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Review Article:

1,4-Dioxane: A Narrative Review of its Pharmacological and Toxicological Attributes

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Abstract

Background: 1,4-dioxane (DX) was first discovered in 1863 and has been made accessible for commercial purposes around the 1930s as a solvent for cellulose and in the production of plastics. **Aim:** The purpose of this review was to highlight the chemistry of DX as well as its various reported pharmacological and toxicological attributes. **Methods:** The reviewed data was abstracted by using some scientific platforms, such as Google Scholar, Scopus, and Web of Science, with no limitation to the publishing date. **Results:** Chemically, DX is an organic heterocyclic molecule that can be described as an ether and found as a colorless liquid with a slightly sweet smell, akin to diethyl ether. Also, this old molecule is usually referred to as dioxane because its other structural isomers (1,2- and 1,3-) are seldom encountered. Given its pharmacokinetic profile, DX is quickly and entirely absorbed after oral intake and inhalation exposure, with the cutaneous route accounting for substantially less absorption. The main product of the metabolism of DX in humans and rats is β-hydroxy ethoxy acetic acid, which is a urine-eliminated metabolite. Pharmacologically, it has been found that DX and its derivatives have therapeutic benefits against cancer in general and hematologic malignancies in particular. Also, the studied molecule can function as an antimicrobial prospect against various pathogenic microbes. Depending on the dose and time frame, DX can cause two types of toxicity, including acute and chronic, with various attributes for each. **Conclusion:** Based on the examined information, it is possible to employ DX as a bioactive scaffold for developing potent antitumor and antimicrobial agents that can serve better in therapeutics.

1. Introduction

1.1. General aspects

In 1863, 1,4-dioxane (DX), with chemical structure displayed in **Figure 1**, was originally discovered and started working around 1930s as a commercial solvent used in the creation of plastics. From the 1950s onwards, DX was employed as a stabilizing agent for the manufacture of chlorinated organic solvents (1,2). Given that DX is a groundwater pollutant because of its high mobility in soil and water systems, scientists considered this chemical as an eco-hazardous waste. This has restricted the utilization of DX in the production of cosmetics, detergents, and shampoos (3,4).

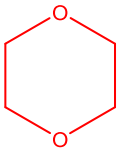

Figure 1. The DX chemical structure

DX is a colorless dioxo-hexagon that can be defined as a cyclic diether and characterized by a slightly pleasant smell akin to its aliphatic counterpart, diethyl ether. The molecule is commonly referred to as only dioxane because

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of its extensive abundance among the other dioxane isomers; 1,2- and 1,3-dioxane. In the lab, DX is utilized as a solvent for many practical purposes related to the synthesis and purification. Also, it acts as a stabilizer for the aluminum during the transportation of chlorinated hydrocarbons containers (5,6). Given its centrosymmetric, DX molecule assumes the chair conformation, which is feature shared by cousins of cyclohexane. However, the molecule shows structural flexibility enabling the easy taking of the boat shape, as shown by the metal cation chelation. For instance, because DX has only two ethyleneoxyl units, it resembled an extremely small crown ether (7,8).

After oral or inhalation exposure, DX is quickly and completely absorbed, with substantially less absorption occurring through the skin. In humans and rats, this chemical is principally metabolized into β-hydroxyethoxyacetic acid (HEAA), which is a urine-eliminated metabolite (9). The mode of the DX metabolism in humans is linear at an inhalation exposure level up to 50 ppm. On the other hand, a single intravenous dose of DX showed a dose-related modification of DX metabolism from linear (first-order) to nonlinear (saturable) when the DX plasma concentration ranged between 30 and 100 mg/ml (10). Furthermore, the tests of oral gavage in rats showed a rise in DX plasma concentration and a reduction in the chemical released to urine (11).

The elimination half-life of DX is reported to be approximately 1 hour after oral intake at 50 ppm in humans and less than that when the chemical is exhaled. The same half-life was noted in rats given low doses (10 mg/kg) of DX intravenously or orally (12). However, the formation of HEAA and its clearance from the plasma in rats are decreased when the given dose is 410 mg/kg, while an increase in unchanged DX concentrations in the breath and urine has been detected when the chemical is given orally or intravenously (13). DX biotransformation to HEAA is a significantly saturable process that is altered by the amount of the dose that was given. Oral doses given several times a day have been eliminated more quickly than a corresponding single dose, suggesting that high doses may induce DX metabolism (14). It has been reported in more than one article that DX can induce the mixed-function oxidase enzyme system in the liver of the mouse (15–17).

1.2. Pharmacological attributes

Although there are a few studies conducted to investigate the pharmacological attributes of DX and its based compounds, the currently available articles are concerned with two main ones, which are antitumor and antimicrobial attributes, as shown in **Figure 2** (18–22).

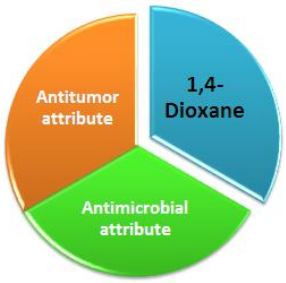


Figure 2. The main two investigated pharmacological attributes of DX and its derived compounds.

1.2.1. Antitumor attribute

Cancer is a group of disorders characterized by their foxy characteristics that are detected only by routine clinical investigation or at the delayed stage of developing cases (23–25). The medical community focused its effort for fighting cancer in two directions: first, explore new antitumor agents by either isolating them from natural sources (26–28) or synthesizing them in the lab (29–31). In this regard, many chemical scaffolds have been discovered, with a particular interest attracted to the heterocyclic-based ones (32–34). The second direction includes developing the currently-in-clinical utilization drugs to avoid the cancer-mediated resistance and minimize the off-side negative consequences that reduce patient compliance (35–37).

Over the last ten years, it has been detected that DX can function as a bioactive moiety when it is a part of molecules that target various tumor-involving receptors (38,39). Compounds **1** and **2**, as displayed in **Figure 3**, have been reported to be powerful, noncompetitive antagonists of the N-methyl-D-aspartate (NMDA) receptor with binding characteristics and biological properties similar to those of the esketamine (**Figure 3**), a dissociative anesthetic, and far away from those detected in dizocilpine (**Figure 3**), an MNDA antagonist (40). Moreover, compound **1** has been recently complexed with copper (II), forming a complex with a potent impact as an antitumor agent against several human-abstracted tumor cellular lines, including SKBR3 and MCF-7 (41,42). Concerning its mechanism of tumor growth inhibition, this copper complex may propose to induce cytotoxicity through modulating some apoptosis-regulating mediators (43).

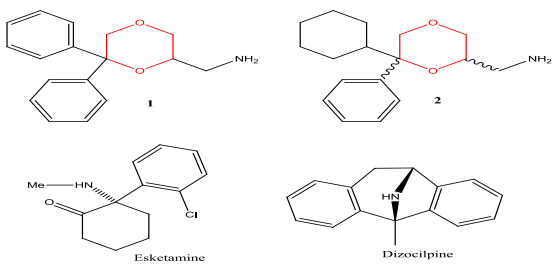


Figure 3. The chemical structures of compounds **1** and **2**, as well as esketamine and dizocilpine

The abovementioned findings inspired further evaluations of the role of the NMDA receptor in the propagation of breast cancer. These evaluations employed the sulforhodamine B assay to investigate the anticancer attribute of the chemicals displayed in **Figure 3** against two breast cancer-derived cell lines, namely MCF-7 and SKBR3 (44–46). The outcomes demonstrated that MCF-7 and SKBR3 cellular proliferation is inhibited by compounds **1** and **2** with similar GI_{50} (growth inhibition to the half) values, which are significantly lower than those of the esketamine and dizocilpine. This result suggests that there is no defined connection between the anti-breast cancer impact of the investigational compounds and their binding affinity to the NMDA receptor (47,48).

To extend the antitumor benefits arising from compounds **1** and **2**, structural modification has been conducted on the former one. This modification included shifting the diphenyl motif from position-6 of the DX to position-2 (compound **3**) or position-3 (compound **4**). Also, the freely moved 2-methylamine unit has been modified to a more rigid piperidine ring at position-6. The synthesized compounds, as displayed in **Figure 4**, have been investigated for their binding capacity with α1-adrenergic (α1) and serotonin 1A (5-HT1A) receptor subtypes. The results suggested that compound **4** showed antagonistic activity against 5-HT1A, while its counterpart compound **1** exhibited agonistic activity (49,50). On the other hand, compound **3** demonstrated a mixed inhibitory behavior against the two investigated receptors. These results supported that both receptors could play a role in tumor propagation, and their inhibition offers a promising option in tumor management (51,52). To document this hypothesis, compounds **3** and **4** have been examined as anti-prostate cancer candidates by performing *in vitro* assays against two related cellular lines named PC-3 and DU-145 (53,54). The latter investigation has been made in the presence of natural mediators, including serotonin and norepinephrine, and the outcomes supported the proposed theory (55,56).

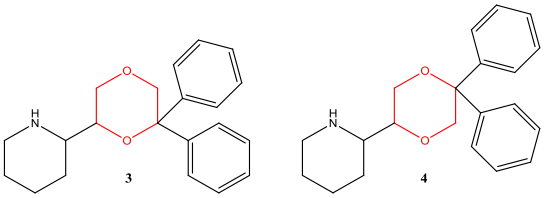


Figure 4. The chemical frameworks of compounds **3** and **4**

The therapeutic usefulness of the chemotherapeutic drug melphalan for managing hematologic malignancies has been restricted recently because of its fast excretion, low aqueous solubility, and off-side toxicity (57). To handle these clinical drawbacks, a prodrug strategy has been employed by conjugating the drug with carboxymethyl chitosan through a peptide linker (58). All the prepared prodrugs have been characterized and examined for the aqueous solubility and drug-releasing capability (59,60). The results indicated that the prepared prodrugs exhibited good aqueous solubility, while the latter attribute has been dependent on the molecular weight and the spacer type. In this regard, the drug-releasing capability can be improved by lowing the molecular weight of the employed chitosan and minimizing the spacer size (61). To enrich the acquired results, an MTT assay was conducted against many cancer-derived cell lines. Collectively, it is concluded that the use of a prodrug approach involving the utilization of chitosan, and a small peptide spacer can enhance the drug release and sensitivity, and subsequently the drug can serve better in chemotherapy (62–64).

1.2.2. Antimicrobial attribute

For many decades ago to present, humans and pathogenic microbes were involved in an existing battle (65,66). The most important weapons in the microbial hands are developing new strains with high violence infectiveness and innovating new resistance strategies toward the marketed antimicrobial drugs (67,68). To face these microbial weapons, the human arsenal of antimicrobials must be continuously enriched by new agents (69,70). These theoretically must function through un-previously targeted microbial pathways or can, in some novel ways, avoid the microbial resistance mechanisms (71,72). To date, the victory in this universal battle is not decided, necessitating heavy research about new, potent, and biocompatible antimicrobial prospects (73,74).

The lipophilic binding region of the crystal structure of the *Sindbis virus* contains one or two solvent-derived dioxane molecules. By joining two DX units through a three-carbon bridge and carrying out stereotypical production, a bis-DX antiviral medication (**5**, as displayed in **Figure 5**) was created by Kim *et al.* This led to the development of a potent antiviral prospect with an EC_{50} (half maximal effective concentration) of 14 µM that prevented the reproduction of the virus under study. An intermediate in the synthetic process named (R)-2-hydroxymethyl-[1,4]dioxane (**6**, as displayed in **Figure 5**) was found to exhibit an interesting activity. This chemical had a higher antiviral efficacy than the target compound against the tested virus, as shown by its EC_{50} of 3.4 µM. At 1 mM, neither of the target compound nor of its intermediate was harmful to BHK cells (renal fibroblasts of an uninfected golden hamster), suggesting the biosafety of these chemicals (75).

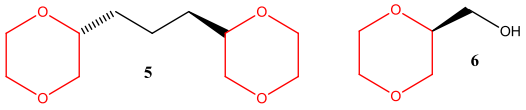
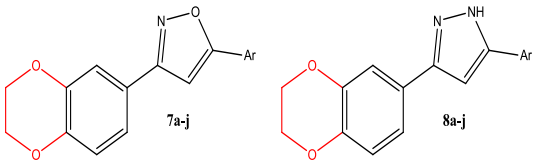


Figure 5. The chemical structures of the compound **5** and intermediate **6** as reported by Kim *et al.*

Basavaiah and his collaborators reported the synthesis, characterization, and antibacterial activity of many 1,4-benzodioxinylisoxazoles (**7a-j**) and 1,4-benzodioxinylpyrazoles (**8a-j**), as shown in **Figure 6**. The studied bacterial strains were *Staphylococcus auerus*, *Bacillus subtilis*, *Escherichia coli*, and *Salmonella typhi*. The

findings indicated that derivatives of **7** demonstrated a higher antibacterial activity against the investigated bacterial strains than those derived from **8**. Also, the best results were obtained when the 1,2-heterocyclic ring is functionalized with a deactivated aromatic ring; accordingly, the derivatives with a nitro group (**7g**, **7h**, **8g**, and **8h**) showed the greatest activity against the bacteria under study (76).



a: Ar = benzene; **b**: Ar = 4-methylbenzene; **c**: Ar = 4-methoxybenzene; **d**: Ar= 3,4,5-trimethoxybenzene; **e**: Ar = 4-chlorobenzene; **f**: Ar = 4-flourobenzene; **g**: Ar = 4-nitrobenzene; **h**: Ar = 3-nitrobenzene; **i**: Ar = naphthalene; **j**: Ar = 2-thiophene

Figure 6. The chemical structures of the compounds created by Basavaiah and his collaborators

1.3. Toxicological attributes

1.3.1. Acute toxicity manifestations

When they ingest or inhale large amounts of DX, animals may feel symptoms immediately. These include eye irritation, nervous system-related narcosis, edema, respiratory tract congestion, renal damage, hepatic necrosis, and, in advanced stages, death (77,78). The oral fatal dosage 50% (LD_{50}) for rats ranged from 5.4 to 7.1 g/kg, for mice from 5.9 to 6.8 g/kg, and for guinea pigs from 3.2 to 4.1 g/kg. The lethal concentration 50% (LC_{50}) value for rats was identified to be 0.05 mg/1iter after four hours of breathing DX (79). Direct contact with high concentrations of this chemical can irritate the skin, eyes, and respiratory system. It also negatively affects the renal, hepatic, and nervous systems (80).

In 1933, five textile factory workers accidentally inhaled a large amount of DX, resulting in acute toxicity and death. The symptoms were irritation of the upper respiratory tract, coughing, irritation of the eyes, nausea, vomiting, tiredness, uremia, coma, anorexia, vertigo, headaches, and mortality (81,82). Among the signs and symptoms, autopsies revealed significant hepatic and renal damage and congestion, as well as edema of the lung and brain. Research including human participants revealed that it was acceptable to be exposed to 200 ppm of DX for 15 minutes, but exposure of the nose, throat, and eyes developed irritation at doses above 300 ppm (83).

1.3.2. Chronic toxicity manifestations

After a wide period of exposure to DX through ingestion or inhalation, mice and rats develop renal and hepatic toxicities. The manifestations of the former toxicity may include necrosis with bleeding, cortical tube degeneration, and glomerulonephritis. On the other hand, those of hepatic toxicity can be recognized as hepatitis, spongiosis, hyperplasia, hepatocyte enlargement, necrosis, and clear or mixed focal points in hepatocytes (84). In addition to that, rats that are subject to inhalation on a regular basis have shown indications for lesions inside the nose. Increased size of the epithelial nuclei, atrophy, altered vacuole, inflammation, hydropic changes, respiratory and squamous cell metaplasia, hyperplasia, and sclerosis are a few of the abnormalities of the affected nose (85).

Exposure to DX during work has been associated with different fatal cases of centrilobular necrosis of the hepatic cells and hemorrhagic nephritis through inhalation and skin contact (86). The prolonged exposure to DX pollutant leads to neurological disorders, such as headache and hypertension, while the repeated contact and inhalation exposure has been associated with agitation, restlessness, and coma. In the case of mortality, autopsy revealed demyelination foci and perivascular enlargement throughout several regions of the brain (87).

2. Conclusion

Funding articles that described the pharmacological and toxicological attributes of DX and its derived compounds is a challenging mission. This can be attributed to the rare research handling the biochemical characteristics of DX heterocyclic molecule and its based compounds. It has been found that DX-based compounds can work as antitumor and antimicrobial prospects against various pathogens and malignancies, respectively. However, this conclusion needs to be supported by further investigation through initiating studies dealing with the synthesis of DX-based compounds and exploring their biomedical activities. The focus can be directed toward the antimicrobial and antitumor attributes in general and breast cancer in particular.

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1,4-ديوكسان: مراجعة سردية لخصائصه الدوائية والسُمية

الخلاصة:

المقدمة: تم اكتشاف 1,4-ديوكسان (DX) لأول مرة في عام 1863 وتم إنتاجه للأغراض التجارية حوالي ثلاثينيات القرن العشرين كمذيب للسليلوز وفي إنتاج البلاستيك. **الهدف:** كان الغرض من هذه المراجعة تسليط الضوء على كيمياء DX بالإضافة إلى خصائصه الدوائية والسمية المختلفة المبلغ عنها. **الطرق:** تم تلخيص البيانات التي تمت مراجعتها باستخدام بعض المنصات العلمية، مثل Google Scholar وScopus وWeb of Science، دون أي قيود على تاريخ النشر. **النتائج:** كيميائيًا، يعد DX جزيئًا غير متجانس عضوي يمكن وصفه بأنه إيثير ويوجد على شكل سائل عديم اللون ذو رائحة حلوة قليلاً، على غرار ثنائي إيثيل الإيثر. أيضًا، يُشار إلى هذا الجزيء القديم عادةً باسم الديوكسان لأن أيزومراته البنيوية الأخرى (1,2- و1,3-) نادرًا ما يتم العثور عليها. نظرًا لملفه الدوائي الحركي، يتم امتصاص DX بسرعة وبشكل كامل بعد تناوله عن طريق الفم والتعرض للاستنشاق، مع كون الطريق الجلدي مسؤولاً عن امتصاص أقل بكثير. المنتج الرئيسي لعملية التمثيل الغذائي لـ DX في البشر والجرذان هو حمض بيتا هيدروكسي إيثوكسي الأسيتيك، وهو مستقلب يتم إخراجه في البول. من الناحية الدوائية، وجد أن DX ومشتقاته لها فوائد علاجية ضد السرطان بشكل عام والأورام الخبيثة في الدم بشكل خاص. أيضًا، يمكن للجزيء المدروس أن يعمل كمضاد للميكروبات ضد العديد من الميكروبات المسببة للأمراض. اعتمادًا على الجرعة والإطار الزمني، يمكن أن يسبب DX نوعين من السمية، بما في ذلك الحادة والمزمنة، مع سمات مختلفة لكل منهما. **الاستنتاج:** بناءً على المعلومات المدروسة، من الممكن استخدام DX كسقالة حيوية لتطوير عوامل مضادة للأورام ومضادة للميكروبات قوية يمكن أن تخدم بشكل أفضل في العلاج.

الكلمات المفتاحية: 1,4-ديوكسان، الخصائص الكيميائية، السمات الدوائية، ملف السمية.