SHORT REPORT

The Potential Use of Bear Bile in Coronavirus Diseases (COVID-19)

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Disclosure

The authors of this review have no competing interest in this subject.

Disclaimer

This review is essentially a brief report, prepared on an urgent basis, to reflect the highest level of evidence available regarding the subject at this specific time. The conclusion draws on restricted reviews from analysis of pertinent literature, on expert opinion and/or regulatory status where appropriate. All efforts have been made to ensure all relevant published material has been reviewed but this document may still not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of this review.

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Introduction

- Amid the COVID-19 pandemic, there is an urgency of conducting research to find an effective treatment for the disease as well as to contain its causative pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As the first country that reported mass outbreaks of COVID-19 cases, the Chinese government has listed out both Western and traditional medicine recommended to treat the disease as compiled and published by China's National Health Commission, the government body responsible for national health policy. One of the recommendations was to use an injection containing bear bile, which is part of traditional Chinese medicine (TCM) formulation namely Tan Re Qing. (1)

- Tan Re Qing is traditionally used for bronchitis and upper respiratory infections by TCM practitioners (2). Its medicinal indications were well documented in ancient Chinese medicinal and modern Chinese medicine publications (3).

- The use of Tan Re Qing formulation is condemned by wildlife advocates due to its bear bile constituent which is believed to be acquired using unethical and cruel ways towards the animal, as well as concerns for several bear species that are now listed as species threatened with extinction under the Convention on International Trade in Endangered Species of Wild Fauna and Flora. Bear bile can be obtained from either wild or farmed bears that are especially famous in China and Vietnam. One of the species most commonly farmed for bile is the Asiatic black bear, which is listed as vulnerable to extinction on the International Union for Conservation of Nature's (IUCN) Red List. The bears have to endure physical and psychological torture during the farming and bile extraction process. It requires inserting a catheter, syringe, or pipe into their gallbladder, which can cause long term health problems and suffering. (4–6)

- Based on news reports, there is no evidence in western studies of bear bile for treating COVID-19. Instead, ursodeoxycholic acid (UDCA) contained in bear bile might be able to keep human cells alive and may alleviate symptoms of COVID-19 due to its anti-inflammatory properties and ability to suppress the immune response (2).

What is bear bile and ursodeoxycholic acid (UDCA)?

- Bear bile in this context is bile secreted by the liver and stored in the gallbladder of various species of bears, including Asiatic black bears and brown bears (1).

- Traditionally, bear bile was considered as a cold medicine, bitter in flavour, cool in nature and used for liver, gallbladder, and heart by clearing heat to relieve toxin, stop endogenous wind to arrest convulsion and clear away liver fire to improve eyesight (7–10). In Chinese Materia Medica, bear bile is clinically used for fever fighting, detoxification, inflammation, swelling and pain reduction. It was also used in the cure of carbuncle of heat type, pyocutaneous diseases, haemorrhoid, overabundance of liver-fire, convulsion caused by the overabundance of heat, epilepsy, tic, and redness of eyes due to liver heat. The recommended dosage is 0.25–2.5 g to be taken as a dose in pill or powder. It is mainly singly used and rarely used together with other herbs. Due to its fishy and bitter taste that may induce vomiting, it is recommended to be given as capsules. For external use, the fine powder can be applied directly to the local area or used with water. (10)

- Bear bile is part of an injection formula known as Tan Re Qing, which consists of the following ingredients (11).
    - Scutellariae radix (SR, Huangqin in Chinese), root of *Scutellaria baicalensis* Georgi (family Labiatae)
    - Bear bile powder
    - Caprae hircus cornu
    - Lonicerae japonicae flos
    - Forsythiae fructus

- Bear bile contains high levels of UDCA, a dihydroxy bile acid which is also known as ursodiol. Study have also shown that bear bile contains tauro conjugate of UDCA, called tauro-UDCA (TUDCA) (12). UDCA is clinically proven to help dissolve gallstones and treat acute and chronic liver diseases. The various mechanisms of action of this hydrophilic bile acid include direct cytoprotection, detergent action on dysfunctional microtubules, immunomodulation, and induction of hypercholeresis. UDCA has been available as a synthetic drug worldwide for decades. (13)

Safety

Bear bile

- Due to the bear farming where the bile is extracted via 'free-dripping Fistula technique', the bear specimens were found to have inflammation of the hepatic and cholalic system. This suggests that bile extracted from live bears may contain hepatic carcinoma and inflammatory cells and consequent cytokine, which is harmful to human health. (14,15)

UDCA/ TUDCA

- UDCA is approved for human use by the United States Food and Drug Administration (US FDA) and is generally considered to be safe. According to the approved product insert, the recommended dose is 13–15 mg/kg/day administered in two to four divided doses with food for treatment of primary biliary cirrhosis (PBC) for adults. Its safety and efficacy have not been established in children. It was also non carcinogenic, non-mutagenic and does not negatively affect the reproductive system in animal studies. (16)

- A meta-analysis evaluated the efficacy and safety of UDCA-based treatments available for PBC was found that monotherapy with UDCA and combined therapy of UCDA with corticosteroids (COT) were the most effective and safest in reducing the risk of mortality or liver transplantation (MOLT) with a weighted benefit-risk ratio for patients with PBC. Combination of UCDA with bezafibrate (BEF) could provide further survival benefit but with increased adverse effect. The study concluded that UDCA is safe and may be useful for preventing the progression of PBC, which is the only therapy approved by the US FDA. However, the effects of UDCA remain controversial. (17)

- In a randomised, cross over study in 60 PBC patients administered UDCA, four patients (6.7%) experienced one serious adverse event each (diabetes mellitus, cyst, and breast neoplasm). No deaths were reported. Forty-three patients (n = 43, 71.7%) experienced at least one treatment-emergent adverse event (TEAEs) during the study. The most common (> 5%) TEAEs were asthenia (11.7%), dyspepsia (10%), peripheral edema (8.3%), hypertension (8.3%), nausea (8.3%), gastrointestinal disorders (5%), chest pain (5%), and puritius (5%). Seven patients (11.6%) reported nine events that were possibly or probably related to UDCA. These nine TEAEs included abdominal pain and asthenia (n = 1), nausea (n = 3), dyspepsia (n = 2), anorexia (n = 1), and esophagitis (n = 1). One patient on the twice daily regimen (13-15 mg/kg/day; total dose 1,000 mg) withdrew due to nausea. All

of these nine TEAEs, except esophagitis, were observed with the twice daily regimen at a total daily dose of 1,000 mg) or greater (above 1,000 mg). (16)

- In a multicenter, randomised, double-blind trial comparing the efficacy and safety of TUDCA and UDCA in 299 Chinese patients with primary biliary cholangitis, four patients (3.1%) administered TUDCA exhibited drug related adverse events: diarrhea (n = 1), pruritus (n = 2), rash (n = 1), dysmenorrhea (n = 1). In the UDCA group, only three adverse events (three patients, 4.4%) were considered to be drug related: rash (n = 1), and nausea (n = 2). No serious adverse events occurred during the study. There was no significant difference in observed adverse effects between UDCA and TUDCA. There was no control arm treated with placebo. (18)

- In a randomised, controlled trial study using UDCA treatment in patients with PBC, PBC showed a small but significant (p = 0.005) weight gain among patients during the first 12 months of treatment compared to placebo (67/86 [78%] versus 43/73 [57%] respectively). Weight gain persists for the duration of treatment, and occurs independent of baseline body mass index. The UDCA was administered in the form of 250-mg tablets at a dose of 13 to 15 mg/kg/day in divided doses given with meals and a bedtime snack. Patients in the UDCA group gained an average of 3.6 ± 6.5% kg (2.2 ± 5.1 kg), which was significantly greater than the average of 0.6 ± 6.9% kg (0.6 ± 4.9 kg) gained in the placebo group (p = 0.04). The reason for this weight gain is unclear and it is not a threat enough for health problems. It could be possibly due to the improved patients' wellbeing after consuming the drug, so consequently increased their appetite and body mass, or UDCA probably improved bile salt levels in the gut, thus preventing malabsorption in the users. However, patients treated with UDCA may expect a modest weight gain effect while on this drug. (19)

- A safety study evaluated on chronic hepatitis C patients administered with UDCA showed overall incidences of adverse reactions 18.1%, 21.5% and 17.8% in the 150, 600 and 900 mg/day treatment groups, respectively, with no significant difference between the groups. The adverse reactions were based on 1% or more incidence observed in patients showing signs and symptoms and abnormal laboratory test results which are abdominal distension, upper abdominal pain, constipation, diarrhoea, dyspepsia, loose stool, stomach discomfort, and pruritus. Diarrhoea was mostly reported with no severe adverse reactions were observed. (20)

Antiviral efficacy evidence

Bear bile

- In a metabolomics and proteomics study, 38 biomarkers from bear bile powder (4%) were identified and two unique metabolic pathways were indicated to be differentially affected in HCV-positive adult male tree shrews (*T. belangeri chinensis*, n = 38) (21).

UDCA/ TUDCA

- A meta-analysis of five randomised controlled trials indicated that acetylcysteine was superior to UDCA or silibinin to reduce aminotransferase (ALT) level, whereas UDCA was superior to acetylcysteine or silibinin to reduce total bilirubin level compare with placebo in patients with hepatitis B (22).

- A Cochrane systematic review evaluated on the effects on bile acids and viral hepatitis. Bile acids (21 trials UDCA; four trials TUDCA) significantly improve serum transaminase activities in hepatitis B and C patients. However, there is insufficient evidence either to support or to refute effects on viral markers (i.e. direct antiviral effects), mortality, incidence of cirrhosis, or liver histology. More trials with high methodological quality are required in the future. (23)

- A clinical trial showed that the persistence of the hepatitis B virus infection at 12 months of follow-up, was observed in one of 33 patients in the UDCA treated group and in six of 25 patients in the placebo group ($p = 0.02$). Gallstones detected by entry ultrasound dissolved in four of eight cases in the UDCA group and in none of six in the placebo group. Hence, UDCA may have beneficial effects on the course of acute viral hepatitis. It may enhance the clearance of the hepatitis B virus and thus prevent the development of chronic hepatitis. However, full text of this article could not be obtained and thus, the information was extracted based on abstract only. (24)

- A clinical trial of 401 chronic hepatitis B patients who were diagnosed with hepatocellular carcinoma (HCC) were divided into three groups; 1: received no medication, 2: hepatoprotective agents such as UDCA and silymarin, 3: and antiviral agents at two years before HCC diagnosis. Compared to no treatment, patients administered with hepatoprotective agents (UDCA, silymarin) and antiviral agents had higher rates of good compliance to regular surveillance and enabled early detection of HCC, which is associated with enhanced survival. (25)

- A clinical trial of 38 chronic hepatitis C patients (25 males and 13 females) reported no differences in proportion of HCV reactivation, time of HCV appearance, as well as initial and late response parameters to treatments among patients treated with interferon alone compared to interferon plus UDCA (10 mg/kg/day) for six months. (26)

- A randomized clinical trial involving 152 subjects was conducted to study the role of UDCA in liver diseases of children with acute hepatitis infection (HAV). The treatment group was given oral UDCA (exquisite, 10–15 mg/kg body weight, two to three times daily in association with their meals) while the control group did not receive any medication. Blood samples were obtained before the intervention, as well as two weeks, four weeks, two months, three months, four months, and six months. The result showed that UDCA administration in children with acute HAV infection accelerated the normalisation of liver enzymes. However, there were no significant differences in the ratios of aspartate transaminase (AST) and ALT normalisation between children receiving UDCA and non-treated children after six months of therapy. (27)

- A double-blinded trial of 247 patients with chronic hepatitis C (CH-C) investigated the long-term effects of UDCA. After 20 weeks, UDCA (600 mg/day) was shown to effectively decrease ALT and AST levels in CH-C patients by at least 15%, without serious adverse effects, while gamma-glutamyl transpeptidase (GGT) was significantly lower in the 900 mg/day group when compared to 600 mg/day group. However, there is no significant changes in HCV-RNA levels from the baseline for 3 groups (150 mg/day, 600 mg/day, 900 mg/day). (20)

- A pilot study involving 79 subjects was conducted to study the potential effects of UDCA in acute viral hepatitis patients. The intervention group (40 patients) was given UDCA (300 mg twice daily) for three weeks while the control group (39 patients) received no treatment. Cholestatic indexes (AST, ALT, GGT, ALP, bilirubin, albumin) and serum bile acid were determined at weekly intervals. The result showed that cholestatic indexes decreased significantly more quickly in patients treated with UDCA than in the control group. No adverse events related to UDCA were recorded. (28)

- A case report of an 84-year-old man with asymptomatic chronic HCV infection was treated with 12-week course of a combination of direct-acting antiviral agents (DAAs) Elbasvir/Grazoprevir (50/100 mg orally once a day). At the end of antiviral therapy, the laboratory tests showed an abrupt increase in

cholestasis parameters and aminotransferases, associated with anti-mitochondria antibodies positivity. Therefore, primary biliary cholangitis (PCB) was diagnosed. The patient was then treated with UDCA at the dosage of 900 mg/day (13.5 mg/kg/day), resulting in a rapid normalisation of the aminotransferases (ALT 9 IU/L, AST 19 IU/L) and a progessive decrease in gamma-glutamyl transpeptidase (GGT) (131 IU/L) as well as alkaline phosphatase (ALP) (64 IU/L) levels after 6 months of treatment. (29)

- In an in vitro study, UDCA (50 µg/mL), given in triple combination with the antiviral amantadine (20 µg/mL) and biphenyl dimethyl dicarboxylate (100 µg/mL) demonstrated anti hepatitis B virus properties via inhibition of HBsAg and HBcAg gene expression, compared to control, potentially through inhibiting viral gene replication (nitric oxide production) and STAT1alpha mediated antiviral effects. This effect was not superior to standard treatment of interferon. (30)

Effects on inflammation and immune system

Bear bile

- A patent held by Heilongjiang GAP Research Centre, U.S was filed and approved for producing a bear bile macromolecular extract with shown activity against hepatitis C virus using *in vitro* test (31).

- In an *ex vivo* study, refined bear gall (bile powder) at 50 and 100 µg/mL demonstrated anti-inflammatory activities in mast cells harvested from rats stimulated with immunoglobulin E (IgE), via reduction of tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and NF-kappa-B transcription complex (NFkB) p65 (32).

- Possible immunomodulatory mechanisms from animal studies could be bear bile can promote the proliferation of T cells, decrease regulatory T cells, and enhance the activation of T cells, which means bear bile may improve immune response in liver disease (33–35).

UDCA/ TUDCA

- In an in vitro study, lipopolysaccharide stimulated RAW 264.7 macrophages, UDCA decreased the release of inflammatory mediator nitric oxide as well as pro-inflammatory cytokines TNF-α, interleukin (IL) 1-α, IL-1β, and IL-6 in mRNA and protein levels. The UDCA also increased the anti-inflammatory

cytokine IL-10. The potential anti-inflammatory mechanisms demonstrated include suppression of the phosphorylation of extracellular receptor kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 signals related to inflammatory pathways, as well as inhibiting inhibitor of nuclear factor kappa B (IκBα). (36)

- In an in vitro study, UDCA demonstrated anti-inflammatory properties by significantly reducing IL-1β and TNFα-induced expression of IL-1, IL-6, and IL-8 in gingival fibroblasts and the squamous carcinoma HSC-2 cell line. In RAW 264.7 macrophages, UDCA attenuated the expression of the pro-inflammatory cytokines IL-1α, IL-1β, and IL-6 that was increased by saliva. (37)

- In a mice model of steatohepatitis, although TUDCA did not significantly reduce hepatocyte lipoapoptosis and steatohepatitis. Although this study was designed to study apoptosis, there are some evidence suggesting TUDCA's anti-inflammatory effects as represented by the down regulation of cytokines chemokine ligand 2 (CCL2) and TNF-α. (38)

Clinical and preclinical evidence of Tan Re Qing (TRQ)

- Currently there are two clinical trials registered investigating the use of Tan Re Qing for the treatment of SARS-CoV-2 infection which include, a phase 4 controlled clinical trial to study on the efficacy and safety of large dose Tan Re Qing Injection; and a phase 0 randomised controlled trial using Tan Re Qing Capsules. (39)

- The details of preclinical and clinical evidence including systematic reviews and meta-analysis of published articles with regards to TRQ in respiratory diseases are as shown in the table below:

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No.	Experimental system	Type of Disease	Major findings	References
1	Systematic review	Acute bronchitis	A total of 49 included trials showed that TRQ has potentially beneficial effect in improving effective rates, reducing the time to resolution of fever, cough, crackles and absorption of shadows on	(40)

			X-ray. However, due to the limitations of methodological quality of the included trials, it is difficult to make a conclusive recommendation about TRQ treating patients with acute bronchitis.	
2	Systematic review	Community acquired pneumonia	A total of 12 included RCTs showed that TRQ injection plus antibiotics and basic therapy is better than that of antibiotics plus basic therapy where TRQ injection can improve the symptoms of cough and expectoration, shorten the fever time and facilitate the absorption of chest X-ray shadow, without any significant adverse reactions although better future methodological trials is required.	(41) **[abstract access only]**
3	Systematic review	Chronic obstructive pulmonary disease (COPD)	A total of 14 included trials showed that TRQ injection administered via intravenous drip plus conventional Western medicine showed improved arterial partial pressure of oxygen (Po2), clinical efficacy, and lung function; reduced arterial partial pressure of carbon dioxide (Pco2) and shortened the length of hospital stay compared to conventional Western medicine alone.	(42)
4	Meta analysis	Mycoplasma pneumoniae Pneumonia	A total of 89 RCTs were included, involving 8 kinds of traditional Chinese medical injections including TRQ injection, and 8936 patients. The results show that TRQ injection has a significant clinical efficacy in the adjuvant treatment of various symptoms of mycoplasma pneumoniae pneumonia in children.	(43)
5	Meta analysis	Pulmonary Tuberculosis	A 26 RCTs involving 2404 patients were included in this study to evaluate the efficacy of TRQ injection alone versus antibiotics and TRQ injection plus antibiotics versus antibiotics. The results showed that TRQ injection alone has the same overall efficacy as the conventional antibiotics while TRQ injection plus antibiotics have an improved clinical efficacy in Pulmonary Tuberculosis. TRQ may have synergistic effect on antibiotics through bacteriostatic activity and eliminating inflammatory mediators. Its antibacterial	(44)

			activity may be better than some antibiotics and does not increase adverse drug reaction.	
6	Human trial	Acute lung injury	A total of 59 patients enrolled in the study where the group (n = 29) that received TRQ injection showed reduce the serum levels of inflammatory factors as TNF-α, IL-6 and IL-8. It also slows down the progress of systemic inflammatory response syndrome and improve gas exchange in acute lung injury compared to general treatment group (n = 30).	(45) **[abstract access only]**
7	Human trial	Mycoplasma pneumoniae Pneumonia (MMP)	A total of 56 children with MMP were randomly divided into treatment group (Azithromycin + TRQ) and control group (Azithromycin only). The treatment group showed a higher rate of clinical efficacy (89.3%) which was significantly higher than that of the control group (53.6%) (P0.05); the adverse reactions of the treatment group was significantly lower than that of the control group(P0.05).	(46) **[abstract access only]**
8	Animal study	Influenza FM	TRQ injection administered to mice infected with influenza virus FM showed reduced viral titres and relevant pathological damages, improved T lymphocyte replication, and increased levels of serum IFN-γ.	(47) **[abstract access only]**
9	Animal study	Influenza FM	TRQ injection (large, medium and small dose) was administered to mice infected with influenza virus FM1 showed that it directly stimulates TB lymphocyte multiplication, adjust the balance of Th1 and Th2 cells by cytokine IL-2, IFN-γ and TNF-α and improve anti-virus immune function.	(48) **[abstract access only]**
10	Animal study	Inflammation and fever caused by endotoxemia	TRQ injection (single & double dosages) administered to healthy Sprague-Dawley rats and healthy LCR mice where endotoxemia was induced via administration of lipopolysaccharide (LPS) Ecoli055B5 strain through sublingual vein of rat and that of mouse was made by i.p. injecting LPS (Ecoli055B5). Results showed TRQ	(49) **[abstract access only]**

			inhibiting inflammation caused by endotoxemia and the increase of content of PGE_2 and cAMP in hypothalamus.	
11	Animal study	Acute Inflammatory airway diseases	TRQ injection (low and high dose) was administered intraperitoneally to rats where acute bronchopneumonia was induced by intratracheal instillation of LPS. Results showed that TRQ possesses potent exhibitory effects in LPS-induced airway inflammation by, at least partially, suppressing the MAPKs and NF-*κ*B signaling pathways, in a general dose-dependent manner.	(50)
12	In vitro	Pneumonia	In this study, TRQ combined with penicillin demonstrated the synergistic activity against forming and mature *Staphylococcus aureus* biofilm, as the acute upper respiratory infections and early stage pneumonia are all typical biofilm related diseases.	(51)

Interpretation of evidence

Based on the traditional use and research publications, research of bear bile, UDCA, and TUDCA were mostly focused on hepatobiliary diseases such as acute and chronic Hepatitis C. Although hepatoprotective effects have been demonstrated, the specific mechanisms of action of bear bile powder are unclear while good quality evidence of direct antiviral effects are limited. There is also some preclinical evidence for the potential anti-inflammatory and immunomodulatory properties of bear bile, UDCA, and TUDCA. This corresponds to bear bile's traditional and current documented use based on Chinese Medicine philosophy, which is for the cure of overabundance of liver fire and redness of eyes due to liver heat. Due to this, currently bear bile appears to have more potential to be of a supportive treatment for potential complications related or unrelated to respiratory infections such as the COVID-19 pneumonia, rather than a direct treatment and cure for COVID-19. Research on the antiviral effect of bear bile should cover parameters such as evidence of direct viral suppressive effects, or on inflammatory parameters such as white blood cell count, lymphocytes (CD3+, CD4+, CD8+, CD4/CD8), C-reactive protein level, erythrocyte sedimentation rate, and clinical imaging such as CT scan of the chest. There is also concern where perception that farmed bear bile is of lower quality due to the high rate of extraction and poor nutrition. (52)

Recommendation against use of Bear bile for treatment of COVID-19 and alternatives for liver problems associated with COVID-19

- International cooperation is essential to ensure that Convention on the Trade in Endangered Species (CITES) is adhered internationally in individual countries, where the same agreement in banning trade control should be enforced. The ban should apply to all bear species regardless of methods such as bear farming or bear killing.

- There are four alternatives suggested on replacing bear bile use for liver problems associated with COVID-19, as following (53).
    - **Artificial bear bile:** It contains almost similar compositions and structures of various synthetic or natural bile acids (especially TUDCA), amino acids, minerals, cholesterol, and bilirubin to the natural ones.

    - **Synthetics compounds:** The two important compounds to be produced synthetically are UDCA (UDCA is a second bile acid, which is the metabolite of primary bile acid by intestinal microbiota by human) and TUDCA (made directly from cholesterol by hepatocytes and then conjugates with taurin to form TUDCA in bear). Therefore, it is important to have a successful synthetic technique of DCA-based acids that not only meets the need in quantity but also provides more stable quality of drugs. However, the drawbacks include unstable composition, poor quality control and ability to exert integrative effects due to single compound.

    - **Biles from other animals:** Many studies were conducted to compare the compositions of bile derived from other animals with bear bile as well as the pharmacological actions. Both bear bile and pig bile possess comparable bioactivities, such as anti-inflammatory and analgesic effects with pig bile possessing additional antiallergic effect. However, there are contradictory findings on the UDCA and TUDCA contents with another study claiming that the quantity of UDCA content in pig bile was too little for large scale production. (14) However, using bile from livestock as alternatives of bear bile not only protects endangered species and prevents crucial extraction but also avoids the waste of resources.

    - **Plant-based resources:** Instead of comparing efficacy based on bioactive compounds, medicinal plant substitutes can be evaluated and

used as alternatives based on claims. Since bear bile was characterized under the category of clearing heat and detoxification drugs, plants with similar claims can be researched on its efficacy with bear bile as comparison. For example, research has shown that berberine and Rhizoma coptidis treat fibrosis better than that of bear bile in the same experimental condition. The only drawback would be substitution with different compositions makes it challenging to explain the similar intended effects, which therefore requires more investigation of mechanisms of action.

- Therefore, future research should focus on identifying the bioactive compounds and mechanisms of bear bile in exerting its medicinal effects, to aid in the discovery and design of feasible and humane substitutes, synthetic or natural.

- Alternatively, as TRQ is not the only formulation recommended, other listed formulations which have less environmental impact and are more humane should be given heavier weightage when choosing a treatment, based on assessment on individual characteristics and syndrome imbalances according to TCM principals. Furthermore, the guideline was developed specifically for the local patients of Hubei province in Wuhan during the winter season when the climate is cold and humid locally, which therefore should not be viewed as generalisable to other areas. As TRQ is only recommended to be given in patients with severe symptoms, as prescribed, monitored, and dose optimised by qualified TCM practitioners in hospital settings, it is unsuitable for the public to self-purchase and self-medicate, which may subsequently drive the demand for bear bile and encourage illegal poaching. As there is still no clinically proven treatment for COVID-19, social distancing and hand hygiene remains the most efficient and important strategy in prevention of transmission.

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