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The Potentials of Medicinal Plants in the Treatment of Covid-19 Patients: A Review

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Review Article

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Abstract

COVID-19 pandemic (corona virus disease 2019 is a life threatening SARS-Cov-19 severe acute respiratory syndrome virus 2) situation that was declared a public health emergency by WHO in early 2020. Today's primary emphasis is on the treatment of COVID-19 yet the specific mode of action of antiviral agents being employed must be identified. At present, the human on risk are being vaccinated but there is no clear anti-COVID 19 medicine. This study focuses on herbal approaches as a potential alternative therapy for COVID-19, based on medicinal plants. Some herbs are well-known in different traditional medicines for prevention, cure and recovery of the diseases like COVID-19. Mostly the plant's herbal extract inhibits viral replication; however several studies have shown that conventional herbal extracts may interact with important viral proteins associated with the virulence. The update on traditional medicines suggested for the prevention of COVID-19 has been analyzed here.

Keywords: Covid-19; Medical Plants; Health Authorities

Introduction

Coronaviruses are crown like in shape with a regular size of sixty nm to 140 nm in diameter under the electron microscope and these are enveloped single-stranded RNA positive senses viruses [1]. The novel corona virus (nCoV-2019) [2], or SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2) was firstly reported from Wuhan of Hubei Province of China before its detection in the world (Halaji, Farahani *et al*. 2020) [3]. The 1st patient with covid-19 was detected in December 2019, after those 5 more cases with acute respiratory signs were hospitalized and one of them died [4]. The World Health Organization on 30 January 2020 [2], announced a public health emergency of international concern due to COVID-19 [5]. On 11 March 2020 World Health Organization declared covid-19 as a pandemic. From 20 April 2020 world widely, there have been 2,314,621 confirmed patients as well as 157, 847 confirmed deaths [6]. About five million people were infected with corona virus-19 as well as 0.3 million, have died before May 21st 2020 in the world [7].

Research is in progress to know further about severity, transmissibility, as well as new features related to COVID-19 [8]. It looks like that maximum of the early cases had communication history with the original seafood marketplace [9-11]. Human-to-human transmission through close contact was a secondary source of infection. The numbers of infected people were increased with no history of contact to wildlife and visiting Wuhan city and several medical professionals were also detected with covid-19 [10,12]. It became clear that the COVID-19 infection spread with exposure to the virus, the normal population and immune suppressed individuals seems to be at risk. Different studies have described the age distribution of mature patient aged between 25 and 89 years old. Most of them were between 35 to 55 years old. Few cases were also identified in infants and [13,14]. According to the most recent recommendations from Chinese health authorities,2-14 days is the incubation period for covid-19 patients [9].

Fever, cough and difficulty in breathing are the salient features of coronavirus-19 [15], as well as other symptoms may consist of recurrent trembling along with chills, pain in the head, throat pain, myalgia, anosmia and ageusia [16]. Moreover, dyspnea, insistent chest pressure, difficulty in arousing as well as cyanosed face and lips are emergency cautionary signs of COVID-19 [17]. Patients with minor symptoms found to be recovered within 7 days, on the other hand, severe symptoms have been described the involvement of progressive respiratory failure because of alveolar damage from the virus, that can lead to death. The mortality rate due to COVID-19 is higher in middle-aged as well as elderly individuals with previously affected with diseases for example; coronary heart disease, cirrhosis, tumor surgery, diabetes, hypertension plus Parkinson's disease [18].

Overview of Sar-Cov-19

As of February 3rd, 2021, the World Health Organization (WHO) has reported that 103,362,039 and 2,244,713 death cases have been confirmed worldwide, and it has spread to 223 countries and the second phase of pandemic is been experience [19] With this emerging battle against this deadly virus, the WHO strategized to interrupt human-human contact, isolate patients at early stages, identify and reduce transmission from the animal source, address crucial mysteries about the virus and accelerate research, communicate information correctly to the public and minimize the social and economic impact. Gorbalenya, et al. [20] reported that SAR-CoV-2 shares sequence homology with SAR-CoV and bat coronavirus. This was done after the genomics of the new virus was in other of succession and it was found to have 79.5% genetic sequences similarity with SARS-CoV and that made the international committee on taxonomy of viruses to name it SARS-CoV-2 [21] Moreover the act of transmitting and diagnostic methods are different from the other, the difference appears in their nucleotide, protein and receptor-binding domain (RBD) [22-24]. With the rate of spread of the new coronavirus and its effect on human health, the world researchers have responded quickly to the new virus and research is going on throughout the world.

As the infection spreads so fast, and the mortality rate increasing by the day, it seems difficult and time consuming to synthesize, tests for safety and toxicity of a new drugs within such limited time. However, these restrictions in time have led to repurposing of already known antiviral drugs to slow the rapid mortality effect of the virus. None has been very effective yet, and the search for vaccine and antiviral drugs is still ongoing. Moreover there have been some reports suggesting that some herbs contain some natural products compounds which possess possible antiviral activity against SAR-CoV-2 [25,26]. The use of these natural medicines and existing drugs can be a viable and quick solution to this pandemic. The study and application of Natural products and local medicine has been practiced for thousands of years and it is cheap and easily available.

This review will illuminate the origin, overview, structure, mechanism of spread and replication of SARS-COV-2, the symptoms, mode of transmission, mitigation and various treatment methods of the virus This study aimed at identifying herbal inhibitors of SARS-CoV-2, already existing drug which can also inhibit the virus thereby locating a potential drug lead against the infections and also dietary supplements from selected plants which can be exploited by the locals to improve the immunity of the general population. Coronaviruses have been reported to have total of 39 species under the broad realm of *Riboviria* belonging to the family of *Corona viridae*, suborder *Cornidovirineae* and order *Nidovirales* [20]. It has been reported that all the SARS-CoV fall under the species severe acute respiratory syndrome-related corona virus and genus Beta-corona virus. Almost all of the species are under this head enzootic and only a few of these species infect human [27]. Recently, seven human CoVs (HCoV) have been reported and confirmed. They are named as Human coronavirus NL63 (HCoV-NL63) and Human coronavirus 229E (HCoV-229E, which belong to the alpha-coronavius) genus; However Human coronavirus OC43 (HCoV-OC43), Human coronavirus (HCoV-HKU1), SARS-CoV, SARSCoV-2 and Middle East respiratory syndrome coronavirus (MER-CoV), belong to the beta-coronavirus genus. HCoV-229E, HCoV-NL63, HCoVHKU1 and HCoV-OC43 strains of coronavirus have been reported to cause mild respiratory diseases in humans. The SARS-CoV-2 is a zoonotic virus that belongs to the *Coronaviridae* family that can infect human and several animal species [28]. The SARS-CoV-2 has been reported to belong to the subgenus

Sarbecovirus and mostly resembles a bat corona virus, with which it shares 96.2% sequence homology [29]. Recently, it have been reported that SARS-CoV-2 has been introduced to human by an unidentified intermediary animal and then it has spread from human-to-human.

It have been reported that the human coronaviruses are predominantly concomitant with upper respiratory tract illnesses ranging from mild to moderate including common cold. Most of the people may be infected with one or more of these viruses at some point in their lifetime (Killerby *et al* 2020). It have also been reported that the SARS-CoV and MERS-CoV are the two major causes of severe pneumonia in human [30].

a. **Role of Medicinal Plants in Different Diseases**

The history reveals that it's very nearly 400–500 B.C old to utilize plants in different ailments. In the deprived areas, the supreme and simple way of treatment is always the traditional medication offered by the primary health care system [31]. The developing countries like India, China and Pakistan rely on the traditional medicine system for the healing of various forms of diseases for alternative health care facilities only because of their safe use and efficacy for hundreds of years [32]. All around the world, as a medical mediator for the treatment of several communicable diseases, numerous species of herbal plants are commonly used. Collectively, we can assume that approximately 1/4 of existing approved medications have been derived from sources of botanicals [33].

Potential activities in the management of virus infections include natural ingredients and their derivatives [34,35]. At present, possible antiviral potential has been demonstrated by some herbal extracts and their derivatives. However, sufficient researches on the production of agents from herbal extracts that can combat with COVID-19 are not available [2]. To prevent and combat COVID-19, certain herbal extracts are essential. Chinese Medicine has typically indicated great scientific knowledge, effective and applicable inhibition and treatment of respiratory disorders in herbal formulations. The protocol has been proposed by Chinese herbal medicine with western medicine that prevents viral complications. The 1stpatient with clinical features of covid-19 pneumonia was recovered from the hospital on 24 January 2020 after management with traditional Chinese herbal medicine [36].

The production of new antiviral drugs plus vaccines for treating covid-19 individuals will take months or years to complete. Thus, COVID-19 therapy focuses largely on repurposed medications, including hydroxyl chloroquine, chloroquine, ribavirin, remdesivir, lopinavir/ritonavir umifenovir, favipiravir, interferon-alpha, interferon-beta, etc. There is no clear, reliable and proven traditional medication available as of this time for the treatment of individuals infected with coronavirus-19 till 02.04.2020 [37].

The avoidance of infectious diseases in conventional medicine is focused on the use of botanical detoxifiers, immune stimulating medicines, natural enzymes, hematinic plants and spices. Centered on the fact that COVID-19 is a viral infection, in its prevention and treatment, the use of antiviral medicinal plants may be useful. Given the symptoms of COVID-19 infection, fever, cough, pain in the body, flu, cold and shortness of breath, anti-malarial plants, cough remedies, herbal analgesics and medicinal plants with reasonable therapeutic potentials on infections of the respiratory tract may be useful to prevent COVID-19 infection [38]. So, herbal medicinal plants and their derivatives can be used for the prevention of covid-19. In this review, we can summarize some medicinal plants which can be used against different viruses as well as against covid-19 due to their active constituents against different viruses.

b. **Plants That can be used in Covid-19**

As we know that, botanical detoxifiers, immune boosting remedies, natural antioxidants, plant haematinics and different spices can be used for the prevention of covid-19 [38]. So, we can describe here some medicinal plants having antioxidants, blood purifier, immune boosters and haematinic potentials.

c. **Black Cumin Seeds (*Nigella Sativa*)**

Nigella sativa belongs to the Ranunculaceae family. It is well known as kalonji and black seeds [39]. For decades, black seeds have been used in herbal medicine to cure various disorders such as bronchial asthma, catarrh, head pain, respiratory inflammation, joint pain, etc. [40]. In recent times, black seeds have been used to cure different diseases such as hypertension, obesity, cancer, diabetes, gastrointestinal problems and cardiovascular diseases [41]. Unani, Ayurveda, Chinese medicine as well as other medicinal systems have been validated the medicinal properties of black cumin seeds [42].

A depressed antioxidant system as well as excessive production of reactive oxygen species is responsible for the pathological process of severe acute respiratory syndrome coronavirus-2 [43]. Due to the activation of immunocytes like neutrophils as well as macrophages, coronavirus disease-19 will cause excessive production of various ROS (reactive oxygen species) for example (OH), (O2 −), H2O2. Because of over production of reactive oxygen species that oxidizes membrane lipids plus cellular proteins as well as kills healthy lungs cells and may also cause several organ failures. So, for the protection of organs possible antioxidants like ascorbic acid as well as tocopherol may be suggested [44]. In previous studies, black seeds have revealed certain possible

antioxidant potentials, its antioxidant potential can help mitigate organ oxidative damage.

An experimental study with fifty fatty women (n=50) showed that *Nigella sativa* oil has ominously enhanced the amounts of SOD (superoxide dismutase), an essential antioxidant enzyme that works against oxidative stress in the body [45]. In vivo and in vitro tests have also been reported on Sativa for its successful antioxidant activities. It has been shown that black seeds oil induces pronounced antioxidant activity in human pre-adipocytes [46] and that human retinal pigment epithelial cells are pre-treated using thymoquinone *Nigella sativa* by triggering nuclear factor erythroid 2-related factor 2 or Heme oxygenase-1 (HO-1) pathway [47]. Variable antioxidant activity was demonstrated by bioactive components of N. sativa such as carvacrol, thymoquinone, 4-terpineol as well as t-anethole [48].

In hospitalized COVID-19 patients, over activation of the immune system can be observed plus it is identified as a cytokine storm that may cause several organ failures. It has also been proposed, the early and aggressive immunomodulatory treatment [49], may avoid the compulsion of ventilators as well as ECMO (extracorporeal membrane oxygenation). Other active components of Nigella sativa plus its oil have demonstrated positive immunomodulatory impact by stimulating immunity linked to natural killer cells plus T lymphocytes [50].

Major Coagulopathy as a result of serious coronavirus disease-19 infection [51], and prophylactic doses of LMWH (low molecular weight heparin) in patients with coronavirus disease-19 as well as therapeutic doses of low molecular weight heparin in patients with slightly greater dimer concentrations are advised to avoid venous thromboembolism [52]. In an experimental trial of ninety -four individuals (n=94) with diabetes mellitus (type 2) who obtained capsules having five hundred mg of beached black seed at varying dosages of 1gram, 2gram plus 3gram of Nigella sativa regular for 3 months, randomly divided into three categories. Managed patients with 2000 mg per day of black seeds, at the end of the study, seeds displayed a considerable improvement in PTT (partial thromboplastin time) and a large decrease in heart rate, mean arterial pressure and blood pressure. Administration of black seeds improved partial thromboplastin time, however not PT (Prothrombin Time), suggesting are a tradition of the coagulation mechanism's intrinsic pathway [53].

Nigella sativa has been reported by multiple randomized clinical studies, case reports, preliminary tests during in-vivo and in-vitro studies to possess activities like antioxidant, antiviral, anti-inflammatory, immunomodulatory activity. Moreover, this plant may cause bronchodilation, soothing the covid-19 symptoms with its antitussive potential. Furthermore, black seeds have also revealed blood pressure lowering potential, anti-obesity, glucose lowering effect, lipid lowering effect, anti-ulcer, as well as antineoplastic behaviors to support patients with comorbid disorders with COVID-19. Besides, the energetic components of *Nigella sativa*, like alpha-hederin and nihilledine, have been recognized as possible severe acute respiratory syndrome corona virus-2 inhibitors. For the treatment of patients with coronavirus disease-19, *Nigella sativa* may be used as a complementary medication accompanied by repurposed traditional medications. By helping to lower their doses, adjuvant therapy with *Nigella sativa* can reduce the adverse effects of conventional medicines. On the other hand, further randomized controlled studies are required to validate the possible valuable properties of *Nigella sativa* as an effective herbal medicine for the care of patients with covid-19 [54].

d. **Curcuma Longa**

Curcuma longa is a member of the *Zingiberaceae* family. It is also well-known as Turmeric. Turmeric is extensively used for its taste and colour in foods and having a long history of usage in the Chines and Ayurvedic medicine systems. In biliary conditions, anorexia, cough, diabetic cuts, liver disorders, rheumatism and sinusitis *Curcuma longa* is traditionally used. In pharmacological terminology, antioxidant, anti-inflammatory, antimutagenic, anticarcinogenic, anticoagulant, anti-fertility, anti-diabetes, antibacterial and antifungal activities have been reported [55].

Curcuma longa contains the major phytoconstituents dimethoxy curcumin, curcumin, diacetyl curcumin [56], which are the most prescribed compounds present in medicinal plants that can serve as potential COVID-19 Main Protein (Mpro) inhibitors [57]. In contrast to antimalarial medications, curcumin is closely associated with 3CL-protease of covid-19 and induces major structural improvements in this viral protease, causing enzyme folding [57].

Diacetyl curcumin present in Curcuma longa is more powerful than Nelfinavir (Adem, Eyupoglu *et al.* 2020), on COVID-19 (Mpro). It can be inferred from recent Docking experiments that Curcumin's binding energy (-38.84 kcal/mol) was greater than hydroxychloroquine (HCQ) (-35.87 kcal/mol in the case of S1 receptor binding domain. Curcumin, along with hydroxychloroquine, may also be used as a combination treatment to inhibit the stability of SARS-CoV2 receptor proteins [59].

e. **Allium Sativum**

Garlic is a yearly bulbous herb local to central and south Asia. *Alliaceae* is the family of Garlic [60]. Garlic is used in

Asia and Europe to cure chronic colds, fever, coughs, asthma, and wounds [60]. Because of ear infections, garlic oil has also been used to alleviate pain [61]. In several in-vivo and in-vitro tests, garlic has been reported to possess immunomodulating properties. The key constituents of garlic are responsible for these effects tend to be organ sulfur compounds [62]. Other components have also demonstrated immune modulating ability, like lectins as well as water-soluble fructans [63].

The coronavirus that has recently appeared primarily act on lymphocytes. The severe acute respiratory syndrome corona virus-2 infection mainly disturbs T lymphocytes, especially CD8 + T as well as CD4 + T-Cells, leading to a reduction in the development of IFN-γ. In almost all patients, the absolute number of T lymphocytes, CD4+T and CD8+T cells reduced and were markedly smaller in extreme cases than in mild cases. There are lower levels of regulatory T-cells (Treg) cells in patients with covid-19 and more obviously, harm in extreme cases. In COVID-19 patients, natural killer cells decreased and extreme cases had a lower percentage than moderate cases. Due to their association with the seriousness of the disease in COVID-19 [64,65], these immunological markers could be of significance. On the other hand, after short-term garlic extract supplementation, substantial changes inCD4 +TplusCD8 + T cells were noticed. This result revealed that the use of supplementation of garlic extract promoted the karate athletes' cellular immune system [66].

Garlic has properties that are anti-inflammatory, antimutagenic and antitumour. In laboratory trials, injection in the tumour of a protein fraction purified from fresh garlic bulbs greatly improved CD8+T peripheral blood lymphocytes, increased CD8+T tumour site infiltration, reduced tumour size plus suppressed tumour development [67, 68]. Garlic appears to improve the activities of the immune system. Via pathways include cytokine secretion regulation, immunoglobulin formation, activation of macrophage as well as phagocytosis; It activates lymphocytes, macrophages, natural killer cells, dendritic cells and eosinophils [69]. In garlic-treated rats, CD4+T cells plus overall WBC counts were substantially improved. This showed the potential of garlic to improve the immune system [70].

For patients with covid-19, immune compromised clinical status is life-threatening, so the protective properties of Garlic on the immunity are very significant.

This food can help to inverse certain clinical features present in patients with covid-19, to restore reduced or lost gustatory sensation, to enhance the number of Treg cells, to enhance the cytotoxic and helper T cells, to enhance leptin as well as PPAR-γ receptor levels, to enhance appetite, to protect inhibition of CD4+CD25+FoxP3+to stimulate NK cells, to suppress TNF-α and C reactive protein (Donma and Donma 2020).

f. **Withania Somnifera**

For more than 3000 years, *Withania somnifera* also known as Indian ginseng, ashwagandha, and winter cherry, has been an important herb in the Ayurvedic and indigenous medicinal systems. It belongs to the family Solanaceae [71].

Withania somnifera comprises a host of phytoconstituents such as Withanolide A & B, Withaferin A, Withanone, Withanosides [72]. Withania somnifera root tubers showed antimicrobial activity (protease inhibitor) against a few bacterial and phytopathogenic viruses [73].

Withania somnifera, through regulation of host Th-1/ Th-2 immunity, will be an important agent in controlling COVID-19. WS can be helpful for the activation of anti-viral immunity (due to enhanced IFN-gamma responses) and optimal anti-inflammatory activities (down-regulation of IL-1, IL-6, TNF-alpha and other inflammatory mediators), which are main targets for COVID-19 [74].

According to recent Molecular Docking Research, Withanolide D, Withaferin A, is the most effective 3C-like key protease (3CLpro) inhibitor that can be further investigated in pre-clinical and clinical settings for testing against Coronavirus (COVID-19) [75]. Binding energy lower than the pharmacological inhibitor, N3, has been predicted by Withanolide-B, Withanone and Withaferin-A, main phytochemicals of Withania somnifera. The binding of these primary protease phytochemicals can delay the cleavage of PPs to release NSPs and decrease the viral replication and transcription process [76].

g. **Aloe Vera**

Aloe vera belongs to the Liliaceae family. It is used in the treatment of alopecia, bacterial and fungal diseases of the scalp, untreated leg wounds, parasitic infections, systemic lupus erythematosus, inflammation and skin burn, diabetes mellitus type 2, human immunodeficiency virus, prevention of cancer, inflammation of the colon, curing of wounds (mucositis, pressure ulcers, acne vulgaris, radiation dermatitis, frostbite, aphthous stomatitis and constipation [77].

Aloe vera plant in the Democratic Republic of the Congo was treated as an origin of an extremely potential candidate for SARS-CoV-2 therapy. Many studies have shown that its extract and its bioactive constituents anthraquinones have excellent viricidal activities of a broad spectrum [78]. Zinc is also present in Aloe barbadensis that can prevent retrovirus replication, including SARSCov- 1 [79].

Mpiana and colleagues believe that the zinc-rich extract of Aloe vera and its secondary bioactive metabolites should be used in covid-19 treatment because of their capacity to reduce the appearance of pro inflammatory features that trigger acute respiratory distress as well as improve the immunity [80].

h. **Ocimum Sanctum**

Ocimum sanctum belongs to the Lamiaceae family. It is sometimes referred to as the basil of Tulsi and Holly. In the Ayurveda and Siddha systems, different parts of the herb are historically used for the treatment of various foods such as cancer, skin disease, hepatic condition, common cold and cough, malarial fever and as a remedy for snakebite and scorpion sting [81].

Due to its ability to inhibit replication of COVID-19 backed by its immune-modulatory function and ACE II blocking properties, Tulsi extract may be involved in protective measures against COVID-19. Tulsinol (A, B, C, D, E, F, G and dihydroeugenol-B containing Ocimum sanctum inhibit SARS Coronavirus main protease and papain -like protease [82].

In the treatment of nausea, diarrhea, cough and fever, which are typical symptoms of COVID-19 [83], Ocimum sanctum is used. Ocimum sanctum strengthens the body's immunity and helps to protect the virus and bacteria at risk [84].

i. **Emblica Officinalis**

Euphorbiaceae is the family of *Emblica officinalis*. Amla, Phyllanthus Emblicaor Indian gooseberry are other names used for Emblica officinalis. It is used to treat cancer, diabetes, liver failure, heart disease, ulcers, nausea, fever, cough, snake bites, ophthalmic diseases, etc. [85].

In the fight against SARS-CoV-2 infection, Phyllanthus emblica also has immunomodulatory properties and may have the ability to improve population wellbeing and immunity [74].

Phyllaemblicin-B and Phyllanthus Emblica phyllaemblinol displayed a high binding affinity to the protein helicase, which is one of the key COVID-19 targets. Phyllaemblicin G7 of Phyllanthus emblica has demonstrated a high binding affinity to the COVID-19 spike protein [86]. The secret to its medicinal effect is the antioxidative and anti-inflammatory properties of Phyllanthus emblica [87-94].

Conclusion

For the prevention or cure of different illnesses, herbal plants and natural products are also considered attractive options. Many physicians and practitioners have sought to propose appropriate medicines for the prevention of COVID-19 since its outbreak. A different evidence-based herbal medicine approach plays a prevention role in the COVID-19 pandemic outbreak. Varieties of phytochemicals are derived from medicinal plants. Various trials have been performed worldwide to produce antiviral drugs that are successful against SARS-CoV-2 responsible for coronavirus disease-19. Various secondary metabolites have been isolated from medicinal plants with antiviral effects. Finding the compounds responsible for changing any step in the cycle of virus replication may be the only way to avoid COVID-19 infection.it is important to investigate natural plants that can inhibit the development of structural proteins (spike glycoprotein), non-structural proteins (papain- like protease, helicase) and accessory proteins coded by the SARS-CoV-2 genome. Natural ingredients can usually be a safe and effective tool for identifying medicines responsible for managing the ongoing pandemic. For the treatment of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) compromised people, various substances such as flavonoids, alkaloids, polyphenols, terpenoids as well as proanthocyanidin already reported to have antiviral activities need to be screened. Patients rely on symptomatic treatment and compassionate care in the absence of proven COVID-19 drugs. Therefore, several natural products and herbal extracts can help to treat the symptoms associated with infection with SARS-CoV-19. Moreover the potency of herbal medicine needs to be identified in both in-vivo and in-vitro trials. The combination of allopathic and herbal medicines will lead to the best choices for treatment. Our analysis indicated that more research on conventional herbal medicine will be required to discover the latest constituents of anti-Covid-19 that are helpful for SARS-CoV-2 purging. This highlights how COVID-19 infection can be resolved by herbal related medicine.

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