in cancer cells? Most researchers reported that β-lapachone leads to cell death through apoptosis [25], however a few studies indicated the necrotic signaling [13,26-29] involving in the cell death mediated by β-lapachone. This

kind of cell death, combined both apoptotic and necrotic signals, is now called necroptosis [27,29], a programmed form of necrotic cell death which initiates an extensive discussion recently [16, 18]. Moreover, β-lapachone is also shown to induce autophagic cell death in glioma cells [30].

β-lapachone triggers cell death with various signaling pathways in different types of cancer cells. Two main hypothesis of how β-lapachone causes cell death are proposed: one is the typical apoptosis and the other is atypical apoptosis, which is the necroptosis mentioned above. According to recent researches, β-lapachone may trigger tumor cells undergoing apoptosis through many pathways. First, the oxidoredox cycle of β-lapachone within cells resulting in the generation of reactive oxygen species (ROS) and superoxide anion [11,31-33]. These reactive oxidative species can oxidize thiol groups of the mitochondrial potential transition pore complex, leading to an increase in permeability of the mitochondrial inner membrane, a reduction in mitochondrial membrane depolarization and the release of cytochrome c, causes the activation of poly ADP ribose polymerase (PARP) and caspase cascade and subsequently induces cell death [9,12,29,34-36] (Figure 2). Second, β-lapachone triggers intracellular calcium influx [37], and a large amount of calcium releases from endoplasmic reticulum (ER) causing ER stress [38] in breast and prostate cancers (Figure 2). Third, β-lapachone produces DNA strand breaks [39], impedes DNA repair [40] through inhibiting topoisomerase I [41], II [42] and PARP [39] (Figure 2). Fourth, β-lapachone leads to cell cycle arrest by activating p21 and p27 and suppressing PI3K and AKT [12], the main signaling molecules of cell proliferation. Recently, JNK activation has also been demonstrated to be involved in β-lapachone-induced apoptosis (Figure 2).

In the necroptosis, a large amount of intracellular calcium influx induced by β-lapachone has been observed. The unbalance of intracellular calcium level leads to the activation of calpain, a caspase-independent and neutral Ca^{2+}dependent cysteine protease. Calpain has been shown to be the key executioner in β-lapachone-induced atypical apoptotic cell death in lung, breast and prostate cancers [16,31,34,43-45] (Figure 2).

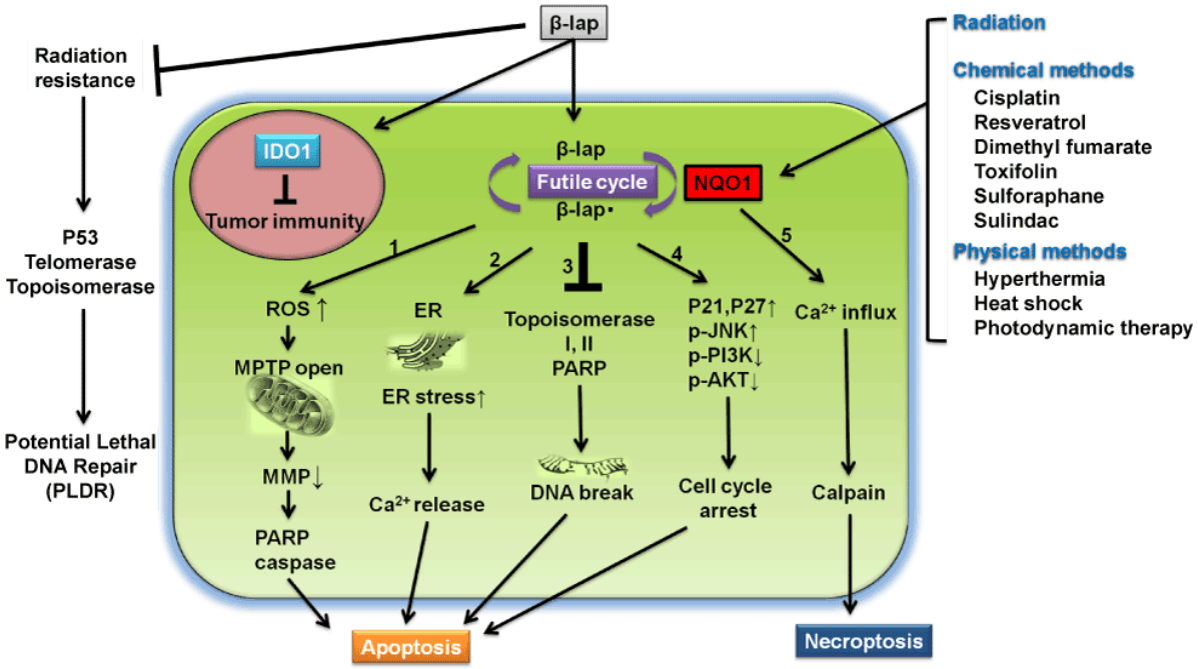

Figure 2: The scheme showing the effects of β-lapachone.

The Synergistic of β-lapachone on Tumors with Radiotherapy

The most effective application currently for tumors is radiotherapy. Radiotherapy leads to cell death in most cancer cells, but unfortunately not in all cancer cells. Some tumor cells have very low sensitivity to radiotherapy. Radiation strength for cancer patients can be increased, but the normal cells inside human bodies will be damaged as well, especially the immune cells. Researchers tend to dig out new methods to increase the radiosensitivity of cancer cells those can survive well under radiotherapy. From 1987, researchers found that β-lapachone increases sensitivity of cancer cells to radiotherapy in various cancers including laryngeal, colon, breast, lung, and prostate cancers [40,46-48]. While radiation breaks DNA in cancer cell, those cells with low radiosensitivity can repair the DNA breaks with some unclear mechanisms, which may be involved in p53 [49], telomerase [50], and topoisomerase, and escape cell death. Since p53 and telomerase are specific targets for β-lapachone [51-56], β-lapachone enhances the lethality of X-rays and radiomimetic agents in cancer cells by inhibiting potentially lethal DNA damage repair (PLDR) [40,57,58] and radiation-induced neoplastic transformation [59].

Additionally, NQO1 is also shown to be upregulated under radiation in cancer cells. In normal condition, NQO1 is a potent antioxidative enzyme that increases its enzyme activity and expression level to protect cells against the radiation-induced oxidative stress. However, the elevation of NQO1 plays a key role in the redox cycle of β-lapachone and increases the β-lapachone cytotoxic effect [31,46-48,58,60-63]. Thus, the more NQO1 in cells, the higher futile

cycle of β-lapachone occurs [23], leading a serious oxidative stress inside cells that triggers cell death in cancer cells under radiation.

Taken together, we conclude that β-lapachone and radiation exert synergistic effects on cancer cells; β-lapachone sensitizes cells to radiation by inhibiting DNA repair, and radiation sensitizes cells to β-lapachone by increasing NQO1 level in tumor cells.

The Synergistic of Drugs with β-lapachone on Tumors

In addition to radiotherapy, chemotherapy is also a key treatment for cancer patients. Searching new drug to raise the survival and life quality of patients is an urgent mission in the clinical use. With the apoptotic or necroptotic effects of β-lapachone, it has the great potential to be a good therapeutic reagent in various cancers.

It is known that NQO1 is the principal determinant of β-lapachone cytotoxicity. Highly expressed NQO1 cells are more sensitive to β-lapachone, cells with low NQO1 level can escape from β-lapachone toxicity. Thus, the main task of increasing β-lapachone sensitivity is to raise the NQO1 level or activity in cancer cells. Recently some chemicals or many physical methods have been demonstrated to upregulate NQO1 level or increase NQO1 activity to enhance the cytotoxic effect of β-lapachone [17,64-67]. In the chemical methods, many drugs including cisplatin [68], resveratrol [69,70], dimethyl fumarate [71], taxifolin [72], sulforaphane [73] etc. are suggested to raise NQO1 level or activity, that may enhance the anticancer effect of β-lapachone. In recent, a Food and Drug Administration (FDA)-approved non-steroidal anti-inflammation drug (NSAID), sulindac [35], is demonstrated by Kung to raise both the NQO1 level and activity, leading to higher sensitivity of cancer cells to β-lapachone cytotoxicity. With long investigation and observation time in clinical use, sulindac and its metabolites are well known about the safe dosage range, disadvantages, and side effects. It can increase the cytotoxic effect and decrease the dosage use of β-lapachone, which makes sulindac become a safer choice for synergistic treatment with β-lapachone.

For the physical methods, hyperthermia [74], heat shock [75,76], and photodynamic therapy (PDT) [77] showed synergistic enhancement of antitumor effect of β-lapachone by induction of NQO1 production. Under proper control of β-lapachone dosage and localization of the tumor, these physical methods can be good for β-lapachone treatment.

Other Targets of β-lapachone

Chemotherapy is a painful process for cancer patients. Although most patients are beneficial from chemotherapy, some are still suffered with the low efficiency or high side effects of chemotherapeutic drugs. One way to rescue those patients is finding the synergistic reagents to not only increase the sensitivity of chemotherapeutic drugs, but also lower the dosage of drugs to decrease the side effects. Except NQO1, there are still other targets of β-lapachone. Paclitaxel [78] or genistein isoflavone [79] combined with β-lapachone respectively are good examples that the toxicities of β-lapachone are significantly increased by targeting molecules other than NQO1. Paclitaxel-lapachone combination kills human retinoblastoma cells by targeting phospho-AKT and increasing nuclear p53 level [78]. Genistein isoflavone and β-lapachone synergistically target cell cycle at various critical checkpoints (G2/M checkpoints for genistein isoflavone; G1/S checkpoints for β-lapachone), that block the cell cycles and cause cell death [79]. In addition to NQO1, the indoleamine 2, 3-dioxygenase 1 (IDO1) enzyme, which has been demonstrated compelling anti-tumor property by modulating tumor immunity [80], is another potential target of β-lapachone. Inhibition of IDO1 has been shown to constrain the immune system from being able to mount an effective anti-tumor response, lower down the resistance to β-lapachone. β-lapachone inhibited the IDO1 activity is totally distinct from its cytotoxic property, and may add a new role of β-lapachone in anti-immunity.

Conclusion

β-lapachone now becomes a popular study object for its promising anti-tumor activity. There will be more targets of β-lapachone found in cancer cells. The more effects of β-lapachone found, the more powerful of β-lapachone. Although normal cells have lower NQO1 and are more insensitive to β-lapachone than cancer cells, the toxicity of β-lapachone toward normal human tissue is still not clear. With more clinical trials, we may find the best dosage range and more clinical uses to increase the efficiency and reduce the side effect of β-lapachone.

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