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Naphthoquinones in the Treatment of Cancer

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Abstract

Naphthoquinones are the naturally occurring pigments that possess important biological activities and are the subtype of quinones. These exhibit anticancer activity together with anti-inflammatory, analgesic, antimalarial, antischistosomal, antiviral, antitrypanosomal, leishmanicide, antifungal, anticancer and antiulcerative activities. The mechanism of action and pharmacological activities of the naphthoquinones mainly depend on their oxidation/reduction and acid/base properties and the activity can be modulated by directly adding a substituent group to the 1,4-naphthoquinone ring. Naphthoquinones, natural as well as synthetically prepared ones have gained a great deal of attention in the scientific community because of their pharmacological effects, including anticancer activity and possible therapeutic significance. Several molecules containing quinone ring exhibit antiproliferative effect against cancerous cells. The cytotoxic activity of naphthoquinones is associated with electron transporter inhibition, uncoupling oxidative phosphorylation, generation of ROS, generation of protein adduct particularly with -SH enzyme groups.

Key words: anti-cancer activity; antiproliferative; naphthoquinones; lapachol.

INTRODUCTION

Cancer is the leading cause of death worldwide and the most common causes of cancer death were due to lung (1.61 million, 19.41% of the total), liver (0.79 million, 9.2%), and stomach cancers (0.68million, 8.7%)[1]

Quinones and their derivatives are substances that are naturally obtained in the laboratory or synthesized with multiple biological functions in different organisms' metabolic cycles. Quinones are classified into anthraquinones, benzoquinones, and naphthoquinones on the basis of their chemical structure's naphthoquinones are coupled with the naphthalenic ring. Wide range of pharmacological activities such as antiallergic, antibacterial, antifungal, anti-inflammatory, antiplatelet, anti-ringworm, antithrombotic, antiviral, apoptosis, lipoxygenase and radical scavenging activity have been demonstrated by the substituents of 1,4 naphthoquinones. Anti-cancer effect of 1,4-naphthoquinones was also reported.[2,3]

NAPTHOQUINONES

Natural occurrence and structural characteristics of naphthoquinones

Naphthoquinones are the phytoconstituents occurring as secondary metabolites of plants and microbes; they play a prominent role in bio-oxidative processes and chemical defence. Examples of natural naphthoquinones derived from plants are lapachol, lawsone, juglone and plumbagin and can be distinguished by their use in traditional Indian medicine.[4]

TABLE 1: Families of the plant containing Naphthoquinone as phytoconstituent.'[5]

Ancistrocladaceae	Droseraceae	Lythraceae
Avicenniaceae	Ebenaceae	Nepenthaceae
Balsaminceae	Euphorbiaceae	Plumbaginaceae
Bignoniaceaea	Gentianaceae	Proteaceaea
Boraginaceae	Iridaceae	Scrophulariaceae
Dioncophyllaceae	Juglandaceae	Verbenaceaea

Among the natural naphthoquinones, lapachol (2-hydroxy-3-[3-methylbutenyl]-1,4-naphthoquinone) is an extensively used natural naphthoquinone, which is obtained from the wood and bark of Tecoma and Tabebuia species. It possesses analgesic, anticancer, anti-inflammatory, antimalarial, antischistosomal, antitrypanosomal, antiulcerative, antiviral, antifungal, and leishmanicidal activities. β-Lapachone, an ortho-naphthoquinone has been subject of interest due to wide range of pharmacological effect on tumor cell lines. Several dose- and time-dependent mechanisms of action related to naphthoquinone moiety are observed. Apoptosis, topoisomerase II-α inhibition, oxidative stress etc can inhibit cell growth.'[6,7]

Classification of Naphthoquinones

1. **Aminonaphthoquinones.**

Among the Aminonaphthoquinones, 1,4-naphthoquinones find numerous medical and biological applications such as antitubercular, antimalarial, antibacterial, anticancer agents, larvicides and molluscicides, herbicides, and fungicides. This experiment evaluated the cytotoxicity of aminonaphthoquinones (ANPQs) against human cancer cells, in vitro. This analysis is part of an initial screening for determination of the potential antitumor of these samples. The human cancer cell strains used were SF-295 (glioblastoma-human), MDAMB-435 (melanoma), HCT-8 (colon), HCT-116 (colon), HL-60 (leukemia), OVCAR-8 (ovarian cancer), NCI-H358M (human bronchoalveolar lung carcinoma) and PC3-M (highly metastatic prostate cancer cell line). Analysis of cytotoxicity by the MTT method has been used in the screening program at the National Cancer Institute of the United States (NCI), which tests over 10,000 samples per year.The study of the cytotoxicity by MTT method allows easily defining the cytotoxicity but not the mechanism of action.

Silva Jr. et al. demonstrated that naphthoquinones and compounds derived from β-lapachone have activity (IC50 values below 2 μM) against cancer cell lines.

The melanoma cancer cell-line was most susceptible to the aminonaphthoquinones. [8,9,10]

2. 2-Arylnaphtho[2,3-d]oxazole-4,9-dione derivatives

2-Arylnaphtho[2,3-d] oxazole-4,9-dione are the derivatives of naphthoquinone containing fused five-membered rings in their structure. They decrease multidrug resistance and potentially even increase cytotoxicity. These compounds have been assessed *in vitro* for their cytotoxic activity by MTT assay to screen for androgendous, LNCaP, and androgen-independent, PC3, human cell-lines of prostate cancer.

3. 2-Aryl-1,4-naphthoquinone-1-oxime Methyl Ethers

The cytotoxicity of a number of derivatives of quinone monooxime was measured against a cell line HeLa S3. A series of eight cancer cell lines consisting of ovarian cancer (HeLa), renal cancer (Caki-1and 786-O), lung cancer (A549), breast cancer (MCF-7) and mesothelioma cancer (H28, H2052, and MSTO-211H) were then further screened for the active compounds. The cytotoxic activity was evaluated using methylene blue stain against HeLa S3 cells. Litchfiels and Wilcoxon method was employed in determining IC50 values. 2-Aryl-1,4-naphthoquinone-1-oxime Methyl Ethers exhibits cytotoxic effect against a wide range of cancer cell lines that were most vulnerable to HeLa and MCF-7 cell lines.

4. Azanaphthoquinone pyrrolo-annelated derivatives

Two independent XTT cytotoxicity assays were used to assess the compounds against five different cancer cell lines such as cervical carcinoma (KB / HeLa), ovarian carcinoma (SKOV-3), CNS glioma (SF-268), non-small cell lung carcinoma (NCIH460), and colon adenocarcinoma (RKOp27, RKOp27IND).

5. Naphthoquinone amides and esters

Kongkathip et al reported the synthesis of 14 new aliphatic naphthoquinone amides and 17 aliphatic naphthoquinone esters. Naphthoquinone amides ' anticancer activity was evaluated by a green fluorescent protein (GFP)-based assay against human cancer cell lines such as oral cavity cancer (KB), small cell lung cancer (NCI-H187), and breast cancer (MCF-7) using the REMA and normal Vero cell lines.[11]

6. Lapachol derivatives

Lapachol is a 1,4-naphthoquinone that occurs naturally. Natural naphthoquinone, Lapachol 83, was studied primarily because of its antibacterial activity,219-221 antifungal,222 trypanocidal223 and anticancer. These compounds ' antiproliferative activity was evaluated using sulforhodamine B (SRB) assay against a panel of six human cancer cell lines such as ovarian (A2780), breast (HBL-100), cervical (HeLa), non-small cell lung (SW1573), breast (T-47D) and colon (WiDr).

7. ß-Lapachone-based 1,2,3-triazoles

A number of ß-Lapachone derivatives were synthesized by various synthetic routes and obtained in moderate to high yields (Figure 25).229 Leukemia (HL-60), melanoma (MDA-MB435), colon (HCT-8) and central nervous system (SF295) cancer cell lines were screened using the MTT assay. Some of the compounds showed highly active IC50 values of less than 2 μM. The best activity was the 1,2,3-triazoles based on ßlapachone. Compounds 101 and 103 have been found to promote apoptosis and genotoxicity induced cell death and suggest that quinone-induced apoptosis is associated with ROS production. The natural product's tumor-selective cytotoxic properties, ß-Lapachone 84 (ARQ 761), contributed to its development into clinical trials. ß-Lapachone is presently being evaluated for its anti-tumour action against advanced solid tumours.[12]

Mechanism of Action of Naphthoquinone

1. Inhibition of the DNA topoisomerases

Both enzymes break DNA using a catalytic tyrosine residue at the phosphodiester bond and are critical to the cell's proper functioning. Any changes in their balance are sufficient to induce apoptosis. Both enzymes break DNA at the phosphodiester bond using a catalytic tyrosine residue and are critical for the correct functioning of the cell. Any alteration in their balance is enough to induce apoptosis.They could be classified into three types: I drugs that bind directly to DNA, usually by intercalation; (ii) hybrid molecules that are designed rationally by linking inhibitors of both enzymes, type I and type II, or by linking pure inhibitors to interactive DNA carriers; and (iii) compounds that recognize structural motifs in both enzymes.[13,14]

Sl.no	**Naphthoquinone**	**Target(s)**	**Effectc**	**Consequence(s)d**
1	1,2-Naphthoquinone	EGFR phosphorylation	↑	Contraction of guinea pig trachea
		eNOS	↓	Suppression of vasorelaxation
		PTP activity, PTP1B activity	↓	Activation of EGFR signaling
		CREB	↓	
		IKKβ/NF-κB/NO signaling	↓	
		Inflammatory mediators	↑	Proinflammatory
		Keap1	↓	Activation of Nrf2
2	1,4-Naphthoquinone	Nrf2	↑	
3	Lapachol	DT diaphorase	↓	
		DNA scission	↑	
4	PPM-18	NF-κB, iNOS	↓	Anti-inflammatory

Topoisomerase I introduce single-strand breaks into the DNA molecule. The catalytic function of topoisomerase II is important during replication, transcription and recombination to preserve the topology of the DNA molecule. Both activities are known as the cleavage of the pre-strand and the post-strand movement respectively. Depending on their mechanism there are two classes of inhibitors. ' Poisons ' are those that stabilize the enzyme's covalent intermediates, usually a ternary complex with DNA, the enzyme and the compound. Catalytic inhibitors exhibit their activity in any stages of catalytic cycle. Eleutherin (18), a natural compound isolated from the Eleutherine americana bulb, was described by Krishnan and Barstow as a reversible catalytic inhibitor of topoisomerase II. He also demonstrated *in vitro* α and β-lapachone inhibition of topoisomerase II and graded it as irreversible catalytic inhibitors.[15,16,]

2. Regulation of the tumor suppressor factors p53

Activation of p53 factor appears to be a Potential target in anticancer therapy involves activation of p53 factor. It also appears to be a significant feature in the pharmacology of naphthoquinones, as the modulation of p53 factor inturn leads to modulation of apoptotic intrinsic pathway. Shikonin is an example of a naphthoquinone that can activate p53 in response to DNA damage, decreasing cdk4 expression, leading to apoptosis in human malignant A375-S2 cells, as well as Bax upregulation and downregulation of Bcl-2.[17]

3. MALT inhibition

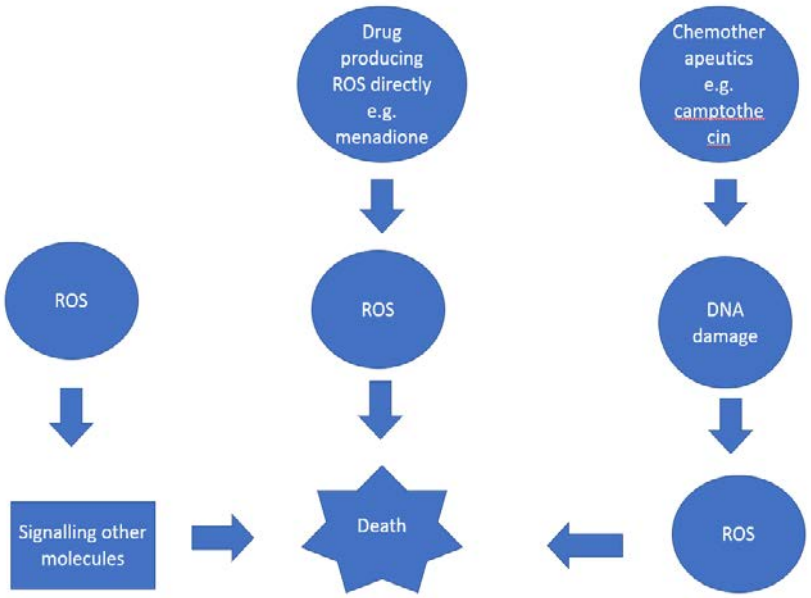
Lim et al on their studies developed new drugs that act as mucosaassociated lymphoid tissue lymphoma translocation protein (MALT1) inhibitors for the treatment of diffuse large B-cell lymphoma, one of the most aggressive varieties of cancer. They found that 1,2-amino-naphthoquinones were good inhibitors but lacked the ability to inhibit the proliferation of OCI-LY3 cells (human B-cell lymphoma) in vitro. In the search for new scaffolds, when testing β-lapachone (12), they found interestingly that it is a rather potent inhibitor of MALT1 (IC50 = 1.9 μM) and is an important inhibitor of cell growth, as mentioned earlier.[18]

4. Inflammation has now been widely recognized as an important factor in tumor initiation and progression, leading to oncogenic transformation. Genetic and epigenetic changes in cancerous cells also generate the inflammatory microenvironment the tumor needs in order to survive and progress. [19]

Kortylewski et al. reported that STAT3 could be used as a target for cancer therapy and that its removal, even under chronic inflammatory conditions, inhibits carcinogenesis and the growth of established tumors. STAT3 is persistently activated in immune cells associated to a tumor, which leads to the suppression of innate and adaptive immune responses.[20]

5. ROS

Cancer cells have a greater concentration of endogenous ROS compared to normal cells. Several theories have been proposed to explain this phenomenon. One theory proposes that because cancer cells are more metabolically active than normal cells, they require more ATP. As a result of the additional metabolic burden (stresses and respiration) on the electron transport chain, more superoxide radical anions (O2-.) are formed. ROS can damage mitochondrial DNA which leads to mutations in members of the oxidative phosphorylation process resulting in more ROS being produced. ROS is believed to increase cancer cell proliferation which leads to uncontrolled tumour growth. One mechanism that has been proposed is that ROS interferes with the MAPK signaling pathway thus disrupting normal metabolic regulation and allows uncontrolled metabolism and growth. A second mechanism by which ROS promotes cancer cell survival is through DNA damage.[21,22,23]



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