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Commentary

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## Multidisciplinary utilization of dimethyl sulfoxide: pharmacological, cellular, and molecular aspects

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### Abstract

DMSO is an amphipathic molecule with a highly polar domain and two apolar methyl groups, making it soluble in both aqueous and organic media. It is one of the most common solvents for the *in vivo* administration of several water-insoluble substances. Despite being frequently used as a solvent in biological studies and as a vehicle for drug therapy, the side-effects of DMSO (undesirable for these purposes) are apparent from its utilization in the laboratory (both *in vivo* and *in vitro*) and in clinical settings. DMSO is a hydrogen-bound disrupter, cell-differentiating agent, hydroxyl radical scavenger, intercellular electrical uncoupler, intracellular low-density lipoprotein-derived cholesterol mobilizing agent, cryoprotectant, solubilizing agent used in sample preparation for electron microscopy, antidote to the extravasation of vesicant anticancer agents, and topical analgesic. Additionally, it is used in the treatment of brain edema, amyloidosis, interstitial cystitis, and schizophrenia. Several systemic side-effects from the use of DMSO have been reported, namely nausea, vomiting, diarrhea, hemolysis, rashes, renal failure, hypertension, bradycardia, heart block, pulmonary edema, cardiac arrest, and bronchospasm. Looking at the multitude of effects of DMSO brought to light by these studies, it is easily understood how many researchers working with DMSO (or studying one of its specific effects) might not be fully aware of the experiences of other groups who are working with it but in a different context.

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### 1. Introduction

DMSO [(CH<sub>3</sub>)<sub>2</sub>SO] is an amphipathic molecule with a highly polar domain and two apolar groups, making it soluble in both aqueous and organic media. Due to these physico-chemical properties, DMSO is a very efficient solvent for water-insoluble compounds and is a hydrogen-bound disrupter (see Ref. [1], for example). Despite being known since the nineteenth century (mainly due to its use in the wood industry), its biologic properties were only discovered in the 1960s. Since then it has been used for diverse laboratory and clinical purposes. DMSO is frequently used as a solvent in biological studies and as a vehicle for drug therapy. However, its side-effects (undesirable for these studies) are often neglected. In this article, we will try to present a global insight over the molecular, cellular, pharmacological, and toxicological effects of DMSO.

### 2. Pharmacological applications of DMSO

DMSO has been used in several human therapeutic situations. In 1978 it received approval by the United States Food and Drug Administration (FDA) for use in the treatment of interstitial cystitis, by intravesical instillation [2]. Its effects do not seem to be related to a detectable histamine release from mast cells [3]. It has been used successfully in the treatment of dermatological [4–6], urinary [7], pulmonary [8], rheumatic and renal [9] manifestations of amyloidosis. Basically through its anti-inflammatory and reactive oxygen species scavenger actions, its use has been purposed in several gastrointestinal diseases [10–14]. DMSO crosses the blood–brain barrier [15] and has been effective in the treatment of traumatic brain edema [16]. It has been also used in the treatment of musculoskeletal disorders [17], pulmonary adenocarcinoma [18], rheumatologic diseases [19,20], chronic prostatitis [21], dermatologic diseases [22–24], schizophrenia [25], and as a topical analgesic [26]. In addition, it has been suggested for the treatment of Alzheimer's disease [27]. Some of the reported effects of

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Table 1  
Brief summary of the reported effects of DMSO in the treatment of different human and experimental animal model diseases

Disease	Actions/effects	Reference(s)
Interstitial cystitis	Improves treatment, but the effect is not related with mast cell release of histamine	[2,3]
Amyloidosis	Helps to control pruritus in macular and lichen amyloidosis, avoiding the recurrent deposition of amyloid in areas of trauma of the epidermis	[4]
	Causes regression of hyaline deposits in lipoid proteinosis	[5]
	Improves primary amyloidosis of the bladder (instillation)	[7]
	Reduces pulmonary infiltration and improves arterial blood gas levels in pulmonary amyloidosis associated with multiple myeloma	[8]
	Is effective in the treatment of some cases of primary amyloidosis when combined with cytoreductive chemotherapy	[28]
	Induces a decrease of the inflammatory activity of rheumatoid arthritis and an improvement of renal function, following 3–6 months of therapy, in patients with secondary amyloidosis	[9]
Gastrointestinal disorders	Induces growth and blackish turn of scalp hair and beard	[6]
	Has an anti-inflammatory effect in ulcerative colitis	[10]
	Associated with H <sub>2</sub> receptor blockers, is more effective for healing acute duodenal ulceration and prevention of its recurrence than H <sub>2</sub> receptor blockers alone	[11]
	Improves survival in patients bearing colon carcinoma	[12]
	Has a beneficial therapeutic effect in the mechanism of abdominal pain caused by alcohol-induced chronic pancreatitis	[13]
Brain edema	Gives protection in stress-induced acute gastric mucosal injury	[14]
	Has a beneficial effect in the treatment of traumatic brain edema	[16]
Rheumatologic disorders	Has a beneficial effect in the treatment of rheumatoid arthritis, reducing the associated pain	[19]
	Enhances the effect of glucocorticoids in the treatment of rheumatoid synovitis	[20]
Chronic prostatitis	Induces a positive result in the treatment of human chronic prostatitis	[21]
Schizophrenia	Has an antipsychotic action	[25]
Pulmonary adenocarcinoma	Improves the antiproliferative effect of interferon- $\alpha$ on human lung adenocarcinoma cells through an unknown mechanism	[18]
Dermatologic disorders	Has a beneficial effect in the topical treatment of herpes zoster	[22]
	Enhances the efficacy of fungicides in the treatment of dermatologic mycosis	[23]
	Is an effective and safe antidote that may be used with local cooling after the extravasation of certain drugs used in chemotherapy given intravenously, preventing the necrosis of tissues and ulceration	[24]
Experimental animal model	Inhibits collagen $\alpha$ 1 gene expression, increase in tissue collagen content, hepatic stellate cell activation, synthesis of tissue inhibitors of metalloproteinase-2 and, consequently, the development of liver cirrhosis in mice	[29]
	Prevents the development of liver cirrhosis induced by thioacetamide	[29]

DMSO in the treatment of different diseases are summarized in Table 1.

Besides all of the previously referred to pharmacological applications in the treatment of different pathologies, several systemic side-effects from the use of DMSO have been reported, namely nausea, vomiting [30], diarrhea [31], severe hemolysis mimicking a hemolytic transfusion reaction [32], anaphylactic reactions manifested by rashes, flushing, and (occasionally) bronchospasm [33,34], renal failure [35], diastolic and systolic hypertension [36], bradycardia, heart block [37–39], and (rarely) pulmonary edema or cardiac arrest [40,41]. A significant side-effect of DMSO is a garlic-like breath odor and taste in the mouth due to the pulmonary excretion of a small percentage of DMSO as dimethyl sulfide [42]. Its topical application, although well tolerated, can cause mild transient local burning [24], skin rash, and pruritus [22]. A case of sulfhemoglobinemia after dermal application of DMSO in the treatment of interstitial cystitis has been reported,

with fatigue, cyanosis, and dyspnea with mild exertion [4]. Serum hyperosmolality in the control of increased intracranial pressure with DMSO given intravenously has also been described [43]. This expected effect was also observed in human blood *in vitro* studies [44]. However, DMSO penetrates the cell membrane and causes an increase in osmolality both inside and outside the cell, preventing any significant hemolysis due to the formation of an osmotic gradient [45].

### 3. Cellular and molecular effects of DMSO

Zhang and Eyzaguirre [46] reported that the rise in intracellular calcium concentration induced by hypoxia in mouse glomous cells is blunted by the presence of DMSO. The studies of Choi *et al.* [47] with human promyelocytic leukemia HL-60 cells also indicated that the neurotensin-induced rise in intracellular [Ca<sup>2+</sup>]

disappeared after treatment with DMSO. Michel [48] showed that in DMSO-treated human erythroleukemia cells, calcium elevations by adrenaline and neuropeptide Y were reduced significantly. Finally, Reynaud *et al.* [49] reported a similar DMSO interference with the heparin A<sub>3</sub> effect on human neutrophils. These four recent findings are in accord with our observation that DMSO prevents the ionophore-induced calcium loading of human erythrocytes [44]. This coherence between results obtained with different biological systems and different modulators of the rise in intracellular [Ca<sup>2+</sup>] suggests a nonspecific

action of DMSO, disabling the expected effect of the modulator.

In the same study [44], we showed that there is an increase in the extracellular concentrations of K<sup>+</sup>, Na<sup>+</sup>, and Ca<sup>2+</sup> in whole blood aliquots incubated with DMSO (2%, v/v). These findings are probably due to a DMSO-induced leakage of ions from human platelets, an effect that does not alter the plasma pH significantly [50]. At the molecular level, an explanation for the effect of DMSO on intracellular and extracellular ion concentrations is prevented by the divergence in the published studies of the

Table 2

Brief summary of the reported effects of DMSO in the study of the inflammation process, observed in experimental models

Actions/effects	Reference(s)
Inhibits interleukin-8 production in a dose-dependent manner, directly at the transcriptional level. Prevents adhesion of neutrophils to endothelium. Scavenges ClO <sup>-</sup> and possibly reduces NADPH-oxidase activity	[57]
Inhibits human platelet aggregation induced by ADP, arachidonic acid (AA), platelet activating factor (PAF), and collagen, in a concentration-dependent manner, being a more effective inhibitor for aggregation induced by ADP and collagen than PAF or AA	[58]
Stimulates prostaglandin E <sub>2</sub> and 12-HETE (hydroxyeicosatetraenoic acid) production by bovine seminal vesicle prostaglandin synthase, and inhibits the production of tri-HETE produced via the lipoxygenase pathway	[58]
Induces a decrease in proteoglycan synthesis in a time-dependent manner, dehydration of the cartilage and chondrocyte death. Equine joints show a decrease in synovial leukocyte counts, reduced inflammatory response, and suppress matrix metabolism	[59,60]
Inhibits sepsis-induced activation of nuclear factor-κB (NF-κB), resulting in the suppression of intercellular adhesion molecule 1 (ICAM-1) gene expression in the livers of peritonitis septic rats	[61]
Enhances human cytomegalovirus replication by up-regulating the major immediate early promoter, in part, related to enhanced NF-κB and cyclic AMP response element binding protein activity	[62]
Potentiated tumor necrosis factor-α (TNF-α)-induced cytotoxicity in various human myeloid cell lines	[56]
Decreases the level of NF-κB activation in a macrophage-like cell line, correlated with decreased expression of cytokine messenger RNA and TNF-α bioactivity, suggesting that modulation of NF-κB activation may provide a mechanism through which antioxidants protect against endotoxemia in murine models	[63]
Enhances the production of several platelet-specific proteins, platelet factor 4, and platelet-activation-dependent granule external membrane protein	[64]
Inhibits formyl-methionyl-leucyl-phenylalanine (fMLP) and leukotriene B <sub>4</sub> -induced leukocyte adherence in a dose-related manner in rat colon venular endothelium	[65]

Table 3

Brief summary of the reported effects of cell cycle, differentiation, and apoptosis studies, observed in experimental models

Type of study	Actions/effects	Reference(s)
Cell cycle	Inhibits <i>c-myc</i> expression, in different cell types	[66–68]
	Inhibits <i>c-myc</i> expression during the G <sub>1</sub> to S transition in adherent fibroblast cells arrested at G <sub>0/1</sub> by serum starvation	[69]
	Arrests the cell cycle of several human and mouse lymphoid cell lines at the G <sub>1</sub> phase	[70]
	Arrests the cell cycle of a transformed human B-cell line at G <sub>1</sub> phase and suppresses interleukin-6-induced differentiation into IgM-producing cells at a concentration lower than that affecting cell proliferation, suggesting that cell proliferation and differentiation are independent of each other	[71]
	Down-regulates <i>c-myc</i> protein in the G <sub>1/0</sub> specific phase prior to the appearance of differentiation-associated markers	[72]
Differentiation	May induce differentiation of malignant cells present in the marrow or alternatively in the body when it is infused back with the transplanted marrow	[73]
	Enhances the differentiation of leukemic cells to mature myelocytes	[74]
	Prevents dedifferentiation of normal cells. Cultured adult rat hepatocytes can be maintained and made to secrete albumin for more than 40 days	[75]
	Leads to the cessation of the proliferation of murine erythroleukemia cells and the production of a number of erythrocyte markers, such as hemoglobin	[76]
Apoptosis	Leads to the collapse of mitochondrial membrane potential, release of cytochrome c from the mitochondria, and activation of caspase-9 and -3, but not of caspase-8 (caspase cascade of mitochondrial apoptotic pathway is indispensable for DMSO-induced apoptosis). Induces apoptotic changes in a murine lymphoma cell line (concentration- and time-dependent effect) and down-regulation of Bcl-2	[77]
	Prevents apoptosis in lymphoma cells	[78]

effects of this solvent on transmembrane ion transport mechanisms. A DMSO-induced reduction of  $\text{Ca}^{2+}$  efflux was described for dorsal root ganglion cells from neonatal rats [51] and for skeletal muscle, cardiac muscle, and cerebellar vesicles [52]. At variance, the studies of Ogura *et al.* [53] with guinea pig ventricular myocytes indicated that incubation with DMSO had little effect on  $\text{Ca}^{2+}$  and inward-rectifier  $\text{K}^+$  currents, moderately inhibited  $\text{Cl}^-$  and  $\text{Na}^+$  currents, partially inhibited the  $\text{Na}^+$  pump current, and markedly depressed the delayed-rectifier  $\text{K}^+$  current. The data found in the literature for ATPase activities is again controversial. Different authors have reported an activation of purified erythrocyte membrane ( $\text{Ca}^{2+} + \text{Mg}^{2+}$ )-ATPase

by DMSO [54,55]. Using human erythrocyte ghosts and the same range of DMSO concentrations, McConnell *et al.* [56] showed that DMSO inhibits calmodulin-stimulated ( $\text{Ca}^{2+} + \text{Mg}^{2+}$ )-ATPase and ( $\text{Na}^+ + \text{K}^+$ )-ATPase, without any significant effect on calmodulin-independent ( $\text{Ca}^{2+} + \text{Mg}^{2+}$ )-ATPase and on  $\text{Mg}^{2+}$ -ATPase activities.

These and other reported cellular and molecular effects of DMSO (such as different effects related to inflammation, lipid metabolism, apoptosis, cell cycle, protein expression, differentiation, molecule binding, enzyme activity, reactive oxygen species scavenging, cell polarization, cryopreservation, and other experimental procedures) are summarized in Tables 2–5.

Table 4

Brief summary of the reported effects of DMSO in lipid metabolism and other studies, observed in experimental models

Type of study	Actions/effects	Reference	
Lipid metabolism	Activates acid sphingomyelinase and accelerates the intracellular mobilization of low density lipoprotein (LDL)-derived cholesterol	[79]	
	Increases the transfer of unesterified cholesterol between membranes	[80]	
	Prevents the expected rise in serum cholesterol by 50%, but does not prevent cholesterol accumulation in aortic tissues, when administered in the drinking water of cholesterol-fed cockerels	[81]	
	Reverse the abnormal processing of LDL cholesterol in mutant Niemann-Pick disease fibroblasts, namely the excessive lysosomal accumulation of LDL cholesterol and the delayed induction of cellular homeostatic responses associated with the uptake of LDL by the mutant cells. Accelerates the intracellular mobilization of LDL-derived cholesterol through effects that may reflect enhanced membrane permeability or cholesterol solubilization. Ameliorates a secondary deficiency of sphingomyelinase activity that can be present in these fibroblasts as a manifestation induced by excessive LDL cholesterol that accumulates in the lysosomes of the cells	[82]	
	Reduces the accumulation of cholesterol in vascular and extravascular tissues, and partially prevents the development of dietary cholesterol-induced atherosclerosis (despite the severe hypercholesterolemia accompanying the cholesterol feeding), when administered in the drinking water of rabbits	[83]	
	Reduces the binding, internalization, and degradation of exogenous LDL in human skin cultured fibroblasts; not acting by increasing the secretion of cholesterol by the cell	[83]	
	Other	Suppresses the expression of CD20	[71]
		Enhances the expression of sialyl Lewis <sup>x</sup> and sialyl dimeric Lewis <sup>x</sup> antigens on the surface of human gastric carcinoma cells, and the binding of <i>Limulus polyphemus</i> agglutinin (which specifically binds to cell-surface sialic acid)	[84]
		Modifies the protein conformation of mutant p53 to one recognized by a wild-type specific monoclonal antibody in a murine erythroleukemia cell line, accompanied by a translocation of the p53 protein from the cytoplasm to the nucleus	[85]
		Increases the synthesis of band 3 protein without noticeable changes in the synthesis of other membrane proteins erythropoietin-induced erythroid cells	[86]
Enhances and maintains thyroid function for more than 13 days, with evidence of <i>de novo</i> synthesis and release of thyroid hormones, when added to the usual culture medium to preserve human thyrocytes extracted from patients with Graves disease		[87]	
Decreases glycosaminoglycan chain length in human erythroleukemia cell proteoglycans		[64]	
Decreases human erythrocyte aggregation indexes and leads to higher plasma concentrations of $\text{K}^+$ , $\text{Na}^+$ , and $\text{Ca}^{2+}$		[44]	
Protects against 1-methyl-4-phenylpyridinium ( $\text{MPP}^+$ ) toxicity through the inhibition of OH radical-mediated oxidative injury in the substantia nigra		[88]	
Has positive and/or negative inotropic effects on perfused heart and isolated cardiac tissue preparations.		[53]	
Depresses nerve conduction velocity and affects enzymatic activity related to $\text{Na}^+$ pumping, second messenger production, and mitochondrial oxidative phosphorylation		[53]	
Is a free radical scavenger, protein kinase C activator, and myocardial contracture relaxant	[53]		
Blocks $\gamma$ -aminobutyric acid-induced $\text{Cl}^-$ current in rat dorsal root ganglion neurons	[53]		
Causes a small hyperpolarization and a prolongation of the action potential of guinea pig papillary muscles	[53]		
Has inotropic and chronotropic effects, affects various ATPase, and protects the heart against ischemic injury	[89]		
Inhibits the binding of prostaglandin $\text{F}_{2\alpha}$ to corporal luteal cell membranes	[83]		
Alters the permeability and stability of lysosomal membranes <i>in vitro</i>	[82]		
Induces an increase of intracellular $[\text{Ca}^{2+}]$ , dependent upon extracellular $[\text{Ca}^{2+}]$ , in dispersed bovine cells and cells isolated from human parathyroid adenomas	[90]		

Table 5  
Brief summary of the reported effects of DMSO in some of its technical applications

Application	Actions/effects	Reference
Cryopreservation	On the cryopreservation of human platelets, induces K <sup>+</sup> , Ca <sup>2+</sup> , and lactate dehydrogenase release from the intracellular space to the extracellular space, and strongly activates complement	[50]
	At moderate concentrations, preserves the structure of the seminiferous epithelium of rat testicular biopsies	[91]
	At 1.5 M, allows the cryopreservation of human islets with superior survival and preservation of post-culture function, when compared with 2.0 M or different ethylene glycol concentrations	[92]
	Together with a controlled rate of freezing, largely prevents the cellular damage in freezing, caused by the formation of ice crystal within the cells	[93]
	A final concentration of 5% (v/v) in autologous plasma, without further additives, is sufficient for cryopreservation of cord blood stem cells in a banking routine	[94]
	Prevents damage in hemopoietic stem cells, during cryopreservation	[95]
	Other procedures	Presents a hydrogen-bound disruption action
Due to its strong scavenging effects, it should be used with caution as a solvent in chemiluminescence studies. Concentrations below 1% (v/v) do not interfere with the results		[96]
Enhances the penetration of chemicals and is added to fixatives to improve cell preservation. At low concentrations, in aldehyde and osmium-dichromate fixatives for electron microscopy, the ultrastructure and cellular details achieve good preservation		[97]
At 1% (v/v), enhances the liposomal delivery of DNA to human breast tumor cells		[98]
Decreases the <i>in vitro</i> binding of ethidium to DNA		[99]

#### 4. Summary

Looking at the multitude of effects of DMSO brought out in this commentary, it is easily understood how many researchers working with DMSO (or studying one of its specific effects) can be unaware of the results of other groups working with it in a different context. The absence of a complete understanding of the effects of DMSO can preclude the reaching of accurate conclusions, since experimental artifacts caused by DMSO can lead to the erroneous interpretation of results. We believe that an increased awareness of the multidisciplinary utilization of this molecule in several research fields can be a valid contribution in order to avoid or minimize these problems.

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