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The Potential Antiviral Activities of Inositol (Vitamin B_8) as a Supplement in Human and Animal Nutrition: A Review

İnsan Ve Hayvan Beslenmesinde Besin Takviyesi Olarak Kullanılan İnositol'ün (Vitamin B8) Potansiyel Antiviral Etkileri

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ABSTRACT

Inositol is categorized as an essential vitamin and is recognized as vitamin B8. It and its derivatives including myo-inositol have some biological activity in several metabolisms. Inositol is well tolerated and is a natural constituent in human and animal nutrition. The toxicity of inositol is low. At the various concentrations, it presented antiviral activity against serious viruses such as rhinovirus, coxsackie, herpesvirus, HIV, and iridovirus threatening biosafety, and human and animal health.

This review aimed to present the structure, role in nutrition, toxicity, and potential antiviral activities of inositol and its derivatives as a dietary supplement in human and animal nutrition with the One-Health concept.

Keywords: antiviral, biosafety, food/feed supplement, inositol, One-Health

ÖZ

İnositol esansiyel vitamin olarak kabul edilmekte ve vitamin B8 olarak tanımlanmaktadır. Inositol ve myo-inositol gibi türevleri çeşitli metabolizmalarda biyolojik aktiviteye sahiptir. İnsan ve hayvan beslenmesinde doğal bir bileşendir. İnositol ve türevleri düşük toksisiteye sahiptir ve iyi tolere edilirler. Çeşitli konsantrasyonlarda, rinovirüs, coxsackie, herpesvirus, HIV ve iridovirus gibi biyogüvenlik açısından önem taşıyan, insan ve hayvan sağlığını tehdit eden virüslere karşı antiviral aktiviteye sahip olduğu bildirilmiştir. Bu derleme ile insan ve hayvan beslenmesinde takviye olarak kullanılan inositol ve türevlerinin yapısını, beslenmedeki rolünü, toksisitesini ve potansiyel antiviral aktivitelerini Tek-Sağlık konsepti ile sunmak amaçlanmıştır.

Anahtar Kelimeler: antiviral, biyogüvenlik, gıda/yem katkısı, inositol, Tek-Sağlık

GENERAL INFORMATION

Researchers have addressed and targeted new potential molecules to prevent the adsorption, penetration, replication, and infectivity of viruses in the antiviral treatment strategies and developing therapeutic agents.

In recent studies, natural and consumable compounds (polysaccharides such as inositol, and their derivatives such as myo-inositol) were used as agents against viruses by in vitro and in vivo techniques (Ni et al., 2002). These compounds have some potential advantages for the development of new strategies against viruses (Lüscher-Mattli, 2000) because of low cytotoxicity; a wide spectrum of antiviral activity [HIV, herpes virus, cytomegalovirus, orthomyxoviruses and paramyxoviruses (influenza A virus, respiratory syncytial virus (RSV)], the ability to inhibit a stage which is important in virus replication, low levels resistant to these compounds and natural, degradable and low environmental pollution.

Inositol is categorized as an essential vitamin and recognised as B8 vitamin. As an inositol isomer, myo-inositol has some biological activity. It is found in many organs and tissues such as the brain, skeletal, heart and reproductive organs. And it is a main component of phosphatidylinositol in cell membranes. It is also synthesised by various tissues and microorganisms. The synthesis by tissues and microorganisms, growth factors and antioxidant effects of inositol were shown in many studies

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The structure of inositol

Inositol or myo-inositol (C6H12O6, 180.16 g/mol, CAS Reg. No. 87-89-8, Figure 1) is a natural sugar synthesized by both animal and plant cells. It is found in the cell membrane and nucleus as a chemopreventive property. It plays the role of cell signalling as a component of intracellular phosphate. It is present in almost all tissues as an essential component of biological membranes, lung surfactants and eukaryotic cells. There are nine stereoisomers. In plant and animal metabolisms, its common form is myo-inositol. Other natural isomers are called scyllo-, muco-, D-chiro – and neo inositol. Myo-inositol is mainly generated and extracted from corn kernels by hydrolysis of plant phytates. Therefore, myo-inositol is similar to the structure of glucose (EFSA, 2016; FDA, 2022).

4/5-nucleobase Derivatives of 3-O-Methyl-D-chiro-inositol as Potential Antiviral Agents. Chem Biodivers. 2006;3(10):1126-1137.

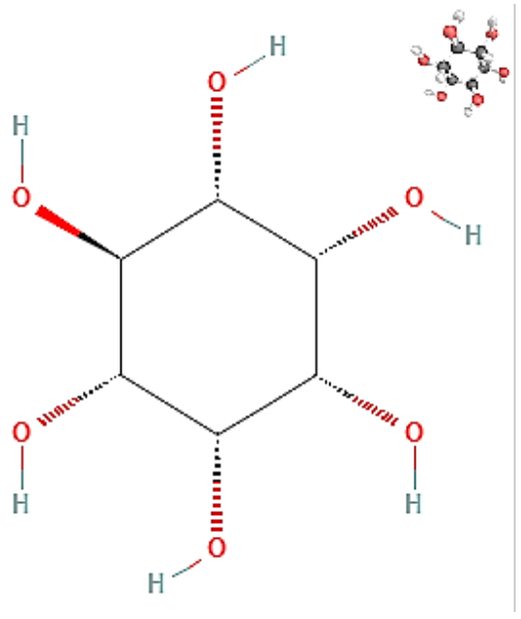

Figure 1. *Chemical structure of inositol (illustrated with ChemDraw, Waltham, USA)*

Inositol in animal and human nutrition

Its common form in plants and animals is myo-inositol. Other natural isomers are scyllo-, muco-, D-chiro – and neo inositol. It is present in almost all tissues as an essential component of biological membranes and lung surfactant and plays an important role as a component of eukaryotic cell structure. Inositol is permitted as a food or feed additive in human nutrition, seafood and animal production. Therefore, inositol is a natural and endogenous active substance. And, no limitation on usage and residue levels in seafood production has been reported by the authorities (EFSA, 2014, 2016)

Also, inositol is considered a pseudovitamin. But, it is not an essential vitamin that deficiency cause disease. Therefore, inositol is an ingredient of over-the-counter (OTC) products. Inositol can be added directly to human food (incl. infant formula) and affirmed as generally recognized as safe (GRAS) without a maximum limit by FDA (FDA, 2022)

In the Turkish Food Codex, inositol is permitted as an ingredient in energy drinks, infant and young children formulas, and diet replacements for weight control (Official Gazette, 2019b). The maximum limits of inositol content are 40 mg/100 kcal and 100 mg/l for infant formula and energy drinks respectively (Official Gazette, 2017, 2019a). However, a maximum limit is not indicated for weight control diets (Official Gazette, 2019c).

In European Pharmacopeia (PHEur), inositol is described and on the list as a pharmacological substance. Also, it can be used as a feed additive permitted by European Union according to the EC 1831/2003 regulation. In European Codex, inositol is authorised as a nutritional additive for use in all animal species as part of the group 'Vitamins, pro-vitamins and chemically well-defined substances having similar effect' under Directive 70/524/EEC. It is permitted to use as a feed additive in the nutrition of fish, crustaceans, cats and dogs. Moreover, there is no maximum residue limit for animal products (EFSA, 2014; European Commission, 2016). Therefore, for aquaculture and animal production, inositol is not limited because of its endogen-active ingredient.

Antiviral activities of inositol

Inositol derivatives were studied in the cytotoxicity and antiviral activity research. Few derivatives have presented an antiviral activity against some viruses. It was observed that inositol hexasulphate derivative inhibited HIV and expressed its antigenicity. However, inositol hexaphosphoric acid presented a moderate antiviral activity against HIV (Otake et al., 1989). Phosphate and sulphate derivatives of myo-inositol had shown antiviral activity against several viruses such as Coxsackie virus, Herpes Simplex virus and Iridovirus. Moreover, CC_{50} and IC_{50} concentrations of them were determined as lower than 50 µg/ml (Tuchnaya et al., 2008). Inositol extracted from Lonicera japonica plant of up to 2000 µg/ml was not cytotoxic on fish spleen cell culture, but, it had antiviral activity against Iridovirus at the rate of up to 90% (Liu et al., 2020).

Many dimeric analogues of inositol-containing phospholipids, which contains two myo-inositol rings, were used to investigate the antiviral activity of compounds against a panel of viruses. Firstly, they determined the cytotoxic effects of the compound on HeLa (uterine melanoma cells), MDCK (dog kidney cells) and GMK (green monkey cells). The CC_{50}s of inositol derivate were determined as between 12 and 50 µg/ml for HeLa cells while 27.8 µg/ml of the references compound (pleconaril). For MDCK and GMK cells, CC50 were higher than 50 µl for all derivate of inositol, as 26.4 µg/ml for pleconaril (Tuchnaya et al., 2008). But, any derivate of inositol did not show antiviral activity against the rhinoviruses with a single-stranded positive-sense RNA (RV2, RV14, RV1A).

As 1,12-dodecanediol monosulfate IX and 2,3,4,5-Tetra-O-benzyl-D, L-iditol disulfate XI derivate of inositol inactivated Coxsackie virus strains (non-envelope, single-stranded, positive-sense RNA), 1,12-Dodecanediol disulfate VIII showed antiviral activity against all viruses experienced. 2,3,4,5-tetraO-benzyl-D,L-iditol diphosphate XIII and 1,12-dodecanediol monosulfate IX inactivated herpes virus 1 and 2 with DNA (Tuchnaya et al., 2008).

The antiviral activity and 50% effective concentration (EC_{50}) of inositol-containing phospholipid dimer analogues were determined against human immunodeficiency virus (HIV-1 with single-stranded RNA) on the cell culture model infected with the virus. The highest antiviral effect of inositol-containing phospholipid and EC_{50} was determined as 3.9 µg/ml. It was suggested that the ability to introduce selectively functional groups into the myo-inositol ring makes inositol-containing phospholipids compounds with potential antiviral activity (Baranova et al., 2014). Meanwhile, myo-inositol hexasulfate and myo-inositol hexaphosphoric acid for their antiviral effect on the human immunodeficiency virus (HIV) were investigated in human lymphocyte CD4+ T-cell (MT-4). The hexasulfate of myo-inositol showed a total inhibition effect against the cytopathic effect of HIV and its specific antigen expression at a concentration of 1.67 mg/ml. Also, myo-inositol hexaphosphoric acid had a moderate inhibition effect on HIV (Otake et al., 1989). Several derivatives of inositol were studied for the antiviral and anticancer activities against several viruses (HIV, HSV) and tumour cells (PG, T-24) in vitro. Five of the derivatives inhibited human lung cancer cell lines at the IC_{50} concentrations between 50 and 100 µmol. However, the other derivatives (up to 200 µmol) did not have any antiviral or anticancer activities (Zhan et al., 2006).

In animal experiments and in vivo studies, plant-based inositol extracted from a medical plant (Lonicera japonica Thunb.) had shown some effects on iridovirus (double-stranded DNA). Firstly, the non-toxic concentration of plant-based inositol was determined as 2 mg/ml for grouper fish spleen cells in vitro. Inositol exhibited dose-depend antiviral activity against iridovirus infection both in vitro, spleen and liver tissues of fish in vivo feeding experiments. Therefore, the study results suggested the inositol extracted from medical plants might be used to prevent and control iridovirus infections in fish farming (Liu et al., 2020). Inositol was experienced in water on air-borne poultry viruses such as Pigeon pox and Rous sarcoma viruses in embryonic egg and animal experiments. When compared aqueous suspensions of viruses with or without inositol, those with inositol were not effective to inhibit and prevent the aerosolization and air-borne infection of Pigeon pox with DNA and Rous sarcoma viruses (enveloped RNA). Unlike, the virulence increased with inositol (Webb et al., 1963).

Recently, the effects of myo-inositol on the immune system of humans and its potential effects on COVID-19 risk have been discussed. Researchers have informed that myo-inositol had anti-inflammatory activity by regulating the expression of IL-6 by phosphatidyl-inositol-3-kinase (PI3K) pathway. Furthermore, myo-inositol act a role in the surfactant production of lung tissue. In that case, they pointed out that myo-inositol could be used as a possible preventive treatment in the condition of COVID-19 infection (Bezerra Espinola et al., 2021).

In the brief of previous studies (Table 1), the non-toxic concentration or CC_{50} of inositol and several derivatives were determined as 12-50 µg/ml for HeLa, higher than 50 µl for MDCK and GMK, 50-100 µmol (approx. 10-20 µg/ml) for human lung cancer cell and 2 mg/ml for grouper fish spleen cells. In this study, the CC_{50} of myo-inositol was determined as 0.373 mg/ml (373 µg/ml) for murine macrophage cells (RAW 264.7).

Table 1. *Summary of previous studies*

Virus	Family	Structure	Inositol Derivative	Results	Referance
Rhinovirus (2, 14, 1a)	Picornaviridae	Non-enveloped, RNA	Several derivatives	Non-effective	(Tuchnaya et al., 2008)
Coxsackie	Picornaviridae	Non-enveloped, RNA	1,12-dodecanediol monosulfate IX 2,3,4,5-Tetra-O-benzyl-D, L-iditol disulfate XI 1,12-Dodecanediol disulfate VIII	Effective	(Tuchnaya et al., 2008)
Herpesvirus (1 and 2)	Herpesviridae	Enveloped, DNA	2,3,4,5-tetraO-benzyl-D,L-iditol diphosphate XIII 1,12-dodecanediol monosulfate IX	Effective	(Tuchnaya et al., 2008)
			Several derivatives	Non-effective	(Zhan et al., 2006)
HIV	Retroviridae	Enveloped, RNA	inositol-containing phospholipid	Effective	(Baranova et al., 2014)
			myo-inositol hexasulfate myo-inositol hexaphosphoric acid	Effective	(Otake et al., 1989)
			Several derivatives	Non-effective	(Zhan et al., 2006)
Iridovirus	Iridoviridae	Enveloped, DNA	Plant-based inositol	Effective	(Liu et al., 2020)

The antiviral activity results of the previous limited number of studies were summarized in Table 1. These viruses studied are mostly high contagious and serious agents that can cause outbreaks and also deaths. This wide spectrum of viruses has got several morphological structures as enveloped or non-enveloped and DNA or RNA genomes. Inositol, myo-inositol or its derivatives have shown antiviral activity against both enveloped or non-enveloped and DNA or RNA viruses in some studies, but not in some. Noroviruses including murine norovirus 1 (MNV-1) are non-enveloped viruses which have single-stranded and positive-sense RNA genome.

Toxicology

Most studies in rodents did not show an adverse effect at the dose of up to 9000 mg/kg bw/day. Previous study results suggested inositol was not toxic or too low. Tilton et al. used 2% myo-inositol in the diet of rats (equivalent to 1800 mg/kg bw per day) and treated the rats with sub-chronic exposure to myo-inositol. Because of only one concentration, they could calculate a no observed adverse effect level (NOAEL) (Tilton et al., 1993). Pugliese et al. and Coppey et al. compared dietary inositol supplement (0.5 to 2 % inositol) in diabetic and non-diabetic rats. The treatment reduced some metabolic syndrome parameters in diabetic rats but did not affect that of non-diabetic rats (Coppey et al., 2002; Pugliese et al., 1990).

In adults, some adverse effects were slightly determined at doses of 67–500 mg/kg inositol bw/day. The results of limited studies suggested inositol may be well tolerated in humans, but not allowed to determine the upper tolerable intake level (UL) of inositol (EFSA, 2014). The FEEDAP Panel of EFSA warmed that inhalation exposure to inositol could cause a health hazard and also inositol has a potential for skin and eye irritation. In fish nutrition, inositol as a feed supplement is not expected to pose a risk to the environment (EFSA, 2014).

CONCLUSION

Inositol and its derivatives such as myo-inositol are natural, edible, endogenous active substance and non-toxic as food and feed supplements. Although there are some limitations on its use in energy drinks, infant and young children formulas, it is not banned or limited in animal nutrition, animal production and aquaculture. Meanwhile, it could have potential antiviral activities against serious viruses such as HIV, herpesviruses, iridoviruses and rhinoviruses in the light of the results of experimental in vitro studies.

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