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Review

The Rationality of Implementation of Dimethyl Sulfoxide as Differentiation-inducing Agent in Cancer Therapy

BA X. HOANG[1], BO HAN[1], WILLIAM H. FANG[2], HAU D. TRAN[3], CUONG HOANG[4], DAVID G. SHAW[5] and THAI Q. NGUYEN[6]

[1]*Nimni-Cordoba Tissue Engineering and Drug Discovery Lab, Department of Surgery, Keck School of Medicine of the University of Southern California, Los Angeles, CA, U.S.A.;*
[2]*Department of Translational Research, Western University of Health Sciences, Pomona, CA, U.S.A.;*
[3]*Department of Oncology, National Children Hospital of Vietnam, Hanoi, Vietnam;*
[4]*Department of Traumatology, National Institute of Ophthalmology of Vietnam, Hanoi, Vietnam;*
[5]*Integrated Medical Associates, Foster City, CA, U.S.A.;*
[6]*Thai Minh Pharmaceutical JSC, Hanoi, Vietnam*

Abstract. *One of the major hallmarks of many cancer cells is dedifferentiated cells (immature cells) with little or no resemblance to normal cells. Besides the poor differentiation, malignant cells also have important features such as aggressiveness and resistance to different therapeutics. Differentiation potentiators hold great promise for cancer treatment. Dimethyl sulfoxide (DMSO) is a well-characterized pharmaceutical solvent. It is used as a component of numerous cancer therapeutic approaches, including cancer treatment and several approved cancer immune therapeutics such as Car-T cell therapy and the FDA-approved drug Mekinist (trametinib DMSO) for melanoma treatment. It is also biologically recognized as a pharmaceutical solvent and cryoprotectant. In the current literature, there are no mentions of DMSO's possible ability to potentiate therapeutic activity as a component of these cancer treatments. This review aimed to summarize scientific evidence and substantiate the concept that DMSO can contribute positively to the overall efficacy of cancer treatment as an adjuvant that is safe, inexpensive, and an effective differentiation-inducing therapeutic agent.*

Correspondence to: Ba X. Hoang, MD, Ph.D., Nimni-Cordoba Tissue Engineering and Drug Discovery Lab, Department of Surgery, Keck School of Medicine of University of Southern California, 1333 San Pablo Street, BMT-302, Los Angeles, CA 90033, USA. Tel: +1 3234422242, e-mail: baxuanho@usc.edu

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Differentiation is the cellular developmental process whereby cells change in form and develop specialized functions. The tumor cell differentiation stage is a crucial aspect of defining histopathological malignancies. The differentiation process is typically unidirectional in normal cells; however, cancer cells, like stem cells, have shown that this process can be reversible, be dedifferentiated or re-differentiated. Higher degrees of differentiation pose a better prognosis than a low degree and are strongly associated with tumor behavior, invasiveness, and resistance to cancer therapy (1).

Treating cancers through the induction of cell differentiation has been an attractive and practical approach (2). Reagents, such as all-trans-retinoic acid (ATRA), nerve growth factor (NGF), dimethyl sulfoxide (DMSO), vitamin D3, 12-0-tetradecanoylphorbol 13-acetate (TPA), peroxisome proliferator-activated receptor-gamma (PPAR-γ), hexamethylene-bis-acetamide (HMBA), transforming growth factor-beta (TGF-β), butyric acid, cAMP, and vesnarinone, have been extensively studied for their differentiation-inducing ability on cancer cells in *in vitro* models and validated in preclinical studies and human trials (3-5). Notably, combining differentiation agents with conventional medicine such as chemotherapy or radiation therapy, can potentiate the treatment effect seen in patients with advanced cancer (6, 7). One example of the most commonly used cellular differentiation treatment for cancer is ATRA, a well-known drug for certain dermatological diseases, and a

redifferentiation agent for hematological malignancies and thyroid cancer for over 20 years (8, 9). When using retinoic acid in combination with cytotoxic chemotherapies for acute promyelocytic leukemia (APML), the remission rates progressively improve from around 50% to more than 90% in newly diagnosed APML patients (3, 10). Despite the success of ATRA, numerous challenges remain for cancer redifferentiation therapy, particularly in solid tumors. There is a lack of understanding of the biology of the normal differentiation pathway; the mechanisms responsible for the inhibition of differentiation vary among different tumor types and patients. Many potential therapeutic agents have been demonstrated to induce differentiation in experimental models but failed to develop into approved drugs (11).

A potential chemical of interest that fits this bill is Dimethyl sulfoxide (DMSO). As an amphipathic agent, DMSO is widely used as a solvent for water-insoluble molecules, cryopreserving agents, and cell therapies (12). It has been used as a cell differentiation inducer, free radical scavenger, and radioprotectant (13-15). In addition, various pharmaceutical and therapeutic properties of DMSO, such as anti-inflammatory, antiviral, antifungal, antibacterial, local, and systemic analgesia, and membrane penetration enhancement, have been applied in preclinical applications (16, 17). DMSO is used as a drug delivery vehicle for various human and animal conditions, including gastrointestinal diseases, amyloidosis, dermatological disorders, traumatic musculoskeletal disorders, brain edema, rheumatologic diseases, soft tissue injuries of chemotherapeutic drugs, and radiotherapy (18-25). FDA has approved DMSO for treating interstitial cystitis in the United States (26).

Previously, our group reported the excellent safety profile and efficacy of DMSO for palliative care and pain control in advanced cancer patients (27-30). Recently, DMSO has been included in biological cancer treatment and several FDA-approved cancer immune therapeutic modalities such as Car-T cell therapy and melanoma drug Mekinist (trametinib DMSO) (31). However, besides its recognized biological role as a pharmaceutical solvent and cryoprotectant, there was no mention of DMSO's possible ability to potentiate therapeutic activity as a component of these cancer treatments.

In this current review, we summarize experimental and clinical evidence to support the implementation of DMSO as a safe, effective, and affordable differentiation inducer to potentiate the efficacy of cancer therapeutic modalities.

DMSO as a differentiation-inducing/signal-transducing agent in experimental cancer studies. In 1971, a series of experimental studies documented DMSO's properties of viable differentiation-inducing activities in erythroleukemic cells (32-34). In these studies, DMSO induced differentiation by altering gene expression *via* regulating DNA and protein interactions through inducing conformational changes. Abnormal cell differentiation, particularly the suppression of terminal cell differentiation, exists in all tumors, especially leukemia. Tumor suppressors are vital in the gateway to terminal cell differentiation. Teimourian *et al*. studied the differentiation-inducing effects of DMSO and ATRA through the phosphatase and tensin homolog gene (PTEN) (35). The researchers inhibited PTEN tumor suppressor gene expression by siRNA to investigate the effect of potentiating cell survival and inhibiting apoptosis on HL-60 cell differentiation by DMSO and ATRA. The results showed that PTEN siRNA significantly increased HL-60 cell differentiation in the presence of DMSO and ATRA (35). At the same time, the presence of siRNA hampered the accumulation of apoptotic cells during incubation. The study suggested that adding DMSO could increase the efficacy of differentiation therapy through the manipulation of PTEN for acute myelogenous leukemia.

Peripheral blood leukocytes from a patient with APML are predominantly promyelocytes. When DMSO was added in the culture medium, cells were induced to differentiate into mature types of granulocytes, including myelocytes, metamyelocytes, and segmented neutrophils. All 150 clones developed from the HL-60 culture showed similar morphological differentiation with functional maturity, causing leukemic cells to lose their proliferative properties in the presence of DMSO (36). The induction of leukemic cell differentiation into mature cells is a major strategy for treating leukemia. Since differentiated leukemic cells lose their proliferative and tumor-forming abilities, different differentiation inducers have been extensively studied as valuable candidates for leukemia treatment. The study by Hong-Nu *et al*. (37) showed that the combination of TNF-α with DMSO had a synergic effect on HL-60 cell differentiation by increasing CD11b expression and cell population in the G1 phase through the activation of the ERK pathway. The results of this study also suggest that TNF-α synergistically increases DMSO-induced differentiation of HL-60 cells through the activation of the ERK/MAPK-signaling pathway.

In another study, the same group of researchers demonstrated that DMSO induced up-regulation of the tumor suppressor PTEN by activating NF-kB (38). It is proposed that the degradation of phosphatidylinositol 3,4,5-trisphosphate (PIP3) to phosphatidylinositol 4,5-bisphosphate inhibits the activity of PI3K. PIP3 is an essential regulator of cell growth and survival through Akt, expressed in HL60 cells (39). Cancer survival signals are mediated mainly by PI3K/Akt (40); hence this pathway may contribute to a resistant phenotype. Therefore, an increased expression of the tumor suppressor PTEN could lead to the inhibition of Akt phosphorylation, allowing HL60 cells to differentiate into neutrophil-like cells.

The highly aggressive prostate cancer cells utilize androgen receptor (AR) to signal their growth and metastasis. Despite the treatment advancement achieved through androgen

deprivation therapy, the recurrence of castration-resistant prostate cancer (CRPC) cannot be prevented. DMSO has been shown to suppress AR levels in the CRPC cell lines by decreasing the expression of hetero-nuclear ribonucleoprotein H1 (41). Treatment with low dose DMSO (0.1-1%) did not exhibit any cytotoxicity or changes in cell viability; minimal cytotoxicity was observed when DMSO concentration increased to 2.5% in a 96-h treatment. These clinical doses of DMSO caused a significant (p<0.01) decrease in the migratory ability of CRPC cell lines, suggesting that DMSO may decrease the metastatic ability of CRPC cells (41).

Low-dose DMSO significantly enhanced the antiproliferative effect of interferon-alpha (IFN-α) in several human lung adenocarcinoma cells *in vitro* and *in vivo* studies (42). DMSO, along with other anti-cancer drugs, hexamethylene bisacetamide (HMBA), doxorubicin, and 5-fluorouracil (5-FU), have been tested on adenocarcinoma cell lines (PC9 & PC14) (43). Different concentrations of DMSO induced morphological changes in the adenocarcinoma cells, with 1% of DMSO causing cells to become cuboidal, polygonal, and adhere closely to each other. Additionally, when tested in conjunction with IFN-α, DMSO increased the sensitivity of the cancer cells compared to other drugs, and also increasing alkaline phosphatase activity (42). Alkaline phosphatase is a marker of type II pneumocyte maturation and differentiation (44), indicating that DMSO could potentiate cancer treatments in lung cancer patients. Another *in vitro* study compared the differentiation-inducing effect of DMSO and retinoic acid on a polyclonal human ovarian cancer cell line (HOC-7) (45). DMSO caused elevation of membrane-associated staining epidermal growth factor-receptor (EGF-R) and desmoplakins I and II (DPI+II) (46). After treatment, evaluation with ELISA and western blotting revealed that both DMSO and retinoic acid caused down-regulation of Myc oncoproteins, with DMSO causing a more significant reduction, leading to a decrease in cell growth. Interestingly, only treatment with DMSO caused increased epithelial cell differentiation.

DMSO and butyrate were studied for their effects on four human intestinal tumor cell lines *in vitro* (47). The growth of all four of these tumor cell lines was significantly inhibited, and doubling times increased by twofold in the presence of 2 mM butyrate and 2% DMSO. Their lectin-binding properties were evaluated using flow cytometric analysis to assess the effects on modulating cell gene expression. All four cell lines showed an increased lectin binding, indicating a differentiation-inducing effect of butyrate and DMSO on these cell lines (47).

Tsao *et al*. (48) evaluated three differentiation-modifying agents, sodium butyrate, DMSO, and retinoic acid, on the human rectal adenocarcinoma cell line (HRT-18) on cell growth, morphology, carcinoembryonic antigen content, cell surface membrane-associated enzyme activities, and glycoprotein profiles *in vitro*. All tested agents caused a marked reversible increase in doubling times, decreased saturation densities, and a markedly reduced colony-forming efficiency. DMSO caused a significant reduction in carcinoembryonic antigen levels and alkaline phosphatase activity, whereas it was shown to increase with butyrate (48).

Table I. *Safety and toxicity of dimethyl sulfoxide (DMSO) usage.*

Category	Risks
Oral delivery	(LD_{50} 14,500-28,300 mg/kg, rat)
Transdermal delivery	(LD_{50} 40,000 mg/kg, rat)
SC injection	(100% at <0.5 ml; <15% at 2.0 ml)
IV injection	IV injectables should limit DMSO use to <10%
Toxicity	Well characterized ADME profile
	Half-life of parent compound and its metabolite of nine hours
	Essentially non-toxic by all routes of administration
	Not carcinogenic, mutagenic or a reproductive toxin (CMR)
	Does not bioaccumulate
	Primary excretion through the kidney, secondary elimination through the respiratory tract and bile

SC: Subcutaneous; IV: intravenous; ADME: absorption, distribution, metabolism, and excretion.

The most attractive potential application of DMSO in cancer treatment is as an adjuvant in immunotherapy. Jiang *et al*. (49) proposed a possible implementation of DMSO to induce anti-tumor immunity during chemotherapy. After treating Hepa1-6 cells with 2% DMSO in the culture medium, there was reduced proliferation with no significant apoptosis or decreased viability. After seven days of treatment with DMSO, the proliferation rate of Hepa1-6 cells was restored in a DMSO-free medium. However, their gene expression profile showed an irreversible alteration in more than 1,000 genes, suggesting that treating viable cells with DMSO may alter biological features by inducing anti-tumor immunity *in vivo*.

In the hepatocellular carcinoma cell line Huh7, regular culture in the absence of DMSO initially formed tightly packed monolayers, but was compromised on day 10 with extensive cell death (50). In the presence of 1% DMSO, the monolayers were composed of mono- and binucleated cells with primary hepatocytes features. The addition of DMSO has been shown to significantly increase the expression of three hepatocellular differentiation markers, including human albumin, A1AT mRNA, and HNF4-a (50). In a subsequent study, Huh7 cells treated with DMSO had increased ability to metabolize drugs, as evidenced by increased levels of various drug-metabolizing enzymes (51). Additionally, DMSO exposure inhibits cell division, arrests the cell cycle

Table II. *Products that contain dimethyl sulfoxide (DMSO).*

Product name	Dosage type	Amount of DMSO	For the treatment of	Approval in regulatory body
Pennsaid (Dimethaid Health Care Ltd, Markham, Ontario)	Topical	1.5% diclofenac sodium topical solution with 45.5% w/v DMSO	Knee Osteoarthritis	Approved in Canada, United States, and several European countries
Ibufoam (Nuvo Research,	Topical	5% NSAID ibuprofen and 45.5% w/v DMSO	Knee Osteoarthritis	Granted a patent by US Patent Office and in Phase 1 clinical trials
Herpid (Astellas Pharma, Tokyo, Japan)	Topical	5% idoxuridine and 100% DMSO	Herpes Zoster and Varicella-zoster virus	Approved in the United Kingdom
Zostum (Galderma, All-Phar Services Limited, Dublin, Ireland)	Topical	5% idoxuridine and 100% DMSO	Herpes Zoster	Approved in Germany
Kemsol (Mylan Institutional LLC, Rockford, IL, USA)	Instillation of 50 ml directly into the bladder by catheter or asepto syringe	50% water and 50% DMSO	Interstitial cystitis	Approved by the U.S. FDA
Rimso-50 (Mylan Institutional LLC, Rockford, IL, USA)	Instillation of 50 ml directly into the bladder by catheter or asepto syringe	50% water and 50% DMSO	Interstitial cystitis	Approved by the U.S. FDA
Prochymal (Osirirs Therapeutics, Columbia, MD, USA)	Infusion	2.5×10^6 hMSCs/ml, 1.9% human serum albumin, and 3.8% DMSO	Graft *vs.* Host disease	Approved by Canada
Dabrafenib (Tafilnar) and Mekinist (Trametinib)	Oral	<2 mg	Anaplastic thyroid cancer	Approved by the U.S. FDA

NSAID: Non-steroidal anti-inflammatory drugs; hMSCs: human mesenchymal stem cells; FDA: Food and Drug Administration.

in G0/G1 state, remaining viable in culture without splitting for over 60 days, and increases cell differentiation characterized by an increase in liver-specific genes (51).

Prados *et al*. (52) demonstrated that the addition of 1.25% DMSO can modulate cell differentiation even in rhabdomyosarcomas, poorly differentiated malignant tumors. After culturing these tumor cells with DMSO for 8 h, there was a significantly increased expression of desmin, and after 12 h, there was a significant increase in the expression of precursor compounds in the cytoplasm (actin) and cytoskeleton (alpha-actin), typical differentiation phenotypes in rhabdomyosarcoma cell lines (53).

The above experimental research indicates a robust differentiation-inducing activity of DMSO in different cancer cell lines, suggesting a possible practical application of this already approved pharmaceutical solvent, cryoprotectant, and drug as adjuvant therapy in conventional cancer treatment.

DMSO safety profile. DMSO is mainly used as a cryoprotective agent and a pharmaceutical solvent in many compounds. When used clinically, it has a very good safety profile. A single dose of iodogen dissolved in DMSO up to 30.0 mg/kg, over 3,000 times the dose in potential human applications, appears safe, with a projected LD_{50} of 60.0 mg/kg in mice (54). The adverse effect of DMSO that may hamper its application is the garlic or onion-like odor and taste. It can persist in the body for up to 2 days. DMSO by itself is odorless, but the pulmonary excretion as dimethyl sulfide causes such malodor (25, 55). DMSO also releases histamine, leading to flushing and allergic reactions, which can lead to potential adverse human effects at higher concentrations (56). When DMSO was administered intravenously, side effects in patients, such as nausea and vomiting, were sometimes observed. However, these symptoms usually disappeared shortly after infusion and were less frequent at lower dosages (57). The most serious reported adverse effect associated with DMSO injection was intravascular hemolysis when a 40% or higher concentration solution was applied. This pathological hemolysis is caused by increased osmotic pressure on erythrocytes through elevated DMSO concentrations (58). This potential adverse effect can be avoided by infusing DMSO at a concentration of 30% or less (59).

Regarding dermatological side effects, the most reported symptoms related to topical application are rash, dry skin, and contact dermatitis. However, the reactions are usually mild and brief and do not re-appear with conditional treatment (60). When comparing adverse event rates, there was no difference

between the trial DMSO drug, placebo, or DMSO vehicle when looking at the skin, gastrointestinal, or cardiac events (61). No cases of lens changes in humans have been reported with prolonged administration of large amounts of DMSO in systemic, topical, or local ophthalmic treatment (62). Therefore, DMSO was proven to have little to no toxicity when used in clinically adequate doses. The pharmacological safety profile of DMSO is listed in Table I (14).

For the past two decades, the registration number of DMSO-based pharmaceutical agents, over-the-counter (OTC) drugs, and medical devices (31) has increased globally. The application of DMSO as an active ingredient or excipient in drug formulations has expanded to topical, oral, and parenteral products (63). DMSO (10%) is commonly used as a cryoprotective agent (CPA), added to the culture media for preserving and storing biological tissues (64). It acts as a penetrating cryopreservation agent to increase the porosity of the cellular membrane, allowing water to flow more freely through the membrane, avoiding ice crystal formation (65). DMSO has remained the gold standard CPA for many different cell types over other agents such as glycerol and polyethylene glycol (66). FDA has approved DMSO as a CPA for sperm, eggs, stem cells, bone marrow cells, and organs for transplant (16). In the concentration ranging from 5% to 17%, DMSO is a critical CPA in many cell therapy products, such as CAR-T, melanoma treatment Mekinist, and stem cell transplantation (31). Table II summarizes the pharmaceutical formulations that incorporate DMSO as an excipient (14).

Discussion and Perspectives

DMSO is a very versatile compound that is currently widely used in tissue/organ preservation and as a cryoprotectant for biologic therapy. There is also a huge potential for medical uses of DMSO in cancer management, including penetration-enhancing and solvent excipients in cancer therapeutics, pain control, palliative care, and treatment of tissue injuries due to radiotherapy and chemotherapy. Numerous experimental and clinical data suggest a possible productive role of DMSO as an active drug or adjuvant therapeutic agent to improve the effectiveness of existing cancer therapies and control abnormal cell differentiation, in particular inhibition of end-cell differentiation, in tumors (67).

Based on the available published research data, DMSO might be implemented as an effective, safe, and inexpensive differentiation-inducing therapeutic agent to enhance the overall efficacy of the established conventional and complementary cancer treatments. Besides the documented robust differentiation-inducing activities, DMSO has also demonstrated several anti-cancer properties that could further benefit cancer patients, including suppressing proliferation and inducing apoptosis (68-70).

Although clinical research on DMSO has regained some enthusiasm in the past 20 years, the development of DMSO as an active pharmaceutical drug or adjuvant therapeutic has not been attractive to the pharmaceutical industry, mainly because of its generic status. DMSO will remain as an important component in the most sophisticated modern cell therapeutics in stem cell transplantation and immunotherapy. Currently, DMSO is widely used in various pharmaceutical preparations to enhance the solubility of drugs, leading to the delivery of a higher concentration of medication to the targets (71).

Since DMSO is inexpensive and non-patentable, pharmaceutical companies lack the financial incentive to develop this therapeutic agent in cancer clinical applications. Future non-profit and doctors-driven explorative and translational clinical investigations are needed to prove and promote the practical implementation of DMSO as a possible adjuvant drug, analgesic, and palliative care therapy for cancer patients.

Conflicts of Interest

No competing financial interests exist in relation to this study.

Authors' Contributions

All Authors contributed equally to the writing and submission of the manuscript.

References

1 Jögi A, Vaapil M, Johansson M and Påhlman S: Cancer cell differentiation heterogeneity and aggressive behavior in solid tumors. Ups J Med Sci *117(2)*: 217-224, 2012. PMID: 22376239. DOI: 10.3109/03009734.2012.659294
2 Yan M and Liu Q: Differentiation therapy: a promising strategy for cancer treatment. Chin J Cancer *35*: 3, 2016. PMID: 26739838. DOI: 10.1186/s40880-015-0059-x
3 Ryningen A, Stapnes C, Paulsen K, Lassalle P, Gjertsen BT and Bruserud O: *In vivo* biological effects of ATRA in the treatment of AML. Expert Opin Investig Drugs *17(11)*: 1623-1633, 2008. PMID: 18922099. DOI: 10.1517/13543784.17.11.1623
4 Cruz FD and Matushansky I: Solid tumor differentiation therapy - is it possible? Oncotarget *3(5)*: 559-567, 2012. PMID: 22643847. DOI: 10.18632/oncotarget.512
5 Kawamata H, Tachibana M, Fujimori T and Imai Y: Differentiation-inducing therapy for solid tumors. Curr Pharm Des *12(3)*: 379-385, 2006. PMID: 16454751. DOI: 10.2174/138161206775201947
6 Beere HM and Hickman JA: Differentiation: a suitable strategy for cancer chemotherapy? Anticancer Drug Des *8(4)*: 299-322, 1993. PMID: 8240658.
7 de Thé H: Differentiation therapy revisited. Nat Rev Cancer *18(2)*: 117-127, 2018. PMID: 29192213. DOI: 10.1038/nrc.2017.103
8 Hong CM and Ahn BC: Redifferentiation of radioiodine refractory differentiated thyroid cancer for reapplication of I-131 therapy. Front Endocrinol (Lausanne) *8*: 260, 2017. PMID: 29085335. DOI: 10.3389/fendo.2017.00260

9 Kastner P, Lawrence HJ, Waltzinger C, Ghyselinck NB, Chambon P and Chan S: Positive and negative regulation of granulopoiesis by endogenous RARalpha. Blood *97(5)*: 1314-1320, 2001. PMID: 11222375. DOI: 10.1182/blood.v97.5.1314

10 Fenaux P, Chevret S, Guerci A, Fegueux N, Dombret H, Thomas X, Sanz M, Link H, Maloisel F, Gardin C, Bordessoule D, Stoppa AM, Sadoun A, Muus P, Wandt H, Mineur P, Whittaker JA, Fey M, Daniel MT, Castaigne S and Degos L: Long-term follow-up confirms the benefit of all-trans retinoic acid in acute promyelocytic leukemia. European APL group. Leukemia *14(8)*: 1371-1377, 2000. PMID: 10942231. DOI: 10.1038/sj.leu.2401859

11 Enane FO, Saunthararajah Y and Korc M: Differentiation therapy and the mechanisms that terminate cancer cell proliferation without harming normal cells. Cell Death Dis *9(9)*: 912, 2018. PMID: 30190481. DOI: 10.1038/s41419-018-0919-9

12 Brayton CF: Dimethyl sulfoxide (DMSO): a review. Cornell Vet *76(1)*: 61-90, 1986. PMID: 3510103.

13 Lyman GH, Preisler HD and Papahadjopoulos D: Membrane action of DMSO and other chemical inducers of Friend leukaemic cell differentiation. Nature *262(5567)*: 361-363, 1976. PMID: 986559. DOI: 10.1038/262360a0

14 Ahkong QF, Fisher D, Tampion W and Lucy JA: Mechanisms of cell fusion. Nature *253(5488)*: 194-195, 1975. PMID: 1110768. DOI: 10.1038/253194a0

15 Lovelock JE and Bishop MW: Prevention of freezing damage to living cells by dimethyl sulphoxide. Nature *183(4672)*: 1394-1395, 1959. PMID: 13657132. DOI: 10.1038/1831394a0

16 Hoang C, Nguyen AK, Nguyen TQ, Fang W, Han B, Hoang BX and Tran HD: Application of dimethyl sulfoxide as a therapeutic agent and drug vehicle for eye diseases. J Ocul Pharmacol Ther *37(8)*: 441-451, 2021. PMID: 34314611. DOI: 10.1089/jop.2021.0043

17 Colucci M, Maione F, Bonito MC, Piscopo A, Di Giannuario A and Pieretti S: New insights of dimethyl sulphoxide effects (DMSO) on experimental *in vivo* models of nociception and inflammation. Pharmacol Res *57(6)*: 419-425, 2008. PMID: 18508278. DOI: 10.1016/j.phrs.2008.04.004

18 Bertelli G, Gozza A, Forno GB, Vidili MG, Silvestro S, Venturini M, Del Mastro L, Garrone O, Rosso R and Dini D: Topical dimethylsulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: a prospective clinical study. J Clin Oncol *13(11)*: 2851-2855, 1995. PMID: 7595748. DOI: 10.1200/JCO.1995.13.11.2851

19 Morassi P, Massa F, Mesesnel E, Magris D and D'Agnolo B: [Treatment of amyloidosis with dimethyl sulfoxide (DMSO)]. Minerva Med *80(1)*: 65-70, 1989. PMID: 2915815.

20 Salim AS: Protection against stress-induced acute gastric mucosal injury by free radical scavengers. Intensive Care Med *17(8)*: 455-460, 1991. PMID: 1797888. DOI: 10.1007/BF01690766

21 Salim AS: Role of oxygen-derived free radical scavengers in the management of recurrent attacks of ulcerative colitis: a new approach. J Lab Clin Med *119(6)*: 710-717, 1992. PMID: 1350610.

22 Ikeda Y and Long DM: Comparative effects of direct and indirect hydroxyl radical scavengers on traumatic brain oedema. Acta Neurochir Suppl (Wien) *51*: 74-76, 1990. PMID: 2128587. DOI: 10.1007/978-3-7091-9115-6_25

23 Rosenstein ED: Topical agents in the treatment of rheumatic disorders. Rheum Dis Clin North Am *25(4)*: 899-918, viii, 1999. PMID: 10573765. DOI: 10.1016/s0889-857x(05)70109-5

24 Murav'ev IuV: [Treatment of rheumatoid synovitis by intra-articular administration of dimethyl sulfoxide and corticosteroids]. Ter Arkh *58(7)*: 104-105, 1986. PMID: 3764723.

25 Santos NC, Figueira-Coelho J, Martins-Silva J and Saldanha C: Multidisciplinary utilization of dimethyl sulfoxide: pharmacological, cellular, and molecular aspects. Biochem Pharmacol *65(7)*: 1035-1041, 2003. PMID: 12663039. DOI: 10.1016/s0006-2952(03)00002-9

26 Parkin J, Shea C and Sant GR: Intravesical dimethyl sulfoxide (DMSO) for interstitial cystitis—a practical approach. Urology *49(5A Suppl)*: 105-107, 1997. PMID: 9146010. DOI: 10.1016/s0090-4295(97)00181-7

27 Hoang BX, Le BT, Tran HD, Hoang C, Tran HQ, Tran DM, Pham CQ, Pham TD, Ha TV, Bui NT and Shaw DG: Dimethyl sulfoxide-sodium bicarbonate infusion for palliative care and pain relief in patients with metastatic prostate cancer. J Pain Palliat Care Pharmacother *25(4)*: 350-355, 2011. PMID: 21936635. DOI: 10.3109/15360288.2011.606294

28 Hoang BX, Tran DM, Tran HQ, Nguyen PT, Pham TD, Dang HV, Ha TV, Tran HD, Hoang C, Luong KN and Shaw DG: Dimethyl sulfoxide and sodium bicarbonate in the treatment of refractory cancer pain. J Pain Palliat Care Pharmacother *25(1)*: 19-24, 2011. PMID: 21426213. DOI: 10.3109/15360288.2010.536306

29 Hoang BX, Tran HQ, Vu UV, Pham QT and Shaw DG: Palliative treatment for advanced biliary adenocarcinomas with combination dimethyl sulfoxide-sodium bicarbonate infusion and S-adenosyl-L-methionine. J Pain Palliat Care Pharmacother *28(3)*: 206-211, 2014. PMID: 25102038. DOI: 10.3109/15360288.2014.938882

30 Hoang BX, Levine SA, Shaw DG, Tran DM, Tran HQ, Nguyen PM, Tran HD, Hoang C and Pham PT: Dimethyl sulfoxide as an excitatory modulator and its possible role in cancer pain management. Inflamm Allergy Drug Targets *9(4)*: 306-312, 2010. PMID: 20887267. DOI: 10.2174/187152810793358732

31 Strub R and McKim AS: Advances in the regulated pharmaceutical use of dimethyl sulfoxide USP, Ph. Eur. Pharm Technol Eur *2016(3)*: s30-s35, 2016.

32 Friend C, Scher W, Holland JG and Sato T: Hemoglobin synthesis in murine virus-induced leukemic cells *in vitro*: stimulation of erythroid differentiation by dimethyl sulfoxide. Proc Natl Acad Sci U.S.A. *68(2)*: 378-382, 1971. PMID: 5277089. DOI: 10.1073/pnas.68.2.378

33 Tanaka M, Levy J, Terada M, Breslow R, Rifkind RA and Marks PA: Induction of erythroid differentiation in murine virus infected eythroleukemia cells by highly polar compounds. Proc Natl Acad Sci U.S.A. *72(3)*: 1003-1006, 1975. PMID: 165480. DOI: 10.1073/pnas.72.3.1003

34 Preisler HD, Christoff G and Taylor E: Cryoprotective agents as inducers of erythroleukemic cell differentiation *in vitro*. Blood *47(3)*: 363-368, 1976. PMID: 1062223.

35 Teimourian S and Moghanloo E: Thwarting PTEN expression by siRNA augments HL-60 cell differentiation to neutrophil-like cells by DMSO and ATRA. DNA Cell Biol *35(10)*: 591-598, 2016. PMID: 27617494. DOI: 10.1089/dna.2016.3317

36 Collins SJ, Ruscetti FW, Gallagher RE and Gallo RC: Terminal differentiation of human promyelocytic leukemia cells induced by dimethyl sulfoxide and other polar compounds. Proc Natl Acad Sci U S A *75(5)*: 2458-2462, 1978. PMID: 276884. DOI: 10.1073/pnas.75.5.2458

37 Yu HN, Lee YR, Noh EM, Lee KS, Song EK, Han MK, Lee YC, Yim CY, Park J, Kim BS, Lee SH, Lee SJ and Kim JS: Tumor necrosis factor-alpha enhances DMSO-induced differentiation of HL-60 cells through the activation of ERK/MAPK pathway. Int J Hematol *87(2)*: 189-194, 2008. PMID: 18256785. DOI: 10.1007/s12185-008-0037-z

38 Lee YR, Shim HJ, Yu HN, Song EK, Park J, Kwon KB, Park JW, Rho HW, Park BH, Han MK and Kim JS: Dimethylsulfoxide induces upregulation of tumor suppressor protein PTEN through nuclear factor-kappaB activation in HL-60 cells. Leuk Res *29(4)*: 401-405, 2005. PMID: 15725474. DOI: 10.1016/j.leukres.2004.09.010

39 Davis WJ, Lehmann PZ and Li W: Nuclear PI3K signaling in cell growth and tumorigenesis. Front Cell Dev Biol *3*: 24, 2015. PMID: 25918701. DOI: 10.3389/fcell.2015.00024

40 Fresno Vara JA, Casado E, de Castro J, Cejas P, Belda-Iniesta C and González-Barón M: PI3K/Akt signalling pathway and cancer. Cancer Treat Rev *30(2)*: 193-204, 2004. PMID: 15023437. DOI: 10.1016/j.ctrv.2003.07.007

41 Khurana N, Kim H, Khan T, Kahhal S, Bukvic A, Abdel-Mageed AB, Sikka SC and Mondal D: Low dose dimethyl sulfoxide (DMSO) downregulates the expression of androgen receptor (AR) and ar-variant 7 (AR-V7) in castration resistant prostate cancer (CRPC) cells. Cancer Res *82(12_Supplement)*: 2446-2446, 2022. DOI: 10.1158/1538-7445.AM2022-2446

42 Goto I, Yamamoto-Yamaguchi Y and Honma Y: Enhancement of sensitivity of human lung adenocarcinoma cells to growth-inhibitory activity of interferon alpha by differentiation-inducing agents. Br J Cancer *74(4)*: 546-554, 1996. PMID: 8761368. DOI: 10.1038/bjc.1996.399

43 Sakiyama S, Nakamura Y and Yasuda S: Expression of epidermal growth factor receptor gene in cultured human lung cancer cells. Jpn J Cancer Res *77(10)*: 965-969, 1986. PMID: 3096922.

44 Edelson JD, Shannon JM and Mason RJ: Alkaline phosphatase: a marker of alveolar type II cell differentiation. Am Rev Respir Dis *138(5)*: 1268-1275, 1988. PMID: 2462386. DOI: 10.1164/ajrccm/138.5.1268

45 Grunt TW, Somay C, Pavelka M, Ellinger A, Dittrich E and Dittrich C: The effects of dimethyl sulfoxide and retinoic acid on the cell growth and the phenotype of ovarian cancer cells. J Cell Sci *100 (Pt 3)*: 657-666, 1991. PMID: 1808213. DOI: 10.1242/jcs.100.3.657

46 Grunt TW, Somay C, Oeller H, Dittrich E and Dittrich C: Comparative analysis of the effects of dimethyl sulfoxide and retinoic acid on the antigenic pattern of human ovarian adenocarcinoma cells. J Cell Sci *103 (Pt 2)*: 501-509, 1992. PMID: 1478951. DOI: 10.1242/jcs.103.2.501

47 Joshi SS, Jackson JD and Sharp JG: Differentiation inducing effects of butyrate and DMSO on human intestinal tumor cell lines in culture. Cancer Detect Prev *8(1-2)*: 237-245, 1985. PMID: 4064044.

48 Tsao D, Morita A, Bella A Jr, Luu P and Kim YS: Differential effects of sodium butyrate, dimethyl sulfoxide, and retinoic acid on membrane-associated antigen, enzymes, and glycoproteins of human rectal adenocarcinoma cells. Cancer Res *42(3)*: 1052-1058, 1982. PMID: 7059970.

49 Jiang Z, Zhang H, Wang Y, Yu B, Wang C, Liu C, Lu J, Chen F, Wang M, Yu X, Lin J, Pan X, Wang P and Zhu H: Altered Hepa1-6 cells by dimethyl sulfoxide (DMSO)-treatment induce anti-tumor immunity *in vivo*. Oncotarget *7(8)*: 9340-9352, 2016. PMID: 26824185. DOI: 10.18632/oncotarget.7009

50 Sainz B Jr and Chisari FV: Production of infectious hepatitis C virus by well-differentiated, growth-arrested human hepatoma-derived cells. J Virol *80(20)*: 10253-10257, 2006. PMID: 17005703. DOI: 10.1128/JVI.01059-06

51 Choi S, Sainz B Jr, Corcoran P, Uprichard S and Jeong H: Characterization of increased drug metabolism activity in dimethyl sulfoxide (dmso)-treated huh7 hepatoma cells. Xenobiotica *39(3)*: 205-217, 2009. PMID: 19280519. DOI: 10.1080/00498250802613620

52 Prados J, Melguizo C, Fernandez JE, Aranega AE, Alvarez L and Aranega A: Actin, tropomyosin and alpha-actinin as markers of differentiation in human rhabdomyosarcoma cell lines induced with dimethyl sulfoxide. Cell Mol Bio (Noisy-le-Grand) *39(5)*: 525-536, 1993. PMID: 8374504.

53 Melguizo C, Prados J, Velez C, Aranega A, Alvarez L and Aranega A: Influence of dimethyl sulphoxide on intermediate filament proteins in human rhabdomyosarcoma cell lines: Modulation at subcellular level. Histochem J *26(6)*: 519-525, 1994. PMID: 7928405. DOI: 10.1007/BF00157897

54 Cona MM, Li J, Chen F, Feng Y, Alpizar YA, Vanstapel F, Talavera K, de Witte P, Verbruggen A and Sun Z: A safety study on single intravenous dose of tetrachloro-diphenyl glycoluril [iodogen] dissolved in dimethyl sulphoxide (dmso). Xenobiotica *43(8)*: 730-737, 2013. PMID: 23294333. DOI: 10.3109/00498254.2012.756559

55 David NA: The pharmacology of dimethyl sulfoxide. Annu Rev Pharmacol *12(1)*: 353-374, 1972. PMID: 4556944, DOI: 10.1146/annurev.pa.12.040172.002033

56 Shu Z, Heimfeld S and Gao D: Hematopoietic sct with cryopreserved grafts: Adverse reactions after transplantation and cryoprotectant removal before infusion. Bone Marrow Transplant *49(4)*: 469-476, 2014. PMID: 24076548. DOI: 10.1038/bmt.2013.152

57 Manjunath P and Shivaprakash B: Pharmacology and clinical use of dimethyl sulfoxide (dmso): A review. Int J Mol Vet Res 3(1), 2013. DOI:10.5376/IJMVR.2013.03.0006

58 Waller FT, Tanabe CT and Paxton HD: Treatment of elevated intracranial pressure with dimethyl sulfoxide. Ann NY Acad Sci *411*: 286-292, 1983. PMID: 6576703. DOI: 10.1111/j.1749-6632.1983.tb47310.x

59 Karaça M, Kiliç E, Yazici B, Demir S and de la Torre J: Ischemic stroke in elderly patients treated with a free radical scavenger–glycolytic intermediate solution: A preliminary pilot trial. Neurol Res *24(1)*: 73-80, 2002. PMID: 11783757. DOI: 10.1179/016164102101199567

60 Scherbel AL, McCormack LJ and Layle JK: Further observations on the effect of dimethyl sulfoxide in patients with generalized scleroderma (progressive systemic sclerosis). Ann NY Acad Sci *141(1)*: 613-629, 1967. PMID: 5232269. DOI: 10.1111/j.1749-6632.1967.tb34931.x

61 Simon LS, Grierson LM, Naseer Z, Bookman AA and Shainhouse JZ: Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (dmso) compared with those of topical placebo, dmso vehicle and oral diclofenac for knee osteoarthritis. PAIN® *143(3)*: 238-245, 2009. PMID: 19380203. DOI: 10.1016/j.pain.2009.03.008

62 Rowley S and Baer R: Lens deposits associated with rimso-50 (dimethylsulphoxide). Eye *15(3)*: 332-333, 2001. PMID: 11450733. DOI: 10.1038/eye.2001.107

63 McKim A and Strub R: Dimethyl sulfoxide usp, pheur in approved pharmaceutical products and medical devices. Pharma Tech *32(5)*: 74, 2008. GALE|A179815292
64 Ock S-A and Rho G-J: Effect of dimethyl sulfoxide (dmso) on cryopreservation of porcine mesenchymal stem cells (pmscs). Cell Transplant *20(8)*: 1231-1239, 2011. PMID: 21294964. DOI: 10.3727/096368910X552835
65 Hornberger K, Yu G, McKenna D and Hubel A: Cryopreservation of hematopoietic stem cells: Emerging assays, cryoprotectant agents, and technology to improve outcomes. Transfus Med Hemother *46(3)*: 188-196, 2019. PMID: 31244587. DOI: 10.1159/000496068
66 van Velthoven AJ, Bertolin M, Barbaro V, Sthijns MM, Nuijts RM, LaPointe VL, Dickman MM and Ferrari S: Increased cell survival of human primary conjunctival stem cells in dimethyl sulfoxide-based cryopreservation media. Biopreserv Biobank *19(1)*: 67-72, 2021. PMID: 33185460. DOI: 10.1089/bio.2020.0091
67 Moussalli MJ, Wu Y, Zuo X, Yang XL, Wistuba II, Raso MG, Morris JS, Bowser JL, Minna JD and Lotan R: Mechanistic contribution of ubiquitous 15-lipoxygenase-1 expression loss in cancer cells to terminal cell differentiation evasion15-lox-1 and terminal cell differentiation loss in cancer. Cancer Pre Res *4(12)*: 1961-1972, 2011. PMID: 21881028. DOI: 10.1158/1940-6207.CAPR-10-0280
68 Breitman TR and He R: Combinations of retinoic acid with either sodium butyrate, dimethyl sulfoxide, or hexamethylene bisacetamide synergistically induce differentiation of the human myeloid leukemia cell line hl60. Cancer Res *50(19)*: 6268-6273, 1990. PMID: 2400989.
69 Wang J, Lin D, Peng H, Huang Y, Huang J and Gu J: Cancer-derived immunoglobulin g promotes tumor cell growth and proliferation through inducing production of reactive oxygen species. Cell Death & Dis *4(12)*: e945-e945, 2013. PMID: 24309932. DOI: 10.1038/cddis.2013.474
70 Koiri RK and Trigun SK: Dimethyl sulfoxide activates tumor necrosis factorα-p53 mediated apoptosis and down regulates d-fructose-6-phosphate-2-kinase and lactate dehydrogenase-5 in dalton's lymphoma in vivo. Leuk Res *35(7)*: 950-956, 2011. PMID: 21269693. DOI: 10.1016/j.leukres.2010.12.029
71 Hoang BX, Hoang HQ and Han B: Zinc iodide in combination with dimethyl sulfoxide for treatment of sars-cov-2 and other viral infections. Med Hypotheses *143*:109866, 2020. PMID: 32473509. DOI: 10.1016/j.mehy.2020.109866

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