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Review

p-Cymene metallo-derivatives: An overview on anticancer activity

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Abstract: Metallo-drugs have gained a huge attention among scientific community in the couple years. These drugs types have become important compounds in cancer therapy, where, for instance, platinum complexes are being used against many tumors worldwide. Nonetheless, to *p*-cymene metallo-derivatives a promising anticancer potential has also been increasingly proposed. In this sense, the present review aims to provide an in-depth revision of *p*-cymene metallo-drugs possible mechanisms of anticancer action for upcoming pharmaceutical and biotechnological prospects. *p*-cymene metallo-derivatives have revealed very interesting anticancer activities in various test systems, including cancer cells, being thus worth of note to deepen knowledge through clinical trials on their upcoming use for cancer chemotherapy combination.

Key words: Cancer; *p*-cymene; Essential oil; Metallo-drugs; Chemotherapy; Combination therapy.

Introduction

In economically developed countries, cancer is the second leading cause of death and the third in emergent nations (1). Many types of cancer still have no effective cure although survival rates have increased due to the efficient use of anticancer drugs and even prevention (2). In cancer therapy, metallo-drugs have become important compounds, and are used worldwide against many tumors (3). These types of complexes are able to overcome drug resistance besides to decrease the likelihood of severe side effects occurrence (4); therefore, they have gained much attention in research (3). For example, a number of interesting properties have been offered by ruthenium complexes use, including a range of physiologically accessible oxidation states and lower toxicity (5), with these compounds also showing more selectivity due to an activation by tumor reduction and efficient uptake as protein adducts, responsible for the low general toxicity (6).

In the clinical treatment of a broad spectrum of cancers, cisplatin, carboplatin and oxaliplatin have been widely used (7). Nonetheless, due to their significant toxicity and both intrinsic and acquired drug resistance, the use of these platinum-based drugs is limited (8). Based on metals other than platinum in current research, a large focus has been directed towards the development of compounds (8,9).

Ruthenium-based complexes have shown to possess anti-metastatic properties and ability to overcome the main limitations of platinum-based drugs (3,10). For example, the organometallic Ru(II) complexes, especially half-sandwich Ru(II)(arene) compounds because of their biological and pharmacological properties can easily be modulated by ligand selection during the last years moved into the focus of interest. By direct coordination of 3-hydroxyflavones to a Ru(II)(cym) moiety (cym = η6-*p*-cymene) or by functionalization of an arene ligand, multitargeted anticancer agents can be prepared by linking metal fragments to the biologically active ligand systems (11). RAPTA-C ([Ru(II)(cym)(PTA)Cl_2] (cym = η6-*p*-cymene), a parent compound, resulted in compounds with glutathione-S-transferase inhibitory activity by tethering the organometallic fragment to ethacrynic acid and by a cleavage of the enzyme that accompanied inhibiting moiety from the metal fragment which can target a second biomolecule, e.g., DNA as RAPTA-C is a metastasis inhibitor and emerged as an *in vivo* anti-metastatic agent (11). KP1019 (imidazolium *trans*-[tetrachlorobis(1H-indazole) ruthenate(III)]) and NAMI-A (imidazolium *trans*-[tetrachloro(dimethylsulfoxide) (1H-imidazole) ruthenate(III)]) are two ruthenium(III)-based compounds that have also undergone phase I clinical eva-

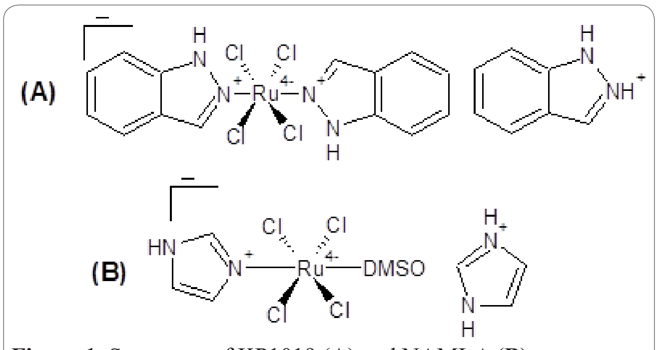

Figure 1. Structures of KP1019 (**A**) and NAMI-A (**B**).

luation (Figure 1). However, in aqueous media/physiological buffer, ruthenium (III) complexes are prone to ligand exchange reactions which hamper, to some extent, the rational design of such new compounds with relevant medicinal properties. For this reason, ruthenium (II)-arene compounds have attracted considerable attention in recent years following encouraging *in vivo* data on two prototypical compounds (Figure 2), [Ru(η^6-*p*-cymene)Cl(en)], where en = ethylenediamine (termed RAED-C) (12) and [Ru(η^6-*p*-cymene)Cl_2(pta)], where pta = 1,3,5-triaza-7-phosphaadamantane (termed RAPTA-C) (13). RAPTA-C has also shown moderate effects on solid tumor metastases, whereas RAED-C have shown a moderate potential to reduce primary tumors growth (14). In the preferential binding site of each molecule to chromatin, these differences have been tentatively attributed to differences, with RAED-C being related to DNA binding sites and RAPTA-C to the histone core (15).

In the hypoxic microenvironment of a tumor, ruthenium (III) complexes act as *prodrugs* which can be reduced to active ruthenium (II) species, and the reduced toxicity to normal tissue may be attributed to the so-called "activation by reduction" mechanism for ruthenium (III) complexes (14). The ruthenium (II) complex RAPTA-C, compared to platinum-based drugs (as judged by the high doses that may be tolerated by animals) appear to be well-tolerated *in vivo*, showing considerably reduced side effects, similar to KP1019 and NAMI-A, which are both based on a ruthenium (III) ion (14). It has also been reported that RAPTA-C showed a strong anti-angiogenic effect (16). RAPTA-C and NAMI-A both are exhibiting anti-metastatic behavior *in vivo,* whereas limited the direct cytotoxic effects on cancer cells *in vitro* (14). In a spontaneously transformed human endothelial cell line (ECV304) through MEK/ERK signaling inhibition, NAMI-A showed its ability to induce apoptosis (17). Although many clinically used VEGF-targeted therapies have been shown to induce pro-metastatic phenotypes in treating tumors, such as VEGF targeted tyrosine kinase inhibitor sunitinib (18), RAPTA-C has been shown to reduce lung metastases growth in CBA mice bearing the MCa breast carcinoma (19).

To niclosamide, a salicylanilide with anticestodal activity, potent anticancer effects similar to that of *p*-cymene have been reported (20). The derivatives of niclosamide, including N-(3,5-Bis(trifluoromethyl)phenyl)-5-chloro-2-hydroxybenzamide exhibited the most significant cytotoxicity against HL-60 cells, whereas the 5-chloro-N-(2-chlorophenyl)-2-hydroxybenzamide showed potent activity against NF-κB but 5-chloro-N-(2-chloro-4 (trifluoromethyl) phenyl)-2-hydroxybenzamide and 5-chloro-2-hydroxy-N-(4 hydroxyphenyl) benzamide inhibited both HL-60 cell proliferation (20), and NF-κB proposed the potential anticancer effect of artemisinin and its derivatives (ARTs) (21). Artemisinin is an extract from the plant *Artemisia annua* with anticancer activity similar to *p*-cymene.

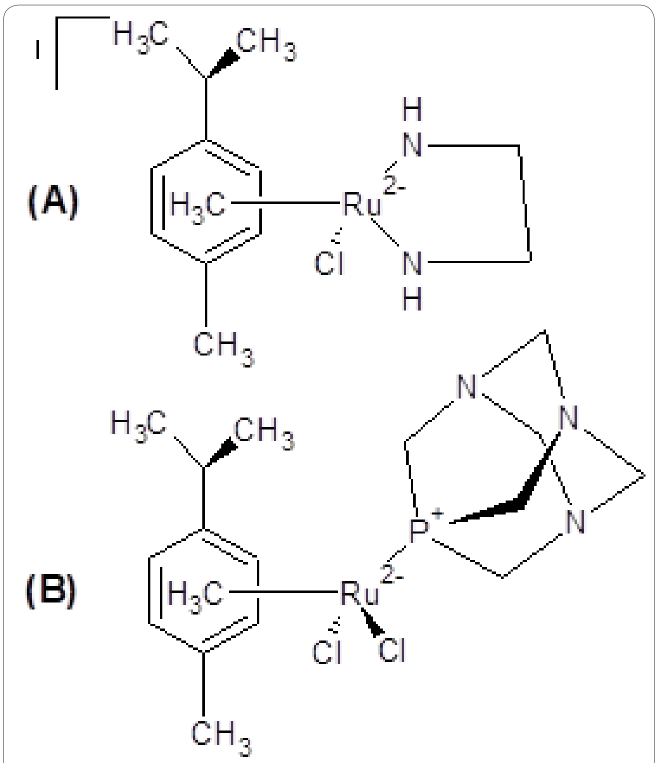

Figure 2. Structures of RAED-C (**A**) and RAPTA-C (**B**).

On the other side, it was also found that [(η6-*p*-cymene)Ru(η2-dppp)Cl][PF6] complex is stable in air and moisture, using commercially available cheap chemicals (22). To form stereo specifically Zdienyl esters, this compound can catalyze the anti-Markovnikov addition of aliphatic and aromatic carboxylic acids to terminal propargylic and the compound octadec-9-enoic acid 3-methyl-buta-1,3-dienyl ester is biocompatible in nature, with potent anticancer activity being stated by the initial biological activity evaluation (22). It has also been reported that *p*-cymene (23) exert potent effect in alcoholism treatment, likewise others drugs, such as tolserol, equanil, thorazine, sparine that have also been used for the same purpose (24).

In this sense, this review aims to provide a detailed and updated overview of *p*-cymene metallo derivatives anticancer effects, based on the most recently available literature data, for future pharmaceutical and biotechnological prospects.

P-cymene metallo-derivatives anticancer effects

Weiss *et al*. suggested that [Ru(η^6-*p*-cymene) Cl_2(pta)] given to chicken chorioallantoic membrane model at low doses (0.2 mg/kg) and in mice at high doses led to primary tumors growth inhibition (14). In addition, it has been suggested that disulfoxide complexes [$RuCl_2$(p-cymene)]$_2$(μ-BESE) and [RuCl(p-cymene)–(BESE)] PF_6 exert cytotoxic effects against human mammary cancer cell lines. In a study, [(η6-*p*-cymene) Ru(ethylenediamine)Cl]PF_6 and [(η6-*p*-cymene)Ru(1,3,5-triaza-7-phosphaadamantane)Cl_2] at 5 or 250 μM exerted anticancer activity on both normal and cancer cell lines, and were found to inhibit metastases and angiogenisis (15).

In a recent study, Ru(II)-arene complexes [Ru2(η6-*p*-cymene)2(1,3-bib)2Cl_2]X_2 was found to act against HeLa (cervix), MCF7 (breast), HepG2 (liver), A549 (lung), and normal cell L02, where an anti-proliferative activity towards cancer cells, namely at cell cycle arrest at G1/G0 phase were observed (25). In another study, complexes [Os(η6-pcym)(bphen)(dca)]PF_6 (Os-dca) and [Ru(η6-pcym)(bphen)(dca)]PF_6 (Ru-dca) in carcinoma cell and noncancerous cell lines (MDA-MB-231) were found to suppress the matrix metalloproteinase activity and/or reduced aquaporins expression and production (26).

Ruthenium(II)-arene complexes, *viz*. [Ru(η6-p cymene)(nap)Cl] 1 [Hnap = naproxen, or (S)-2-(6-methoxy-2-naphthyl)propionic acid], [Ru(η6-*p*-cymene)(diclo) Cl] 2 [Hdiclo = diclofenac or 2-[(2,6-dichlorophenyl) amino] benzeneacetic acid, [Ru(η6-*p*-cymene)(ibu)Cl] 3 [Hibu = ibuprofen or 2-(4 isobutylphenyl)propanoic acid] and [Ru(η6-*p*-cymene)(asp)Cl] were evident to act against A549, MCF7 and HeLa cells at 50 µM (27). The molecular docking studies suggest that these compounds may act through cyclooxygenase (COX)-2 expression inhibition and cell proliferation pathways.

A study proposed that [(η6-pcymene)Ru(HL)(Cl)](Cl), [(η6-*p*-cymene)Ru(HL)(Br)](Br) and [(η6-*p*-cymene)Ru(HL)(I)](I) at 6.4 µM showed anticancer effect against prostate cancer cell line (LNCaP), possibly *via* inhibiting metastasis activity (28). Another study proposed that [Ru(η6-*p*-cymene)Cl2(pta)] exert anticancer effect on A2780 tumors grown in the chicken chorioallantoic membrane (CAM) model in nude mice at a dose <15 µM of erlotinib (29). In this study, 7-(4-(Decanoyl) piperazin-1-yl)-ciprofloxacin, CipA, and its Ru(II) complex [Ru(η(6)-*p*-cymene)(CipA-H) Cl] were evident to act against A2780, A549, HCT116, and PC3 (29).

In a study, f[(η(6)-*p*-cymene)Ru(H_2O)$_3$](2+) with aminohydroxamates (2-amino-N-hydroxyacetamide (α-alahaH), 3-amino-N-hydroxypropanamide (β-alahaH) and 4-amino-N-hydroxybutanamide (γ-abhaH) were found to act against A2780, MCF-7, SKOV-3, HCT-116, and HeLa (30). In this study, an anti-proliferative effect along with antioxidant capacity of the complexes was observed. In another study, [{(*p*-cymene)RuCl_2}$_2$], [{(C_6H_6)RuCl_2}$_2$], [{Cp*RhCl_2}$_2$] and [{Cp*IrCl_2}$_2$] exerted antitumor effects in Dalton's ascites lymphoma mice (n=5) at 100 µg/mL (31). Moreover, [Ru2(p-cym)$_2$(L)$_2$]X_2-mediated anticancer effect was also seen against HL-60, A2780, MCF7 and PC3 cell lines at 40 mg/mL or ~600 µM (32). A study proposed that *p*-cymene from *Solanum erianthum* and *Steriphoma macranthum* essential oils act against Hs578T (breast), HTB-129, and PC-3 cancer cells at doses ranging from 19.5 to 625 µg/mL (33,34), and suggested that [(η^6-*p*-cymene)Ru(pEtTSC)Cl]Cl (26 -150 µM) exerted cytotoxic effect on human colon cancer (HCT-116) cells, where an inhibition of the human topoisomerase enzyme was also stated. Similar findings were also stated using [η(6)-*p*-cymene)Ru(EtATSC)Cl]Cl, where the anticancer potential stated against HCT-116 and Caco-2 cell lines were possibly related to human topoisomerase II enzyme inhibition (35).

Discussion

Cancer is still one of the major triggers of high mortality burden worldwide. It is a complex disease, therefore, substances having diverse (multi-edged like sword) mechanisms of action in cancer cells are the best option as cancer therapeutics (36). This study revealed that various complexes of *p*-cymene, such as [Ru(η^6-*p*-cymene) Cl_2(pta)] (14,29) [(η^6-*p*-cymene)Ru(pEtTSC)Cl]Cl (33) and [η(6)-*p*-cymene)Ru(EtATSC)Cl]Cl (35) exerted anticancer effects through different mechanisms. Scientific reports have suggested that [Ru2(*p*-cym)2(L)2]X2 complex is the strong cytotoxic agent to cancer cells (32). On the other hand, [{(*p*-cymene) RuCl2}$_2$] complex was found to act against pathogenic bacteria along with a number of tumor cells (31). By the half-maximal inhibitory concentration (IC_{50}) values and by using fluorescence-based apoptosis study, the *in vitro* antitumor assessment against Dalton's ascites lymphoma (DL) cells revealed a high antitumor activity. The complex, f[(η(6)-*p*-cymene) Ru(H_2O)$_3$] exerted evident antiproliferative effects against a number of human tumor cell lines, probably *via* pro-oxidative pathway (30). The complexes [{(n^6-*p*-cymene)Ru}2(µ2-α-alahaH–1)(H_2O)Br]Br·H_2O and [{(n^6-*p*-cymene)Ru}2(µ2-α-alahaH–1)(H_2O)Cl]BF4·H_2O were tested for their *in vitro* cytotoxicity using human-derived cancer cell lines (such as A2780, MCF-7, SKOV 3,HCT116, HeLa) and showed no anti-proliferative activity at the micromolar concentration range) (30).

On the other side, the combination chemotherapy is frequently used in the clinic, because of drugs synergistic effects and minimal drug doses required for cancer therapy (37). In a study, [Ru(η(6)-*p*-cymene)(CipA-H) Cl] along with 7-(4-(Decanoyl)piperazin-1-yl)-ciprofloxacin was found to act synergistically with ciprofloxacin against pathogenic bacteria and enhanced the anti-proliferative potential in cancer cells (38). The complex also revealed showed low µM cytotoxicity against HCT116p53 and the complex also retained moderate and dose-dependent anti-bacterial activity against *Escherichia coli*, a clinical isolate highly resistant to 1st, 2nd and 3rd generation β-lactam antibiotics.

Conclusion

p-cymene metallo-derivatives have shown a remarkable anticancer activity in various pre-clinical studies, including cancer cell lines. The increasingly reported diverse anticancer mechanisms of *p*-cymene metallodrugs in the various test models used suggest that these compounds may be one of the best sources of anticancer drugs for upcoming clinical uses. Further studies are needed to deepen knowledge on this aspect and to design proper clinical trials to assess its therapeutic feasibility and effectiveness when combined with other chemotherapeutic agents.

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Conflict of interest
None declared.

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