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Toxicity as prime selection criterion among SARS-active herbal medications

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ABSTRACT

We present here a new selection criterion for prioritizing research on efficacious drugs for the fight against COVID-19: the relative toxicity versus safety of herbal medications, which were effective against SARS in the 2002/2003 epidemic. We rank these medicines according to their toxicity versus safety as basis for preferential rapid research on their potential in the treatment of COVID-19. The data demonstrate that from toxicological information nothing speaks against immediate investigation on, followed by rapid implementation of Lonicera japonica, Morus alba, Forsythia suspensa, and Codonopsis spec. for treatment of COVID-19 patients. Glycyrrhiza spec. and Panax ginseng are ranked in second priority and ephedrine-free Herba Ephedrae extract in third priority (followed by several drugs in lower preferences). Rapid research on their efficacy in the therapy - as well as safety under the specific circumstances of COVID-19 - followed by equally rapid implementation will provide substantial advantages to Public Health including immediate availability, enlargement of medicinal possibilities, in cases where other means are not successful (non-responders), not tolerated (sensitive individuals) or just not available (as is presently the case) and thus minimize sufferings and save lives. Moreover, their moderate costs and convenient oral application are especially advantageous for underprivileged populations in developing countries.

Introduction and background

All over the world researchers are engaged to rapidly find medications useful for the therapy of patients infected with the new coronavirus SARS-CoV-2 and/or for the prevention of COVID-19 (Hoffmann et al., 2020; Magrone et al., 2020). The development of effective and safe vaccines is time-intensive due to several complication factors. A first problem arises by the mutability of the virus. SARS-CoV-2 possesses multiple mutations, which optimize binding properties to ACE2 as its receptor and the polybasic cleavage site in the viral spike protein (Anderson et al., 2020). Coronaviruses rapidly mutate by recombination (Kottier et al., 1995). Mutations of SARS-CoV-2 already led to several strains of SARS-CoV-2 (Wang et al., 2020). Vaccines should be able to deal with all of them as well as with future mutations. Therefore, relatively stable SARS-CoV-2 proteins should be identified as antigens to raise antibodies against SARS-CoV-2. In addition, vaccine-induced aggravation of infections by “antibody-dependent enhancement” (Luo et al., 2018) should be avoided, as well as severe organ damage as observed with vaccines directed against SARS-CoV-1 in ferrets and mice (Tseng et al., 2012). Dealing with all these issues including the required trials predictably will demand quite some time.

The time span to actual readiness of application is of obvious importance. Hence, medications already in clinical use and known for producing only few unwanted effects stand in front line. Thus, repurposing of drugs developed for other disease indications appears to be promising. At present, several such drugs are under clinical development, e.g. the Ebola drug remdesivir, the HIV drugs lopinavir and ritonavir and the antimalarial chloroquine (Costanzo et al., 2020; Kumar et al., 2020; Sanders et al., 2020). Unfortunately, their usefulness is hampered by as yet unknown effectivity (“The FDA has authorised remdesivir for use in COVID-19 patients: but there’s no good evidence it reduces mortality”, Center for Evidence-Based Medicine, communication of May 12, 2020 https://www.cebm.net/covid-19/the-fda-has-authorise...for-use-in-covid-19-patients-but-theres-no-good-evidence).
One treasury of rapidly available medications with acceptable side effects has been largely overlooked thus far: Some herbal remedies used since centuries in traditional medicine may be realistically promising to treat SARS-CoV-2-infected patients based on experiences made with SARS-CoV-infected patients during the 2002/2003 epidemic. These herbal medicines may, therefore, merit immediate, rigorous investigations. It is reasonable to hypothesize that chemical constituents in medicinal plants such as *Lonicera japonica*, *Morus alba*, *Forsythia suspensa*, *Codonopsis* spec., *Glycyrrhiza* spec., *Panax ginseng* which were useful for SARS therapy may also be useful to fight COVID-19.

Undesirable effects of any drug obviously are essential limiting factors. Thus, the degree of toxicity may present a valuable basis for prioritizing urgently needed research on the rapid development of effective and sufficiently safe treatments for COVID-19 patients. This review presents published data regarding the toxicity of herbal medications from Far East traditional medicine, which have been reported to be useful for the therapy of SARS-CoV-1-infected patients during the first SARS epidemic (Liu et al., 2006; 2012a, 2012b; Wang et al., 2014; Luo et al., 2020). Irrespective of whether all these reports withstand rigorous scientific criteria, these herbal drugs are recommended by some physicians in despair and taken by some patients in despair, believing in their safety “as natural products” without knowledge of their respective safety or toxicity.

In China more than 85% of SARS-CoV-2-infected patients received therapies from traditional Chinese medicine (Yang et al., 2020). It is of outstanding importance, therefore, to disseminate the knowledge on the safety versus toxicity of these drugs. Many of them may in fact have therapeutical or preventive potential for COVID-19. The relative safety or toxicity of them may represent a rational basis for prioritizing urgently needed, convincing research on potentially useful herbal drugs with a much longer experience than with relatively newly developed drugs. It is not impossible that some of the latter may lead to adverse effects, which do not become visible in controlled clinical trials, but only after a latency of several decades (as we painfully had to learn with many carcinogens). At present, we do not yet have remedies for immediate use for prevention or treatment of COVID-19. For the sake of the present patients and for attempting prevention of a possible second wave of infections, it is mandatory to keep an open mind to include into proper research all possible sources of medication which realistically promise to be effective for the prevention and/or cure of COVID-19, including herbal drugs used in traditional medicine. Several of them have been more recently investigated using rigorous scientific methods and criteria (Cheng et al., 2016; Rai et al., 2017; Li et al., 2018), including analysis and structure elucidation of their constituents (Yu et al., 2008; Sun et al., 2019; Qu et al., 2020) as well as demanding quality control of preparations for use (Li et al., 2009; Han et al., 2016; Gao et al., 2017). *Lonicera japonica* has proven to be a top candidate for COVID-19 therapy by virtual docking experiments on over 40,000 drugs showing their excellent binding capacity to critical target molecules of SARS-CoV-2 (spike protein, nucleocapsid protein, and 2′-O-ribose methyltransferase) (Kadioglu et al., 2020). Glycyrrhizin has recently been shown to have the potential to bind to ACE2 (Ren et al., 2020), and Glycyrrhizic acid-based carbon dots have been reported to show high antiviral activity by multisite inhibition mechanisms (Tong et al., 2020).

The intention of this review article is to specifically provide an overview on published results on preclinical toxicity studies. Chinese medicine with its millennia-long experience follows holistic principles, i.e. the complexity of the human body is seen in its entirety. Hence, fighting diseases starts already with prevention and disease treatment attempts to restore the disease-causing imbalances in the whole body. This is achieved by influencing the meridians of the body, i.e. invisible channels connecting the organs and allowing body fluids to flow such as the life energy qi (Efferth, 2008). For intervention of meridians, external approaches are applied (e.g. acupuncture and moxibustion, massage, cupping, tai chi chuan etc.) and internal practices are used (e.g. complex herbal mixtures, meditation and others). By contrast, western academic medicine follows reductionistic approaches to reduce the complex diseases to its single disease causes and fight diseases by attacking single disease mechanisms.

Drug development and marketing underlies strict rules and regulations to ensure safety and efficacy of new drugs. Like Western academic medicine, Chinese medicine also aims to apply efficient and safe medications. This is reached by bringing the right plant constituents together in herbal mixtures. In this context, the “emperor-minister-servant” principle is of interest. The “emperor” plant exerts the main pharmacological effect, the “minister plants” support the activity of the “emperor” plant, and the “servant” can reduce possible side effects and toxicities. During the past decades, Chinese medicine gained enormous interest in the Western world as a complement to academic Western medicine. If Chinese medicine should find its way to the European pharmac-market, applicable laws for drug approval have to be followed which are valid for any drug – being of synthetic or natural origin (Efferth and Greten, 2012). Hence, the scientific investigation of pharmacological activity and toxic adverse effects of Chinese plants is of utmost importance to open the European market for Chinese herbal medicine. During the past two decades, we focused on both pharmacology and toxicology of Chinese herbs and their chemical constituents (Efferth et al., 2007; Konkimalla and Efferth, 2008; Youns et al., 2010; Efferth and Kaina, 2011; Quedraogo et al., 2012; Allard et al., 2013; Efferth and Greten, 2012; Bhakta-Guha and Efferth, 2017).

In the present review, our intention is to give an overview on the toxicology of Chinese plants that may help to treat COVID-19. While specific reviews on the toxic effects are rare or even absent as of yet, a tremendous number of investigations on antivirally active Chinese plants to inhibit SARS-CoV-2 and to cure COVID-19 have been published in the year 2020 (Huang et al., 2020; Luo et al., 2020; Li et al., 2020; Yang et al., 2020). Therefore, in the present review we focused only on toxicology and refer the reader to the excellent reviews on the pharmacology of anti-COVID-19 Chinese plants and clinical trials performed with Chinese herbal medicine to treat this pandemic that appeared in parallel in this special issue of Phytomedicine (Hu et al., 2020; Wang et al., 2020; Xia et al., 2020; Zhang et al., 2020; Zhao et al., 2020a; Zhao et al., 2020b; Zheng et al., 2020).

Based on their already existing safety profile, the data presented here may provide a rational basis for ranking individual herbal medications for investigations on efficacy against COVID-19 (or, where the safety profile shows no concern, possibly even carefully controlled, immediate compassionate use). Potential advantages for patients’ welfare and Public Health benefit include: (1) Enlargement and diversification of pharmacological options where other drugs are not effective (non-responders), not tolerated (susceptible individuals) or not available (as is presently the case). (2) Convenient oral application by the patient himself without continuous necessity for professional assistance, and moderate costs, both of these especially advantageous for financially disadvantaged populations in developing countries. (3) Therapy optimization may become possible by using the presented information for complementary, synergistic or adjuvant combination treatment. (4) Finally and of basic importance, in cases where the pharmacological effect does not exceed placebo, the toxicological data presented in this review and the consequent selection of a non-toxic herbal drug will at least allow a psychological support without causing additional toxic effects.

**Lonicera japonica** *(Flos Lonicerae Japonicae)*

*Lonicera japonica* used since thousands of years belongs to the oldest drugs, and is one the most frequently prescribed drugs in Far East traditional medicine (Shang et al., 2011). Nowadays it is widely used
also in cosmetics, soft drinks and health-oriented food (Shang et al., 2011; Li et al., 2019), thus possessing a large fundus of experience. Shang et al. (2011) reviewed in detail the antiviral, antibacterial and antioxidative activities of Lonicera japonica as well as the isolation and characterization of more than 140 of its chemical constituents. Since then many further compounds were isolated from Lonicera japonica and characterized with respect to their pharmacological activities such as antiviral activities (Yu et al., 2008; Ding et al., 2017; Li et al., 2018; Ge et al., 2019), suppression of inflammation-stimulating signaling pathways (Kang et al., 2010; Kao et al., 2015; Kwon et al., 2015; Lee et al., 2015; Han et al., 2016; Zhang et al., 2020) or terminal enzymes (Xu et al., 2007). As already stated in the Introduction, Lonicera japonica is one of the herbal medicines which were successfully used for the therapy of the SARS-CoV infected patients in the 2002/2003 SARS epidemic (Liu et al., 2006; 2012a, 2012b; Wang et al., 2014; Luo et al., 2020).

Regarding the scope of the present review Lonicera japonica (and Lonicera caerulea) did not lead to any toxicologically relevant changes in rats or mice tested up to high doses (Thanabhorn et al., 2006; Lu et al., 2014; Kim et al., 2015; Jeong et al., 2019). No cytotoxicity of polyphenols extracted from Lonicera japonica was observed at doses required for suppressing mediators of neurodegeneration released from lipopolysaccharide-treated microglia (interleukin-1), tumor necrosis factor α, prostataglandin E2) (Han et al., 2016). Lonicera japonica has proven excellent binding properties for SARS-CoV-2 critical target molecules (spike protein, nucleocapsid protein, and 2′-O-ribosyl methytransferase) in virtual docking experiments using supervised machine learning (Kadioglu et al., 2020). Luteolin (the main flavonoid in Lonicera) binds with high affinity to the main protease of SARS-CoV-2. Interaction of luteolin with the main viral protease indicates its potential as antiviral molecule and is worthy of further investigations (Yu et al., 2020).

From the toxicological point of view these findings taken together allow to rank Lonicera japonica for specific investigations on its potential to cure and/or prevent COVID-19 at high priority.

**Morus alba (Folium Mori)**

*Morus alba* has been used since a long time as fodder for animals and as food for humans providing much experience with its use. Antimicrobial, antioxidant, anti-diabetic, anti-hyperlipidemic, anti-atherosclerotic, anti-obesity, cardioprotective, and cognitive enhancement activities of Folium Mori have been reported (Chen et al., 2016). Furthermore, efficacy against airway inflammation (by interruption of NF-κB and JNK/J-c-Jun signaling) by the *Morus* constituent Moracin M (Lee et al., 2016) and inhibition of metalloproteinases were seen (Yiemwattana et al., 2019; Wongwat et al., 2020). Specifically activity against human corona virus of Folium Mori has been observed (Thabti et al., 2020). As already stated in the Introduction section, *Morus alba* is one of the herbal medicines which were successfully used for the therapy of the SARS-CoV infected patients in the 2002/2003 SARS epidemic (Liu et al., 2006; 2012a, 2012b; Wang et al., 2014; Luo et al., 2020).

With respect to safety, the overwhelming majority of publications showed neither toxicity nor genotoxicity for *Morus alba* leaf, fruit or root extracts investigated in vitro as well as in rats and mice in vivo (Chi-chioco-Hernandez et al., 2011; De Oliveira et al., 2015; 2016; Chang et al., 2016; Marx et al., 2016; Wu et al., 2018; Yimam et al., 2018). One investigation showed several forms of damage, if mice were treated with an ethanol extract of *Morus alba* by the less physiological intraperitoneal route, but not after oral treatment (De Oliveira et al., 2015). A clinical study, comparing 25 patients topically treated with 75% mulberry extract oil with 25 placebo-treated individuals (Alvin et al., 2011) and another study on 45 participants with osteopenia perorally exposed to *Morus alba* and Polygonum odoratum leaves containing congee (rice mash) (Wattanathorn et al., 2018) observed clinical improvement, but no adverse effects.

From the toxicological point of view these findings allow to rank *Morus alba* for specific investigations on its potential to prevent and/or cure COVID-19 at high priority.

**Forsythia suspensa (Fructus Forsythiae)**

The aqueous extract of the fruit of *Forsythia* is widely used in traditional medicines against many frequently occurring disorders including inflammation, pain, fever, nausea, vomiting and asbes, leading to a rich treasure of information on its use (Wang et al., 2018). Forsythoside A (Law et al., 2017; Zheng et al., 2019) and labdane diterpenoids (Xiang et al., 2020; Zhao et al., 2020) isolated from the fruits of *Forsythia suspensa* showed antiviral activities and, as already stated in the Introduction, *Forsythia* is one of the herbal medicines, which were successfully used for the therapy of the SARS-CoV infected patients in the 2002/2003 SARS epidemic (Liu et al., 2006; 2012a, 2012b; Wang et al., 2014; Luo et al., 2020).

Studies in rats and mice on *Forsythia* and its major bioactive constituent forsythin did not show toxicities (Shin et al., 2020; Han et al., 2017). Several in vivo and in vitro tests showed no genotoxicity (Shin et al., 2020).

Phylloryrin and forsythoside, important constituents of *Forsythia suspensa*, showed in rats (in vitro and in vivo) significant effects on CYP (cytochrome P450 monooxygenase) 1A2, CYP2C11, CYP2D1 and CYP3A1/2 (Cheng et al., 2017). Their human homologues are important for the metabolism of many clinically used drugs (Oesch-Bartlomowicz and Oesch, 2007). Prior to the introduction of *Forsythia* or its constituents into clinical use, it should be clarified whether CYP interactions are relevant in vivo in human beings at the required doses. Except for this caveat, from the toxicological point of view the findings taken together allow to rank *Forsythia suspensa* for specific investigations on usefulness against COVID-19 at high priority.

**Codonopsis spec. (Radix Codonopsis)**

Codonopsis has widely been used in traditional medicine for hematopoeisis improvement, regulation of gastrointestinal, endocrine and immune function (He et al., 2015; Gao et al., 2018). *Codonopsis lanceolata* extract dampens allergic lung inflammation by inhibiting Th2 cell activation and augmenting mitochondrial superoxide dismutase (SOD2) expression (Seo et al., 2019). Lancemamide A from *Codonopsis lanceolata* prevents hypertension by inhibiting NADPH oxidase 2-mediated MAPK signaling and improving NO bioavailability (Shin et al., 2019) and attenuates the inflammatory responses mediated by monocytes and macrophages by blocking the activation of inhibitor of κB kinase (IKK) and p65/NF-κB (Kim et al., 2014). Phosphorylated *Codonopsis pilulosa* polysaccharide has been reported to inhibit duck hepatitis A virus replication (Ming et al., 2017). As already stated in the Introduction, *Codonopsis* is one of the herbal medicines which were successfully used for the therapy of the SARS-CoV infected patients in the 2002/2003 SARS epidemic (Liu et al., 2006; 2012a, 2012b; Wang et al., 2014; Luo et al., 2020). Moreover, *Codonopsis* has also been and still is used as food such as soup, wine and tea (He et al., 2015). Thus, there exists much experience with its use.

Codonopsis appears to have little toxicity (Gao et al., 2018). Studies in rats, rabbits and in patients on *Codonopsis* itself and on *Codonopsis*-containing medicinal mixtures did not reveal any marked toxicities (Ai et al., 2014; Lee et al., 2015). Isolated constituents such as the saponin codonopsiside showed practically no in vitro cytotoxicity (MTT assay) (Lee et al., 2002). Thus, investigations on the potential usefulness of *Codonopsis* for therapy or prevention of COVID-19 is recommended with high priority. Lau et al. (2013) reported that *Codonopsis tangshen* herb extract inhibited CYP3A4 in vitro. This CYP is responsible for the metabolism of a vast array of clinically used drugs (Oesch-Bartlomowicz et al., 2001; Oesch-Bartlomowicz and Oesch, 2007). This potentially important interaction should, therefore, be tested in vivo prior to a potential clinical use of *Codonopsis* in the fight against COVID-19. Except
for this caveat, from the toxicological point of view the findings taken together allow to rank Codonopsis for specific investigations on its potential to cure and/or prevent COVID-19 at high priority.

**Glycyrrhiza spec. / Radix et Rhizoma Glycyrrhizae**

**Glycyrrhiza gancao (in Chinese) (Radix et Rhizoma Glycyrrhizae)** is among the most frequently used TMC drugs and among the most frequently used medicinal plants, well studied (Ohkuga and Donaldson, 2000; Fiore et al., 2003; Wang et al., 2013; National Library of Medicine, 2018; Pastorino et al., 2018; Luis et al., 2018; Li et al., 2019; Kwon et al., 2020; Wang et al., 2020), including research on antiviral activity (Utsumoimya et al., 1997; Pilcher, 2003; Fiore et al., 2008; Sun et al., 2019; Luo et al., 2020). Favorable effects include several actions which may offer relieve of COVID-19 symptoms such as downregulation of proinflammatory cytokines, reducing the accumulation of intracellular reactive oxygen species and reducing the hyperproduction of airway exudates (Luo et al., 2020) as well as, most notably, binding to ACE2 (Kühn et al., 2004). The glucoside (Glycyrrhizic acid and Rhizoma) constituent Glyasperin F strongly binds to the ACE2 site 1 (grid4) and its constituent isoorhamnetin binds strongly to the ACE2 site 2 (grid4) (Ren et al., 2020). Moreover, antiviral activity, elucidated mechanisms of which include sialylation of the hepatitis B virus surface antigen and inhibition of the fusion of HIV-1 membrane with cell membranes due to reduction of membrane fluidity have been reported (Fiore et al., 2008).

The major licorice constituent glycyrrhizin interferes with HSN1 virus replication and HSN1-induced pro-inflammatory gene expression (Fiore et al., 2008; Nishimoto et al., 2010; Michaelis et al., 2011). Most worthy of note, glycyrrhizin had antiviral activity against the SARS coronavirus of the 2002/2003 epidemic, which was more effective in patients compared with several antiviral drugs (Cinatl et al., 2003). Moreover, licorice is widely used as sweetener and spice (Nazari et al., 2017) as well as thirst quencher (Omar et al., 2012). Therefore, rich experience is documented on its use.

Chronic intake of high doses of “seemingly harmless” licorice in human subjects led to massive disturbance of the renin-angiotensin-aldosterone axis as apparent mineralocorticoid excess syndrome with increased Na\(^+\) and water retention and K\(^-\) loss, alkalosis, hypertension and edema (Narazi et al., 2017). Also, licorice’s modest estrogenic activity (Kundu et al., 2018) and antithrombotic action (Francischetti et al., 1997; Mendes-silva et al., 2003) may lead to undesirable effects. However, in the latter case licorice as thrombin inhibitor (Francischetti et al., 1997; Mendes-silva et al., 2003) may have a beneficial influence on increased coagulation in COVID-19 patients (Tang et al., 2020).

A considerable number of toxicity studies in animals gave non-uniform results tending to tolerable toxicities at moderate doses (Mirsalis et al., 1993; Nakagawa et al., 2008; Shin et al., 2008). The results of genotoxicity tests were in its majority negative (Ibsbrucker and Burdock, 2006; Nakagawa et al., 2008; Chandrasekaran et al., 2011). These results of toxicological investigations together with the wide and long-lasting experience with human use of licorice, apparently safe at moderate, non-chronic doses favor the recommendation of investigations on its usefulness for therapy or prevention of COVID-19 with relatively high priority. However, prior to its clinical use the occurrence of serious drug-drug interactions at the required doses should be excluded, a potential which appears realistic based on previous studies (Oesch-Barlomowicz et al., 2003; Park et al., 2011; Li et al., 2019; Wang et al., 2020). Thus, except of this caveat, from the toxicological point of view the findings taken together recommend to rank Glycyrrhiza spec./Radix et Rhizoma Glycyrrhizae for specific investigations on its potential to cure and/or prevent COVID-19 at relatively high priority, followed by clinical application which should be carefully supervised on grounds on the somewhat unclear picture from the toxicological investigations.

**Panax ginseng (Radix Panaci)**

Radix Panaci is a medicinal herb known in Eastern traditional medicine since ancient times and up to now for its reported anti-inflammatory, anti-aging, anti-cancer and adaptogenic activities (Gillis, 1997; Coon and Ernst, 2002; Murthy et al., 2018). The popularity of Panax ginseng in Western countries has been increasing for several reasons, including wide-spread attempts to restore or enhance vitality and wellness. All of this led to much experience with its use. Activities against a broad range of viruses were reported (Wang et al., 2018). Panax ginseng is one of the herbal medicines which were successfully used for the therapy of the SARS-CoV infected patients in the 2002/2003 SARS epidemic (Liu et al., 2006; 2012a, 2012b; Wang et al., 2014; Luo et al., 2020).

Several studies on potential toxic effects of Panax ginseng in rats and mice did not show any serious general toxicity (Park et al., 2008; 2013; 2018; National Toxicology Program, 2011, Shin et al., 2014) and studies on potential genotoxities were negative (National Toxicology Program, 2011; Shin et al., 2014). Clinical studies did not reveal serious treatment-related adverse effects (Lee et al., 2012; Sergusis et al., 2013; Kim et al., 2015; 2017). Use during pregnancy did not lead to adverse effects (Seely et al., 2008). No human data appear to exist concerning use during lactation, while minimal risks were seen in animal studies (Seely et al., 2018). Special care needs to be taken against excessive doses (leading to problems including hypertension and spontaneous bleeding) as well as interactions with other drugs such as anticoagulants (Paik and Lee, 2015).

Use of Panax ginseng in mixtures with further components did not show any toxic effects in many cases. In few cases, where toxicities were observed, it was unclear which component(s) were responsible (Park et al., 2008; Sco et al., 2019).

If individual components or metabolites of Panax ginseng were tested, some studies showed no toxicities (Shin et al., 2014; Li et al., 2020) while others did (Li et al., 2020), especially embryotoxieties (Chan et al., 2004; Liu et al., 2005; Huang et al., 2019). It is recommended to abstain from the respective preparations and even from Panax ginseng itself during the first trimester of pregnancy, until the safety is sufficiently established.

Investigations on the potential usefulness of Panax ginseng in moderate, non-chronic doses for therapy/prevention of COVID-19 is, therefore, recommended (except during the first trimester of pregnancy). Apart from this caveat, from the toxicological point of view the findings taken together allow to rank Panax ginseng for specific investigations on its potential to cure and/or prevent COVID-19 at relatively high priority, followed by clinical application which should be carefully supervised on grounds on the somewhat unclear picture from the toxicological investigations.

**Ephedra sinica (Herba Ephedrae)**

Herba Ephedrae (Lee, 2011) is used as commercial dietary supplement (Haller et al., 2004; Mehendale et al., 2004), especially for weight loss (Boozer et al., 2002). As already stated in the Introduction, Ephedra sinica is one of the herbal medicines from Traditional Chinese Medicine which were successfully used for the therapy of the SARS-CoV infected patients in the 2002/2003 SARS epidemic (Liu et al., 2006; 2012a, 2012b; Wang et al., 2014; Luo et al., 2020). The severity of toxic reactions to ephedra in comparisons to other botanical products has been described (Woolf et al., 2005). In animal experiments Herba Ephedrae damaged rat kidneys and salivary glands already at only moderately high doses (Han et al., 2018). Humans consuming dietary supplements containing Ephedra alkaloids experienced adverse cardiovascular and central nervous system events (Haller and Benowitz, 2000). Use of Herba Ephedrae was associated with liver damage at low incidence (Woo et al., 2015). More frequently the use of Herba Ephedrae led to myocardial infarction, stroke and sudden death. These cardiovascular
adverse effects did not depend on preexisting vascular or heart disease and did not only occur at massive doses, rather they were reported to have occurred within the manufacturer’s dosing guidelines (Samenuk et al., 2002). This practically excludes Herba Ephedrae from being recommended for its usefulness against COVID-19. However, the anti-viral activity of Herba Ephedrae (Mantani et al., 1999; Wei et al., 2019) may be separable from the adverse effects. Hyuga et al. developed and investigated an ephedrine-free Herba Ephedrae extract, which still exerted anti-influenza virus activity in a comparable manner as the full Herba Ephedrae extract, but without ephedrine-like adverse effects (the ephedrine alkaloids in all likelihood being responsible for myocardial infarction, stroke and sudden death in Herba Ephedrae-treated patients) (Hyuga et al., 2016). From the toxicological point of view this processed, ephedrine-free Herba Ephedrae extract is interesting and is recommended for specific investigations on its usefulness to cure and/or prevent COVID-19 at medium to high priority, followed by clinical application which should be carefully supervised on grounds on the somewhat unclear picture from the toxicological investigations.

Overall conclusions
Several Far East traditional medicines, known for their wide range of pharmacological applications and at present also increasingly used in Western countries with the intention to promote health and improve wellness, had been reported as effective for SARS treatment during the 2002/2003 epidemic. Some of them have been characterized concerning their side effects and/or potential toxicities as discussed above. The available toxicological information allows to rank them as recommendable for immediate investigations on potential usefulness for treatment or prevention of COVID-19, followed by immediate implementation, at various priorities:

- **High priority:** Lonicera japonica, Morus alba, Forsythia suspensa, Codonopsis spec.
- **Relatively high priority:** Glycyrrhiza spec., Panax ginseng
- **Medium to high priority:** Ephedrine-free Herba Ephedrae extract

Further possibilities not discussed in this publication are, on toxicological grounds, recommended at the following lower priorities, based on the review of the available literature by the authors of this publication:

- **Intermediate priority:** Astragalus membranaceus root, Eriobotrya japonica leaves, Galla chinensis, Scutellaria baicalensis root, Panax notoginseng root
- **Relatively low priority:** Chrysanthemum morifolium, Pinellia rhizome, Lithospermum erythrorhizon root
- **Low priority:** Prunus armeniaca seeds, Bupleurum chinense root
- **Low priority at best:** Angelica sinensis root, Toona sinensis, Gardenia jasminoides fruits, Puercaria lobata root

We all hope for a medicinal cup to treat COVID-19 in the very near future. Possibilities include the development of vaccines as well as novel or repurposed synthetic drugs. Although hyped in public discussions, it is realistic to predict a substantial time until they will be a ready-to-use cup of remedy. However, between the cup and mouth is still time to die. We therefore strongly recommend rapid investigation of readily available herbal drugs, which were effective in the therapy of SARS, on their efficacy for the treatment of COVID-19 followed by immediate application in the treatment of COVID-19. As tool for prioritization of the needed research we recommend to use the priorities according to their relative toxicities versus safety as described in this review.

The current emergency threatens the global public health with the tough reality, where no realistic chance should be overlooked or ignored on grounds of emotional prejudices.

Author contribution statement
FO, BOB and TE have equally contributed to the concept of this review. Contributions to writing were in the sequence FO, BO, TE. Critical review of the medical, toxicological and phytochemical aspects was by BO, FO and TE, respectively. All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Competing Interest
FO and BOB are members of Oesch-Tox Toxicological Consulting and Expert Opinions GmbH & Co. KG, Ingelheim-Wackernheim, Germany. All three authors declare that the study was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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