Antiviral Potential of Medicinal Plants and Plant Lectins: Use in COVID-19 Pandemic Era

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Authors’ contributions

This work was carried out in collaboration between both authors. Author EB designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Author IAS managed the analyses of the study. Author EB and IAS managed the literature searches. Both authors read and approved the final manuscript

ABSTRACT

At the time of writing the research paper, the world is faced with an acute respiratory syndrome pandemic that is named as coronavirus 2 (SARS-CoV-2). This pandemic is also called Covid-19, is a respiratory disease based on the lungs caused by the new coronavirus the SARS-CoV-2. In the SARS-CoV-2 pandemic period, decreased food intromission, inflammation concerned catabolism, decreased mobility owing to extend hospital stay as well as older age and comorbidities hence patients can be under hazard of malnutrition. It is understood from the nutrition guidances suggest the nutritional methods and cure take into account as a complementary role of the way to these patients. In any acute, pandemic or chronic disease ideal nutritional care accommodate to life-support cure has probable to develop the results of patients influenced by this life-menacing disease, bearing better and shorter healing from the acute phase. For this reason, in pandemic of
Keywords: The SARS-CoV-2; COVID-19; extracellular matrix; lectins; Salvia officinalis and Malva sylvestris; nutritional care.

1. INTRODUCTION

1.1 Lectins

Lectins are commonly known as higher plants and are inclusive of seven families of structurally and evolutionarily related proteins [1]. One of the non-immune sources and natural proteins are the lectins that bind to and targets sugar-containing compounds and carbohydrates in a specific. Lectins can reversibly bind to precipitate glycoconjugates. This property makes possible lectins to react between a diversity of mammalian cells changing their intracellular metabolism and generating a few biological impacts, like activation of lymphocytes [2-4], platelets [5], basophils, and mast cells [6-9]. Lectins and sulfated glycosaminoglycan (SGAG)-binding proteins are glycans noticing proteins. Lectins include the protected carbohydrate-recognition domain (CRD).

Lectins could be specific bound to oligosaccharide structures on cell surfaces, the extracellular matrix, and excreted glycoproteins. They are contained in intra- and intercellular glycans routing handling oligosaccharides as postal-code analogous and acting as protection molecules coming in foreign or abnormal glycosignatures, as a crosslinking agent in bio-signaling and as coordinator of transient or firm cell-cell/cell-matrix touches (docking). By describing the driving powers toward complex creation, information anent the reasons for certainty can be converted to the design of custom-made high-affinity ligands for clinical practice, e.g. in anti-adhesion therapy, drug selecting or diagnostic histopathology [10]. Mannose-binding lectins and surfactant proteins are known as galectins and collections, respectively. They demonstrate the capability of endogenous glycans linking proteins to act as cytokines, chemokines or growth factors and so modulating native and suitable immune reactions under physiological or pathological states.

Lectins intervene between cell-cell and cell-pathogen interplay and they have the capability to link particular carbohydrate structures. For this some viruses utilization lectins to join themselves to the cells of the host organism along with infection. Cyanobacterial and algal lectins strongly impede the human immunodeficiency virus (HIV-1) input by doing strong affinity carbohydrate-mediated interactions with the HIV-1 envelope glycoprotein gp120. They get an important role for their distinctive biophysical features which is display new protein layers and extraordinarily high carbohydrate affinity. Human organism express and accommodate the wide diversity size and shapes of lectins which can be classified in families by peer structural properties. Amino acid residues of carbohydrate bind and shape of the binding area define lectins specificities. Sometimes metal ions can act a role in coordination. In the beginning of the infection viruses, bacteria's and protozoa's surface lectins work for sticking to host cells. If carbohydrate sticking is blocked, these infections will be prevented. So that anti-adhesive therapy against microbial and viral diseases.

Lectins are carbohydrate-binding proteins that deficiency enzymatic activity on their ligand. They are different from antibodies and free mono- and oligosaccharide sensor or transport proteins. The lectin binding to cellular glycans have vigorously conduce to shaping of the "sugar code" so over a dozen folds and a wide spectrum of binding site structure, ranging from shallow grooves to deep pockets, have developed sugar-binding capacity.

Phytohaemagglutinin (PHA, or phytohemagglutinin) is a generic name for plant lectins and it's found in plants, especially certain legumes. PHA actually occur from two closely related proteins, named leucoagglutinin (PHA-L) and PHA-E. These proteins cause to blood cells to cluster together. Phytohaemagglutinin has carbohydrate-binding specificity for a complex oligosaccharide containing galactose, N-acetylglicosamine, and mannose.

A long time ago in literature was reported that plant lectins inhibited HIV replication in
lymphocyte cell cultures via inhibition of virus-cell fusion.

The SARS-CoV spike protein is slowly glycosylated and includes 23 putative N-glycosylation sites, among which 12 have been defined to be influentially glycosylated [11]. For this reason, coronavirus infectivity to can be inhibited by these lectins that are specific for the glycans present in the spike glycoprotein.

Lectins have 2 or 4 identical or almost identical subunits, each subunit has one carbohydrate-binding site and 2 metal ion-binding sites (see Fig. 1).

2. EXTRACELLULAR MATRIX

The human immune system preserves the host against pathogenic organism as bacteria, viruses, fungi and parasites etc. The human immune system has developed to contain a countless of specific cell types, ECM, communicating molecules and functional responses for overcome the diseases which cause from pathogenic organism. It is always active and develops by being effecting from the secondary molecules, vitamins, trace elements essential nutrients from the nutritional foods.

In all tissues and organs, ECM consists of proteoglycans, hyaluronic acid, fibrous proteins, and various glycoproteins and fills up the extracellular space [12]. Also, ECM holds water, anions and cations so create a straight environment of ambient cells. ECM also constitutes has plural types of molecules that are cross-linked to each other through protein-protein and protein-carbohydrate interactions thereby create the three-dimensional space.

The ECM arranges the attitude of cells physical wharf for tissue construction and an active field of signaling between the cells.

In the three-dimensional space of ECM, diverse signal molecules such as growth factors and chemokines are held, and the concentration gradients of morphogens such as BMPs and Wnts are also created.

The ECM regulating motility and shape of cells operates as a sticky substrate for them. The construction of ECM is re-adjusted with the biosynthesis of its components and their corruption by diverse proteases and glycanases so they are actively working, not constant and static. In this way, the components of ECM’s three-dimensional space are quite significant in the arrangement of cell growth, differentiation, migration, adhesion, tissue morphogenesis [13]. Additionally, intake of great dose glucose can be caused to make a weaker ECM area in inter cells because glucose bind to spike proteins which occur from glycoprotein of the virus.

Fig. 1. Structure of lectin
(https://prezi.com/hv0rgu1dmfgrphytohaemagglutinin/?frame=7a28eb504939ca793934a10d42289d6f9c59fa4)
3. LECTINS OF FUNCTIONAL FOODS AGAINST THE VIRUSES

In time expert comments and applied guidance for how patients should be nutrition in the SARS-CoV-2 pandemic is planned by The European Society for Clinical Nutrition and Metabolism (ESPEN) [14]. More than several years ago, plant lectins were come out as a retain HIV replication in lymphocyte cell cultures owing to inhibition of the virus-cell the fusion [15-17]. At first, it was displayed the an inhibition of the virus replication has occurred through plant lectins with preventing virus adsorption [18], however, it was later understood that they prohibit the fusion of HIV particles with their target cells. Moreover, the antiviral impact of mannose- and n-acetylglucosamine-particular agglutinins on HIV, an inhibitory impact of these plant lectins was observed on cytomegalovirus contamination, respiratory syncytial virus infection and influenza A virus infection in vitro [15,19]. The consumption of functional foods that are plant origin and rich in lectin constitutes a powerful weapon for the effect of corona viruses on spike structures [20]. Plant lectins prevent by immobilization of corona viruses (HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-HKU1, MERS-CoVid, SARS CoVid19-2) and binding to the sugar structure (glucose/mannose-specific) of lectins on the viral spike. Glucose/mannose-specific lectins becomes an active only when the metal-binding sites are occupied. Some of these lectins and their binding metal ions are listed in Table 1 [21].

According to the latest traditional medicine literature experiments of coronaviruses reveal that mannose-binding lectins are the strongest inactivation on coronavirus. Antagonist coronavirus activity was observed by galactose-, n-acetylgalactosamine-, glucose-, and n-acetylgalactosamine-specific plant agglutinins [22].

During virus entry and virus release, probably the lectins interfere with the glycans on spike protein of the virus. When the virus is entry the metabolism, if the plant lectins are in sufficient amount in the extracellular matrix (ECM), lectins, going to bind to spike glycans of the viruses to immobilize the spike activity also the motility, so that inhibiting the host membrane docking (membrane fusion). In previous the SARS-CoV experiments reveal that plant lectins inhibit virus replication by preventing virus adsorption [23].

4. THE SARS-CoV-2 AND LECTINS

In China in December, there was occurred a virus named as SARS-CoV-2 or COVID-19 that liable some acute respiratory syndrome [24]. In almost six months, this betacoronavirus has spread globally and turn into a pandemic event, with more than 117 million people global cases worldwide resulting in greater than 2.612.0000 deaths as of March 10, 2021 [25]. In 2002, the SARS-CoV-1 virus had an acute respiratory syndrome, too. So at present, the researchers think that the SARS-CoV-2 almost 80% identical at the genomic level with the SARS-CoV-1 [26-27]. According to the press all literature surveys, sudden view and diffuse of this new virus, there is any effective accepted the SARS-CoV-2-specific clinically treatment methods. The greatest defined in any of RNA viruses, genome length is almost 30 kb and huge, enveloped single-stunt that are known as coronaviruses.

<table>
<thead>
<tr>
<th>Lectin source</th>
<th>Sugar specificity</th>
<th>Binding metal</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canavalia ensiformis</td>
<td>glucose/mannose</td>
<td>Ca$^{2+}$, Mn$^{2+}$</td>
<td>15</td>
</tr>
<tr>
<td>Canavalia brasiiliensis</td>
<td>glucose/mannose</td>
<td>Ca$^{2+}$, Mn$^{2+}$</td>
<td>15</td>
</tr>
<tr>
<td>Parkia platyccephala</td>
<td>glucose/mannose</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>Cymbosema roseum</td>
<td>mannose</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>Cymbosema reseum</td>
<td>lactose</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>Triticum vulgaris</td>
<td>N-acetylglucosamine/sialic acid</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>Vatairea macrocarpa</td>
<td>galactose/N-acetylglactosamine</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>Ulex europeae I</td>
<td>fucose</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>Maackia amurensis</td>
<td>sialic acid</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>Glycine max</td>
<td>N-acetylglactosamine</td>
<td>Ca$^{2+}$, Mn$^{2+}$</td>
<td>15</td>
</tr>
</tbody>
</table>
Coronavirus experiment was focal point of the veterinary area before it turned into the pandemic. Focal points were destroying epizootics of respiratory or enteric illness in livestock and poultry. Literature surveys described that in virus replication, plant lectins are an active role through prohibiting virus adsorption [15], whereas subsequently, they avert of HIV particles in terms of they have that target cells [19,21]. Lectins which have an antiviral impact on HIV with mannose- and N acetylgalactosamine-specific also have an active a role in cytomegalovirus infection, respiratory syncytial virus infection and influenza A virus infection in vitro [19,21,28]. Infectivity of coronavirus could have occurred with plant lectins which are particular for the glycans located in the spike glycoprotein. Because spike protein of coronavirus is seriously glycosylated and has 23 supposed Nglycosylation sites in that effectively glycosylated only 12 among them. Perhaps for this reason specific for the spike glycoprotein of coronaviruses these lectins play a role in the inhibition of the coronaviruses.

In accordance to the literature surveys about mutation of SARS-CoV-2, as SARS-CoV-2 extended around the world, it has a many of mutant variants. These types of variants have gained different genetic changes according to first SARS-CoV-2 in China in 2019 December. A mutation (viral mutation or genetic mutation) of the SARS-CoV-2 virus is a modify in the genetic sequence of the SARS-CoV-2 virus when crosschecked with a reference sequence such as Wuhan-Hu1 (the first genetic sequence identified) or USA-WA1/2020 (the first identified in the United States). SARS-CoV-2 mutations (virus variant or genetic variant) may have one or more mutations that diversify it from the first sequence of the virus variants earlier excursive in the world human population. As per the variants of SARS-CoV-2 may have different attribute in terms of spread, resistance to available treatment choice or hazardousness. Making more elaborating with high resolution the mechanisms of virus-host interplays in the variants of SARS-CoV-2 will set light to developing the new more effective and protective treatments [21].

The spike protein of SARS-CoV-2 (illustrated in Fig. 2. is made from the glycosyl (O-glycosylation and N-glycosylation) with numerous fucose, mannose and sialyl residues. These sugar components have the potential to bind to C-lectin type receptors (CLR), mannose receptor (MR), dendritic cell-specific intracellular adhesion molecule-3-grabbing non-integrin (DC SIGN), homologue dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin related (L-SIGN), macrophage galactose-type lectin (MGL), toll-like receptors (TLR), and lucose regulated protein 78 (GRP78).

Replication mechanism of SARS-CoV-2 was explained the below; see Fig. 3.

(I) The spike protein (S) on SARS-CoV-2 easily attachment to the host cell through the ACE2, TMPRSS2. The S protein has two subunits, S1 and S2 (a). The S1 subunit binds to ACE2 (b) following which TMPRSS2 divides ACE2 (c). The S2 subunit facilitates fusion of the viral particle with the host cell membrane so guiding to viral entry (c).

(II and III) As an alternatively, the viral entry can also begin with endocytosis.

(IV) After entry, release of the viral genome (+ strand).

(V) Translation of the strand leads to the formation of polyproteins (pp1a and pp1ab) which are divided by the main protease (MPro) and papain-like protease (PLPro) into the nonstructural proteins (nsps).

(VI) RdRp replicates the genome.

(VII) The sub-genomic transcripts that encode the structural proteins are occurred by the transcription of the genome.

(VIII) In the cytoplasm, the nucleocapsid is translated.

(IX) In the endoplasmic reticulum (ER), the other structural proteins are translated.

(X) The genomic RNA is made from the nucleocapsid and the genomic strand.

(XI) In the golgi bodies, the structural proteins are glycosylated.

(XII) A budding vesicle occur from with accumulation the virion particles.

(XIII) Exocytosis of the accumulated viral particle occurs.

(XIV) The newly released viral particles can now infect other host cells.

The plant lectins probably interfere with to the glycans on the spike protein of SARS-CoV-2 pending virus entry and virus release. They play a negatively effect role on the virus in terms of their nature of sugar specificity. Mostly, the mannose-specific plant lectins render extremely inactive position the coronaviruses.
Plant lectins may have strong inactivator molecules of coronaviruses by interfering with two ways in the replication cycle of the virus. The first way was found at beginning in the replication period as a probably viral binding, the second way was found at last period of the contagious virus cycle [29].

Additionally, plant lectins may varied particularly interfere with different targets required for viral docking, related to the area of the glycans that are aimed. The spike protein of SARS-CoV-2 have 12 N-glycosylation regions. It has been described that these regions can bind to sugar molecules. So, lectins can be used for strengthening the cells against viral microorganisms. While lectins strengthen the extracellular matrix (ECM) area, excess glucose in the ECM causes the virus to become stronger. Therefore, glucose intake should be reduced or none while lectin-based nutrition to increase the potential strength of the human immune system.

5. Salvia officinalis AND Malva sylvestris ROLE AGAINST THE SARS-CoV-2

In phytoterapeutics applications against the illness, a major distinction is true teas based on...
the medicinal and aromatic plant infusions versus specific types of herbal teas for especially using for the treatment [30]. The medicinal and aromatic plants are boiled in water generating complex aqueous solutions or infusions. Especially members of the Lamiaceae family comprising plants such as sage (Salvia officinalis) is used to prepare herbal teas in phytoterapeutics applications against many diseases. Significant the medicinal and aromatic spices such as basil, mint, rosemary, marjoram, oregano, thyme, and lavender spp (L. angustifolia, L. latifolia, L. stoechas and L. x intermedia) also belong in the family of Lamiaceae. In the diseases of pneumonia and cough, medicinal effect of plants of the Lamiaceae family is good explained [31].

Saracoglu suggested two mixed the medicinal plants (sage and malva) against the SARS-CoV-2 syndrome. This suggestion belongs to cup of tea that corresponds to ca. 250 ml of volume boiled water contain 1.5-2.25 g mixture of Salvia officinalis and Malva sylvestris (3:1, w/w). This mixture should be used as a mouth and nasal wash 3 times a day. This medicinal and aromatic plants were described as potential play a role against viral diseases and respiratory illness in documents of European Medicines Agency (EMA). In according to the literature, Salvia officinalis may have antiviral activity with safficinolide and sage one, two diterpenoids that are found in plants aerial parts [32].

In the latest literature survey of phytoterapeutics applications which include against the SARS-CoV-2 intriguingly revealed that as little as 30 min of treatment, after which the tea (containing of Salvia officinalis) was removed, were sufficient to significantly diminish the SARS-CoV-2 replication. In antiviral activity against the retrovirus, plants of the Lamiaceae family have already been explained [33-35].

For some medicinal and aromatic plants like Salvia officinalis and Malva sylvestris are provened efficacy in medicine, they can use in prevent and/or relieve some of the hardness and suffering of the COVID-19 pandemic in accordance their inexpensive and universal availability [36-37].

Since herbal teas are simple available, almost unpaid of charge, and display great protective profiles given their consumption as spices, we propose to add Salvia officinalis and Malva sylvestris infusions to such combinatorial treatment regimens.

<table>
<thead>
<tr>
<th>Pheno</th>
<th>Phenolic glycosides</th>
</tr>
</thead>
<tbody>
<tr>
<td>glycosides</td>
<td>picein (4-hydroxy acetophenone glucoside)</td>
</tr>
</tbody>
</table>

4-hydroxy-acetophenone-4-(6'-apiosyl)-glucoside
 cis- and trans-p-coumaric acid 4-(2'-apiosyl)-glucoside
 isolariciresinol 3-glucoside
 1-hydroxy-pinoresinol 1-glucoside

<table>
<thead>
<tr>
<th>Active essential oils (EO)</th>
<th>α-thujone</th>
</tr>
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<tbody>
<tr>
<td>β-thujone</td>
<td>camphor</td>
</tr>
<tr>
<td>1,8-cineole</td>
<td>α-humulene</td>
</tr>
<tr>
<td>β-caryophyllene</td>
<td>viridflorol</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Flavones and it's glycosides</th>
<th>luteolin; its 7-glucoside, 7-glucuronide, 3'-glucuronide and 7- methyl ether</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-hydroxyluteolin; its 7-glucoside and 7-glucuronide</td>
<td></td>
</tr>
<tr>
<td>6 methoxy-luteolin; its 7-methyl ether</td>
<td></td>
</tr>
<tr>
<td>apigenin; its 7-glucoside, 7-methyl ether (=genkwanin)</td>
<td></td>
</tr>
<tr>
<td>6-methoxy-apigenin (=hispidulin) and its 7-methyl ether (=cirsimaritin)</td>
<td></td>
</tr>
<tr>
<td>vicenin-2 (=apigenin 6,8-di-C-glucoside)</td>
<td></td>
</tr>
<tr>
<td>5-methoxy-salvigenin</td>
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</tbody>
</table>

Table 2. Some secondary metabolites of Salvia officinalis
Table 3. Some of secondary metabolites of Malva slyvestris

<table>
<thead>
<tr>
<th>Anthocyanins</th>
<th>Malvidin 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-diglucoside</td>
<td></td>
</tr>
<tr>
<td>malvidin 3-glucoside</td>
<td></td>
</tr>
<tr>
<td>malvidin 3-(6- malonylglucoside)-5-glucoside</td>
<td></td>
</tr>
<tr>
<td>delphinidin 3-glucoside</td>
<td></td>
</tr>
<tr>
<td>petunidin</td>
<td></td>
</tr>
<tr>
<td>cyanidin</td>
<td></td>
</tr>
<tr>
<td>malvidin chloride</td>
<td></td>
</tr>
<tr>
<td>malvidin chloride</td>
<td></td>
</tr>
<tr>
<td>Flavonoids</td>
<td>Luteolin, kaempferol, myricetin, apigenin, genistein, quercetin</td>
</tr>
<tr>
<td></td>
<td>Kaempferol-3-O-rutinoside and quercetin-3-O-rutinoside</td>
</tr>
<tr>
<td>Organic acids</td>
<td>Oxalic acid, malic acid, ascorbic acid, citric acid, fumaric acid</td>
</tr>
<tr>
<td>Phenolics</td>
<td>4-hydroxybenzoic acid, 4 methoxybenzoic acid, 4-hydroxy-3-methoxybenzoic acid, 2-hydroxybenzoic acid, 4-hydroxy-2 methoxybenzoic acid, 4-hydroxybenzyliccohol, 4hydroxydihydrocinnamic acid,4-hydroxy-3-methoxyhydro- cinnamic acid, 4-hydroxycinnamic acid, ferulic acid and tyrosol</td>
</tr>
<tr>
<td>Terpenoids</td>
<td>linalool-1-oic acid, (6R,7E, 9S)-9-hydroxy-4,7-megastigmadien-3-one, (3S,5R,6S,7E, 9R)-5,6-epoxy 3,9-dihydroxy-7-megastigmen, blumenol A, (3R,7E)-3-hydroxy-5,7-megastigmadien-9-one,(+)-dehydrovomifoliol, (3S,5R,6R,7E,9R)-3,5,6,9-tetrahydroxy-7-megastigmene and (6E,8S,10E,14R) 3,7,11,15-tetramethylhexadeca-1,6,10-trien-3,8,14,15-tetraol</td>
</tr>
</tbody>
</table>

Salvia officinalis (Sage), is a member of the mint family Lamiaceae and native to the Mediterranean region, though it has been naturalized in many places throughout the world.

Salvia officinalis and Malva slyvestris have include many of biocompatible secondary metabolites. If these secondary metabolites are intake the metabolism as a whole infusion solutions, owing to strong antiviral activity of these plants, human immune system can sufficiently deal with against to the virus.

6. SECONDARY METABOLITES OF
Salvia officinalis AND Malva slyvestris

Some active secondary metabolites are; (see Table 2.

The Medicinal use of Salvia officinalis, folium in herbal teas and herbal preparations have been documented continuously in many pharmacognosy texts, handbooks and compendia.

Malva slyvestris (Mallow) is herbal the medicinal plant which belongs to the Malvaceae family. The following active secondary metabolites were found in Malva slyvestris flowers; see Table 3.

7. CONCLUSION

Results from this paper, Lectins, Salvia officinalis and Malva slyvestris are included in various biological processes, including cell–cell recognition, cell multiplication, cell migration, cell adhesion to the extracellular matrix, and host-parasite interactions in the ECM. If these secondary metabolites and plant lectins are intake the metabolism as a whole infusion solutions, owing to strong antiviral activity of these plants, human immune system can sufficiently deal with against to the virus.

This study would make possible improvement of dietary recommendations and alternative medicinal treatments for especially at risk groups.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.
COMPETING INTERESTS

Authors have declared that no competing interests exist.

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