REVIEW ON T-2 TOXIN

Kalantari H1*, Moosavi M1

1Department of Pharmacology and Toxicology, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

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Abstract

T-2 toxin is a member of the fungal metabolites known as trichothecene mycotoxin. The major attribute of T-2 toxin is that it inhibit protein synthesis which is followed by a secondary disruption of DNA and RNA synthesis. T-2 toxin affects the actively dividing cells such as those lining the gastrointestinal tract, skin, lymphoid and erythroid cells. It can decrease antibody levels, immunoglobolines and certain other humoral factors. In addition, in this review article acute and chronic effects on health, toxicokinetics, regulatory matters related to its use as a potential warfare and treatment strategies that may be undertaken will be briefly covered.

Keywords:
Fusarium fungi, T-2 toxin, Health issue.

Introduction

Mycotoxins are toxic secondary metabolites produced by various fungi cause toxic effect called mycotoxicosis. Many mycotoxin diseases are associated with various species of fungal genera and their secondary metabolites (1). The adverse effect of fungal products have caused mass poisoning in both man and farm animal over many countries (1). T-2 toxin is one of the closely related compounds produced by several Fusarium species. These compounds are derivatives of a ring system referred as trichothecenes (2). There are more than 20 naturally occurring compounds produced by Fusarium species which contain similar structures, including diacetoxyscirpenol, nivalenol, deoxynivalenol, T-2 toxin, H-T-2 toxin and fusaron-x. (3).

Chemical structure of T-2 toxin

The basic structure of these molecules is tetracyclic, with a sesquiterpenoid 12, 13 epoxycyclopane-9-ene ring system (4). Its chemical structure is characterised by a hydroxyl (OH) group at the C-3 position, acetylxy (-OCOCH3) groups at C-4 and C-15 positions, atom of hydrogen at C-7 position and an ester-linked isovaleryl [OCOCH2CH(CH3)2] group at the C-8 position (Figure 1) (5).

Incidence of T-2 toxin

Although reported natural occurrence of T-2 toxin and related mycotoxins shows their worldwide presence, they are predominant in tropical and subtropical regions. Warm and moist weather conditions favour plant infection with Fusarium spp., while improper storage and handling of grain with high moisture content can lead to T-2 toxin contamination (6). In short, the most important factors that influence T-2 toxin production are weather conditions, grain defects and moisture content (13 to 22 %) (6).
T-2 toxin is produced at a wide temperature range (0 to 32 °C), with maximum production at temperatures below 15 °C (7). Namely, *F. sporotrichioides* has a low optimal temperature (6 to 12 °C) for T-2 toxin production and can produce this mycotoxin during overwintering under a snow cover in the field and/or during storage (7).

**Mechanism of action**

A variety of mechanisms of action have been proposed for T-2 toxin. The T-2 toxin reacts with the thiol groups of sulfhydryl enzymes and as a result is potent protein and DNA synthesis inhibitor (8). T-2 toxin can impair the production of antibodies (9), alter membrane functions (10), reduce lymphocyte proliferation (11) and alter the maturation process of dendritic cells (12). T-2 toxin produces both in vivo and in vitro, single strand breaks in the DNA of lymphoid cells. In vitro T-2 toxin causes apoptosis in various cell types like HL60, Jurkat, U937 (13) Vero cells (14) and human hepatoma cells (15). Apoptosis was also reported in vivo in thymic and spleenic lymphocytes as well as other tissues of mice like bone marrow intestinal epithelial cells (16,17) skin (18), kidney (19) and brain (20). Oxidative damage are usually critical biomolecules such as nucleic acids, proteins, and lipids (21). Trichothecenes bind to sub cellular structures, disrupting and altering the morphology of mitochondria, rough endoplasmic reticulum, myofibers and membranes (22). They inhibit succinic dehydrogenase activity with effects on cellular energetics with decreases in succinate, pyruvate and malate oxidation and inhibition of mitochondrial protein synthesis (22). Treatment with T-2 toxin leading to increased cell death (apoptosis) in a variety of cell types via mitochondrial and non-mitochondrial mechanisms (23, 24, 25). Furthermore, trichothecenes readily cross the placenta and have been shown to cause increased cell death (apoptosis) in mouse fetuses (26).

**Toxicokinetic**

In general T-2 toxin is toxic to humans, other mammals (domestic and research), birds, invertebrates, plants and eukaryote cells. The early signs and symptoms of T-2 toxin poisoning is depend on dose and rout of exposure (27). T-2 toxin is rapidly absorbed after ingestion in most animal species and it is distributed in the organism with little or no accumulation in any specific organs. Maximum plasma concentrations occurred after about 30 minutes in rodents (28). Four hours after intravenous administration of radioactive labelled T-2 toxin to pigs, 15-24 % of the radioactivity given was found in the...
gastrointestinal tract and 4.7-5.2 % in the remaining tissues, mainly muscle and liver. The plasma half-life for T-2 toxin is less than 20 minutes (28). T-2 toxin is rapidly metabolised and secreted and no significant accumulation of T-2 is observed in the species tested (e.g. pig, cattle, dog, guinea pig) (28).

**Acute toxicological effects**

Acute effects of oral, parental, dermal or aerosal exposures to trichothecenes produce a variety of adverse effects. The effects observed include non-specific symptoms like weight loss, feed refusal, dermatitis, vomiting, diarrhoea, haemorrhages and necrosis of the epithelium of stomach and intestine, bone marrow, spleen, testis and ovary(28).

It is more toxic via the lungs relative to other means of exposure. For example, in the rat, intranasal (0.6 mg/kg) and inhalational (0.05 mg/kg) exposures are more toxic than intravenous (0.7-1.2 mg/kg), intraperitoneal (1.3-2.6 mg/kg) and intragastric (2.3-5.2 mg/kg) administration of T-2 toxin (36) (Table 1). The most frequent symptoms included vomiting (71%), diarrhea (53%), skin irritation, burning and itching (44%), rash or blisters (33%), bleeding (53%) and dyspnea (48%) (29).

**Chronic toxicological effects**

Chronic exposure to T-2 toxin cause alimentary toxic aleukia (ATA) in humans and mycotoxicosis in domestic animals. ATA occurred in Russia during and prior to WW II when peasants consumed field grains contaminated with trichothecene mycotoxins infested with *Fusarium* (31). The chronic toxicity of trichothecenes is characterized by inflammation of the G.I. tract mucosa, vomiting, diarrhea, abdominal pain, excessive salivation, headache, dizziness, weakness, fatigue, secondary infections, including pneumonia (32). Due to the limited available data concerning the toxicity of T-2 toxin the Scientific Committee of Food of the European Commission has set a temporary combined TDI of 0.06 mg/kg/body weight/day for T-2 and HT-2 toxin (28).

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Mouse LD50 (mg/kg)</th>
<th>Rat LD50 (mg/kg)</th>
<th>Guinea Pig LD50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>4.2-7.3</td>
<td>0.7-1.2</td>
<td>1-2</td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>5.2-9.1</td>
<td>1.3-2.6</td>
<td>–</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>2.1-3.3</td>
<td>0.6-2</td>
<td>1-2</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>–</td>
<td>0.5-0.9</td>
<td>1</td>
</tr>
<tr>
<td>Intragastric</td>
<td>9.6-10.5</td>
<td>2.3-5.2</td>
<td>3.1-5.3</td>
</tr>
<tr>
<td>Intranasal</td>
<td>–</td>
<td>0.6</td>
<td>–</td>
</tr>
<tr>
<td>Intratracheal</td>
<td>0.16</td>
<td>0.1</td>
<td>–</td>
</tr>
<tr>
<td>Inhalational</td>
<td>0.24</td>
<td>0.05</td>
<td>0.6-2</td>
</tr>
<tr>
<td>Dermal</td>
<td>6.6</td>
<td>4.3</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Table 1: Comparative LD50 values of T-2 toxin by various routes of administration in different animal species (30)
Toxic effects of T-2 toxin on different organ systems

Effects on blood
The effects of T-2 toxin and HT-2 toxin on red cell, leukocyte and platelet progenitor cells from mice, rats and humans in vitro have been investigated with respect to effects on proliferation, differentiation and cytotoxicity. After oral exposure of T-2 toxin, mean of haemoglobin (Hb) values were significantly lower as control. The reduction in Hb recorded may be due to decreased protein synthesis in intoxicated animal (33). Haematopoietic tissue in vivo is a target of toxicity in several animal species such as mice, rats, cats, rabbits and guinea-pigs following acute exposure to one or more doses of T-2 toxin or HT-2 toxin (29). In guinea-pigs 0.9 mg T-2 toxin/kg body weight and day for 27 days caused erythopenia, leukopenia, lymphopenia and reduced lymphocyte content of the bone marrow (34). Mice fed T-2 toxin in the diet, 20 mg/dry diet (equivalent to about 3 mg/kg body weight) for 21 and 41 days showed hypoplastic lymphoid tissues, bone marrow and splenic red pulp resulting in anemia (29).

Effects on immune system
Trichothecenes are extremely toxic to leukocytes and other rapidly dividing cells (35). Various studies with T-2 toxin demonstrate effects on the production of antibodies, both in assays measuring T-dependent responses (e.g. response to sheep red blood cells, SRBC) and T-independent response (e.g. dinitrophenyl-bovine serum albumin or lipopolysaccharides, LPS) having effects on both humoral and cellular immune responses (29). On the other hand, depending on the dose, timing and route of exposure, mycotoxins can also have stimulatory effects on immune cells. It can affect both cell mediated and humoral immune compartments. Trichothecenes, as demonstrated for T-2 toxin and DON, can cause both suppression and stimulation of immunoglobulin production, depending on the doses and timing of exposure (29). Specific effects ascribed to the trichothecenes include suppressed mitogenic response in human T and B lymphocytes (36). Furthermore, mycotoxin has also been shown to super induce IL-2, IL-4 and IL-5 cytokine mRNA expression and production (37). Immunostimulation is caused by low doses of the toxin, and is evidenced by increased serum IgA and IgE antibodies because of rapid and transient activation of the genes responsible for the function of the immune system as well as genes important for inflammation response (38). Thymus atrophy has been found in mice and rats after oral and intraperitoneal exposure. The lowest oral dose shown to induce thymus atrophy, particularly some subpopulations of thymocytes, in mice is 0.75 mg/kg body weight (LOAEL = 0.75 mg/kg body weight) (39). Although molecular and cellular mechanisms of action of T-2 toxin and other mycotoxins (aflatoxin, ochratoxin and related trichothecenes) are quite different, immunosuppressive effects are the result of direct or indirect inhibition of protein synthesis (40). Vitamin E supplementation partially reduced the risk of DNA damage in immune cells due to the action of DON and T-2 toxin and partially increased synthesis of IgG which was impaired by T-2 toxin. Enhancement of antioxidant status with vitamin E in the case of DON and T-2 toxin intoxication can be beneficial for remaining the lymphocyte DNA integrity (41).

Effects on digestive system
T-2 toxin can have toxic effects on almost all cellular processes in the digestive system. Even a small dose of the toxin can
damage the mucosa of the digestive tract and impair resorption of nutrients. Necrotic damages have been detected in the mouth, gizzard tissue, intestinal mucosa and liver (42, 43). Necrotic lesions in the digestive tract are characterised by white-yellowish mucosal bulge containing caseous-necrotic material (44). T-2 toxin and related trichothecenes are quickly absorbed in the intestinal tract, metabolised, and eliminated almost completely (80 to 90%) within 48 hours (45). However, their toxic effect can be increased by enterohepatic recirculation (46).

Effects on liver

The main target of the toxic effects of T-2 toxin in vivo is the liver. Inhibition of protein synthesis is reduces the activity of the enzymes necessary for the metabolism of toxic substances, induces lipidperoxidation, and increases the activity of glutathione reductase (47). T-2 toxin cause morphological and functional changes in biological membranes that have been observed in the liver (48). Previous studies have shown that there is a similarity between the hemolysis of rat erythrocytes caused by T-2 toxin and that caused by the free radicals (49). Furthermore, T-2 toxin administration leads to a pronounced increase in the thiobarbituric acid reactive compounds in liver homogenate of T-2 toxin-treated rats. This was interpreted as an indicator of the presence of lipid peroxidation substances such as 2-alkenals, 4-hydroxyalkenals and malondialdehyde (MDA), which were reported to be present in the liver after acute exposure to T-2 toxin (49, 50).

Effects on the nervous system

Exposure to T-2 changed the levels of neurotransmitters (dopamine, serotonin, tryptophan, 5-hydroxy-3 indoleacetic acid, 3,4-dihydroxyphenylacetic acid) in rat brain following dietary exposure to 2-21 mg T-2 toxin /kg body weight /day. The LOAEL was 2 mg /kg body weight /day (51). The level of 5-hydroxy-3 indoleacetic acid was increased in rats given 2.5 and 10 ppm T-2 toxin in the feed (equivalent to 0.1 and 0.4 mg/kg bw/day) (51). In various behavioural tests rats given a single oral dose of 2.0 mg/kg body weight showed reduced motor activity and performance in the passive avoidance test. No effect (NOAEL) was observed in rats receiving 0.4 mg/kg body weight (52).

Effects on skin

Dermotoxic effects of T-2 toxin are characterized as necrohaemorrhagic dermatitis. Some animals showed depigmentation of the skin of the legs and comb cyanosis. Very low feather quality and abnormal position of the wings were found in animals that consumed feed contaminated with high levels of T-2 toxin (4 mg/kg to 16 mg/kg) (53). T-2 toxin produces edema, intradermal haemorrhage and necrosis of the skin. Guinea pig is the most sensitive species. The effect on skin has been used as a biological assay for detection of trichothecenes. T-2 toxin can be detected at 0.2 µg with a skin necrosis assay. The minimum effective amount needed to elicit irritation is much less. The mechanism for skin toxicity has not been established (29). The healing effect of quince seed mucilage and aloe vera mucilage on dermal toxicity by T-2 toxin on rabbit skin showed protective effect (54, 55).

Effects on pregnancy

T-2 toxin readily passes through the placenta and is distributed to embryo/fetal tissues which include many component cells bearing high proliferating activity (56). Previous studies examined the maternal toxicity in detail in pregnant rats exposed to a single oral dose of T-2 toxin (2 mg/kg) on day 13 of gestation. In their experiments, apoptosis was induced in lymphoid, hematopoietic and
gastrointestinal tissues and liver in adult mice (57,58). It is said that the c-fos gene plays an important role in the early phase of T-2 toxin-induced apoptosis in the lymphoid and hematopoietic tissues probably through the synthesis of a certain apoptosis-related protein (59). The elevation of c-fos expression requires the mobilization of [Ca²⁺], and partially involves a protein kinase C (PKC)-dependent pathway, and the mobilization of [Ca²⁺], activates calcium-dependent caspases, resulting in inter nucleosomal DNA fragmentation (60). T-2 toxin-induced apoptosis in hematopoietic and lymphoid tissues is considered to be independent of the Fas/Fas ligand pathway (61) and the p53-related pathway (62). As mentioned above, T-2 toxin readily passes through the placenta and is distributed to the fetal tissues (63), resulting in the induction of embryo/fetal death, fetal brain damage and fetal bone malformation (63). Bone malformation such as incomplete ossification, absence of bones, wavy bones and fused bones that is one of the most frequently observed fetotoxicities of T-2 toxin (63). Although, T-2 toxin passes through the placenta, and the blood brain barrier is not completely developed before embryonic day 18 in rats (64). T-2 toxin and its metabolite, HT-2, have a lipophilic nature and the fetal brain is rich in lipids. Therefore, T-2 toxin may be easily distributed to the fetal brain (65). The mechanisms of T-2 toxin-induced maternal and fetal toxicities are due to oxidative stress, followed by activation of the MAPK pathway, finally inducing apoptotic cell death (65).

Genotoxic and cytotoxic effects
T-2 toxin inhibits DNA, RNA, and protein synthesis in eukaryotic cells, affects the cell cycle, and induces apoptosis both in vivo and in vitro (28). The chemical structure of T-2 toxin molecule (position of chemical groups on the trichothecone ring) again has an essential role that determines the mode and target of action, because it specifies the interaction with protein molecule. Thus T-2 toxin, like HT-2 toxin and diacetoxyscirpenol, inhibits polypeptide chain initiation, while other trichothecces affect elongation (trichothecin) and termination (deoxynivalenol). Cytotoxic effects of T-2 toxin have been reported in lymphoid cells (66), while induction of DNA strand breaks caused impairment of the immune system (67). Cytotoxic radiomimetic effects of T-2 toxin are considered to be a result of primarily impaired protein synthesis, and consequently of the inhibition of DNA and RNA synthesis (68). According to the results of studies on the genotoxicity of T-2 toxin in vitro, T-2 toxin can induce gene mutations and sister chromatide exchange, formation of micronucleus, and inhibition of intercellular communication in Chinese hamster V79 cells (69). Another study showed that T-2 toxin caused DNA fragmentation to chicken leukocytes at a concentration of 10 mg/kg of feed. In addition, T-2 toxin and related mycotoxins can induce apoptosis in vitro and in vivo in haematopoietic tissue, spleen, liver and intestinal crypts of mice (28).

Apoptosis
T-2 toxin as well as metabolites such as T-2 triol and T-2 tetraol can activate the stress-activated kinases c-Jun N-terminal kinase 1 (JNK1) and/or p38MAPK (SAPK2). It has been suggested that trichothecces and other peptidyl transferase inhibitors trigger a ribotoxic stress response causing the activation of MAP kinases (70). It has also been reported that T-2 toxin and other trichothecces can activate other MAP kinases, i.e. extracellular signal regulated protein kinase 1 and 2 (ERK1/2), which usually mediates cell proliferation (71). The balance between ERK1/2 pathway and the stress activated JNK/p38 MAP kinase pathway has been proposed to be
fundamental for whether cell survival or apoptosis occurs. It appears that different metabolites of T-2 toxin as well as other trichothecenes differ in their ability to inhibit protein synthesis and activate the MAP kinases and induce apoptosis (70,71). Another study suggest that T-2 toxin creates a pro-apoptotic environment by inducing Fas up-regulation on the chondrocyte surface, and then up-regulate P53 proteins, which in turn increases both the Bax/Bcl-2 and the Bax/Bcl-xL ratios, activates caspase-3 , and induces apoptosis(72). It has also been demonstrated that T-2 toxin induced cytotoxicity in HeLa cells is mediated by generation of ROS leading to DNA damage and transactivation of p53 protein expression. This leads to shift in the ratio of Bax/Bcl-2 in favour of apoptosis and subsequent release of Cyt-c from mitochondria followed by caspase cascade. In addition, caspase independent AIF pathway also leads to DNA fragmentation and apoptosis in T-2 toxin treated HeLa cells (73).

T-2 toxin as a biological warfare
Unlike most biological toxins that do not affect the skin, T-2 mycotoxin is a potent active dermal irritant. Moreover, it is the only potential biological weapon agent that can be absorbed through intact skin causing systemic toxicity. Clinical symptoms may be present within seconds of exposure. While larger amounts of T-2 toxin is required for a lethal dose than for other chemical warfare agents such as VX, soman, or sarin, its potent effect as a blistering agent is well noted. T-2 toxin can be delivered via food or water sources, as well as, via droplets, aerosols, or smoke from various dispersal systems and exploding munitions. These properties make T-2 mycotoxin a potentially viable biological warfare agent. The reported LD₅₀ of T-2 toxin is approximately 1 mg/kg (74). Based on extensive eyewitness and victim accounts, the aerosolized form of T-2 toxin called "yellow rain" was delivered by low-flying aircraft that dropped the yellow oily liquid on the victims. T-2 toxin has been used during the military conflicts in Laos (1975-81), Kampuchea (1979-81), and Afghanistan (1979-81) to produce lethal and nonlethal casualties. More than 6300 deaths in Laos, 1000 in Kampuchea, and 3000 in Afghanistan have been attributed to yellow rain exposure (75). Early symptoms beginning within minutes of exposure include burning skin pain, redness, tenderness, blistering, and progression to skin necrosis with leathery blackening and sloughing of large areas of skin in lethal cases. Nasal contact is manifested by nasal itching and pain, sneezing, epistaxis and rhinorrhea, pulmonary/tracheobronchial toxicity by dyspnea, wheezing, and cough; and mouth and throat exposure by pain and blood tinged saliva and sputum. Anorexia, nausea, vomiting and watery or bloody diarrhea with abdominal crampy pain occurs with gastrointestinal toxicity. Eye pain, tearing, redness, foreign body sensation and blurred vision may follow entry of toxin into the eyes. Skin symptoms occur in minutes to hours and eye symptoms in minutes. Systemic toxicity is manifested by weakness, prostration, dizziness, ataxia, and loss of coordination. Tachycardia, hypothermia, and hypotension follow in fatal cases. Death may occur in minutes, hours or days. The most common symptoms are vomiting, diarrhea, skin involvement with burning pain, redness and pruritus, rash or blisters, bleeding, and dyspnea (74).

Regulatory measures related to use of T-2 toxin and recommendations
Some countries have set their guidance values for T-2 toxin in products intended for animal feed. In China, T-2 toxin limit in complete feed for all animals is 0.08 mg/ kg. A limit of 0.1 mg/kg for T-2 toxin has been set in Iran for complete feed
intended for sheep, goats and beef cattle (76). In Canada, feed for swine and poultry can contain up to 1.0 mg/kg of T-2 toxin, while feed for cattle and poultry has also a limit of 0.1 mg/kg of HT-2 toxin (76). Therefore, mycotoxins represent a public health concern. Several reports have associated outbreaks of human disease with the presence of thichothecenes in food. Additionally, animals consuming contaminated feed can indirectly pose a threat for humans because of potentially present residues of these toxins in animal-derived food products (76).

**Treatment of toxic manifestation due to T-2 toxin**

There is no specific antidote other than detoxifying with natural substances and replenishing lipids, nutrients, enzymes, amino acids, and probiotics, and restricted diet. Superactivated charcoal should be given orally if the toxin is swallowed. On extremely rare occasions, radical treatments such as prescriptions like antifungal treatment may be necessary if natural treatment is not effective (74). Superactivated charcoal adsorsbs ingested toxin, thereby preventing absorption and removing toxin from the GI tract, preventing further cellular damage. Dose for adult 1 g/kg PO/NG; repeat dose of 20-50 g q 2-6 h may be used and dose for pediatric <1 year: 1 g/kg PO, for 1-12 years: 25-50 g PO and for adolescents: 25-100 g PO repeat doses in children not established; half initial dose recommended (74).

**Isolation and decontamination**

Standard precautions should be done. Outer clothing should be removed and exposed skin should be decontaminated with soap and water. Eye exposure should be treated with copious saline irrigation. Once decontamination is complete, isolation is not required. Environmental decontamination requires the use of a hypochlorite solution under alkaline conditions such as 1% sodium hypochlorite and 0.1M NAOH with 1 hour contact time. Controlled UV light and ozone can be the only method to decontaminate porous substances with human exposure (74).

**Conclusion**

Mycotoxines are toxic secondary metabolites produced by various fungi which cause toxic effect called mycotoxicosis. The adverse effect of fungal products have caused mass poisoning in both man and farm animal over many countries. T-2 toxin is one of the closely related compounds produced by several Fusarium species. Although reported natural occurrence of T-2 toxin and related mycotoxins shows their worldwide presence, they are predominant in tropical and subtropical regions. In short, the most important factors that influence T-2 toxin production are weather conditions, grain defects and moisture content. At very low dose, T-2 toxin can damage the mucosa of the digestive tract and impair resorption of nutrients. T-2 toxin induced oxidative stress causing DNA damage in rat liver cells and it produces edema, intradermal haemorrhage and necrosis of the skin. The properties of T-2 toxin make it as a potentially viable biological warfare agent. T-2 toxin has been used during the military conflicts in Laos (1975-81), Kampuchea (1979-81), and Afghanistan (1979-81) to produce lethal and nonlethal casualties. More than 6300 deaths in Laos, 1000 in Kampuchea, and 3000 in Afghanistan have been attributed to yellow rain exposure (75). As genotoxicity and cytotoxicity data indicate that T-2 toxin is highly toxic, and as it is widespread in cereals and food, additional research of its toxic potential in animals and in humans is necessary.
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