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REVIEW

Inferences of actinobacterial metabolites to combat Corona virus

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Abstract
The entire globe is reeling under the magnitude of the current corona virus pandemic. This menace has proposed severe health and economic threats for all, thereby challenging our human existence itself. Since its outbreak, it has raised the concern and imperative need of developing novel and effective agents to combat viral diseases and now its variants as well. Despite the sincere and concerted efforts of scientists and pharma giants all over the world, there seems to be no ideal recourse found till date. Natural products are rich sources of novel compounds used in the treatment of infectious and non-infectious diseases. There are reports on natural products from microbes, plants and marine organisms that are active against viral targets. Actinobacteria, the largest phylum under the bacterial kingdom, is known for its secondary metabolite production with diverse bioactive potentials. Nearly 65% of antibiotics used in medicine are contributed by Actinobacteria. Compared to antibacterial and antifungal agents, antiviral compounds from Actinobacteria are less studied. In recent years Actinobacteria from under studied/extreme ecosystems are explored for their antiviral properties. Ivermectin and teicoplanin are examples of Actinobacteria-derived antiviral drugs available for commercial use. This review highlights the importance of actinobacteria as future sources of antiviral drug discovery.

Keywords Actinobacteria · Corona viruses · Natural products · Drug discovery · Antivirals

Introduction: viral diseases

The occurrence of novel human pathogens and resurgence of various diseases are prominent challenges faced in the present-day era. Totally more than 1400 species of human pathogens have been recognized in which about 60 per cent are of zoonotic origin (Woolhouse and Gowtage-Sequeria 2005). Among the wide array of communicable diseases, the global public health is highly threatened by the emerging viral infections (Luo and Gao 2020) and they are known to cause potential epidemic and pandemic outbreaks. Most of the emerging viruses possess RNA genomes and they adeptly undergo selection of new strains and rapid mutation in response to environmental changes in accessible target species and host count. Moreover, one third of emerging and re-emerging infections are caused by the RNA viruses (Howard and Fletcher 2012). The lower respiratory infections are the deadliest communicable disease wherein the transmissible aerosols of the tracheobronchial tree designate systematic means for spreading of viral pathogens, eventually affecting the respiratory tract (Takizawa and Yamasaki 2018; Mourya et al. 2019). Prevention and treatment of viral infections are much more difficult than that of bacterial and fungal infections since the development of effective vaccines and antiviral drugs are difficult and time consuming. However, due to continual efforts, there are life saving viral vaccines and antiviral drugs that are developed around the world to combat some viral infections in humans (Anderson et al. 2020). But several fundamental and important questions about viral disease still remain to be answered with respect to their biology, pathogenesis, transmission, virulence, diagnosis, drug discovery, and vaccine development.

Coronaviruses and their threats

Corona viruses (CoVs), comes under the family coronaviridae. They are pleomorphic, positive stranded segmented RNA containing enveloped viruses with the size ranged from 80 to 120 nm in diameter (Neuman et al. 2011). In

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general the genome of RNA viruses are usually < 10 kb in length (hence their mutation rate is high). But CoV remains the largest known RNA virus with a genome of roughly 30 kb in length. CoVs can affect human, birds, livestock, mouse, bat and a wide range of other animals by infecting their respiratory, hepatic, and gastrointestinal and central nervous system (Chen et al., 2020). CoVs are proved to be the contributory agents of Severe Acute Respiratory Syndrome (SARS CoV) and Middle East Respiratory Syndrome (MERS-CoV). Initially three strains of CoV have been reported based on their serological properties. In 1960, two strains, HCoV-229E and HCoV-OC43, causing well controlled common cold symptoms have been identified. Third strain is the life-threatening SARS-CoV strain which causes lethal pneumonia. The fourth strain, isolated from a 6 months old child, is the HCoV-NL63 with its genomic sequence identified (Chafekar and Fielding 2018). In the last couple of decades, several CoV infections have created several threats claiming thousands of human deaths. The recent one is a novel strain of lethal Corona virus that stuck Wuhan province, China, causing thousands of deaths during Jan–Mar 2020. It is a corona virus of type beta, presented with the name nCoV-19 (SARS-CoV-2). It was initially recognized when few cases of pneumonia appeared during the first week of December 2019 in the city of Wuhan, China. The symptoms were noted among the people who visited the local Huanan seafood market where zoonotic transmission was suspected as the main route of disease origin (Hui et al. 2020).

Treatment of Corona viral diseases and need for new drugs

Recent corona virus pandemic raised the issue of developing novel and effective agents to combat n-CoV-19 (Wu et al. 2020). Several drugs such as Lupinavir/Ritonavir, Remdesvir, neuraminase inhibitors, Traditional Chinese Medicine (TCM), hydroxychloroquine and microbial product like ivermectin are proposed to be treatment options for nCoV-19. Most choices of drugs are derived from previous experience for treating MERS, SARS or some other influenza viruses. Regardless, the safety and efficacy of such drugs still needs to be evaluated and verified through clinical trials before being used as a treatment option of nCoV-19 (Lu 2020). Some common approaches to be followed for anti nCoV-19 drug discovery include (1) exploring the existing drugs (antiviral, antibiotics or antiparasitic agents) (repurposing), (2) Screening of a chemical library containing many existing compounds, and iii. Bioinformatics or computer aided drug design (CADD). However, there are very few studies initiated on screening natural resources to find novel molecules effective against nCoV-19.

Natural products in antiviral drug discovery

Initiation for the identification of novel antiviral agents is resourced by chemical libraries that comprise small molecule compounds with known structure. However, the largest of small molecule libraries usually contains 10^6 compounds or more, denoting a negligibly small proportion of chemically feasible drug-like molecules (Dobson 2004; Lipinski and Hopkins 2004). An unconventional procedure takes advantage of complex biosynthetic pathways of organisms that can provide unlimited chemical diversity of natural products (Verdine 1996). Natural products have been and still are rich sources of drugs for the treatment of various infectious and non infectious diseases including viral diseases (Martinez et al. 2015). Natural products have facilitated the advancement of antiviral drugs by delivering perceptiveness into the synthesis of chemical compounds. In the field of antiviral drug development, natural products like arabinosyl nucleosides spongouridine and spongothymidine (isolated from marine sponges) have provided some motivation to develop new nucleoside analog vidarabine (arabinosyladenine) which is used for the treatment of HSV infections. Hence, natural products continue to proffer the best possibilities for discovery of novel agents/active models, which when operated alongside biologists and synthetic chemists, provide the feasibility to determine novel structures that can be employed to act as effective agents in a variety of human diseases (Newman and Cragg 2020). In order to propagate, viruses need host cellular machineries; hence the development of antivirals from natural products is complex and consists of i. directly acting antivirals (DAAs) and ii. host acting antivirals (HAAs).

According to the recent report by Newman and Cragg (2020), in the period between 1981 and 2019, only a very significant number of approved agents are vaccines in the field of antiviral agents. There are no outstanding reports on antiviral agents from natural products or from their inspiration, unlike in the fields of antibacterial, antifungal and anticancer natural product discovery. Importantly, there are several antiviral studies carried out on plant extracts followed by extracts from marine organisms. Recent status and success of broad spectrum antivirals from natural resources has been described in detail by Martinez et al. (2015) where they reported natural antiviral compounds from plants, microbes and marine organisms against various viral targets.

Natural product drug discovery against Corona viruses

Recent nCoV-19 crisis motivated researchers to investigate natural products or their derivatives to combat coronavirus.

There is an urgent need for competent research on progress of antiviral agents from natural sources against CoV. Sayed et al. (2020) has described in detail about the structural/mechanistic rationale behind the natural products as potential anti SARS-CoV drug leads. They summarized potential candidates from natural resources, mainly from plants with well-stated in vitro potency against SARS-CoV. As per the data given in published literatures in recent times, a wide range of natural products with discrete chemical structures has confirmed to be promising agents as anti-SARS-CoV. Owing to their promising pharmacokinetic profiles, phenolic derivatives such as flavonoids, were the highest reported active agents (Islam et al. 2020). Vellingiri et al. (2020) also highlighted the possible effect of Indian medicinal plants on COVID-19.

Actinobacteria: treasure house for novel drugs

Members coming under the phylum actinobacteria are Gram positive organisms comprised of several genera with high Guanine + Cytosine content in their DNA, existing in filamentous or non filamentous morphologies (Fig. 1) (Barka et al. 2016). Primarily they are recognized as common soil habitants, but now they are known to have a ubiquitous distribution even in extreme environments. From ecological and economical standpoint, actinobacteria are prominent prokaryotes with an exceptional capability to provide novel metabolites. Being the largest phylum under the kingdom Bacteria, Actinobacteria has earned immense attention from the scientific association as prolific producers of novel natural products with diverse bioactive properties such as antibiotic, anticancer, antiviral, anti-inflammatory, and several others (Radhakrishnan et al. 2019). To correspond concretely with biological targets, metabolites from Actinobacteria have significantly evolved through millions of years (Heul et al. 2018). Since most of its antibiotics are too intricate to be incorporated by combinatorial chemistry, the breakthrough of novel active metabolites from Actinobacteria has labelled an era in antibiotic research (Baltz 2007; Barka et al. 2016). Till now, Actinobacteria have bestowed over and above 65% of antibiotics used in medicine; of which the members of the genus *Streptomyces* alone has produced more than 10,000 bioactive compounds (Subramani and Aalbersberg 2012; Karuppiah et al. 2016). On basis of its evident incomparable ability in synthesizing a broad range of compounds with diverse bioactivities, the genus *Streptomyces* still remains in the spotlight of microbial product research despite years of bioprospecting research (Tan et al. 2016; Ser et al. 2017). In accordance with some estimation, of the top 10 cm global soil containing 10^{25}–10^{26} actinobacteria, only over 10^{7} has been screened for production of antibiotics in the last fifty years, leaving a vast range of scope for further research (Baltz 2007). On the other side, the discovery of novel bioactive products from this promising bacterial group has dropped significantly over the years as a result of superfluous investigations on routine terrestrial habitats. Rare ecosystems like deserts, forests, mountains, caves and marine ecosystems are potential store houses for novel actinobacteria that produce unique bioactive metabolites. The growing awareness of diversity of actinobacteria has motivated researchers to explore their natural product chemistry for biomedical applications. In recent years, there are several articles published on novel natural products from certain extremosphere actinobacteria notably from marine environments. Arenamides, Arenicolides and Salinisporamide are some of novel bioactive natural products reported from novel deep sea actinobacteria. In addition, there are several other bioactive molecules reported from actinobacteria isolated from rare/extreme ecosystems like caves, forests, deserts, hot springs, alkaline soil, deep sea sediments and Cryosphere.

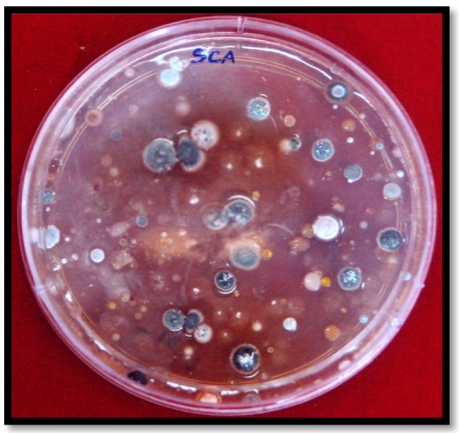

Fig. 1 Colonies of actinobacteria on starch casein agar plates

Research on antivirals from actinobacteria

Nearly 70 years ago there were no effective screening methods for screening antiviral substances eventually resulting in no potent antiviral agents mainly. The methods employed for screening of antiviral agents included animal experiments using mice or chick embryo. Regardless, these approaches were not quantitative and not efficacious enough to screen large number of samples in short period of time. There upon tissue culture has been intended as a simple in vitro technique for screening large number of extracts and compounds for antiviral properties (Kuroya et al. 1957). Takizawa and Yamasaki (2018) described the antiviral compounds isolated from microbial resources mostly from the genus *Streptomyces* at the Institute of Microbial Chemistry, Japan.

Attributable to fermentation, extract preparation, virus cultivation and preservation procedures, there are a number of actinobacterial metabolites and compounds screened

using in vitro cell culture platform. Nevertheless, the number of antiviral compounds recorded from actinobacteria is significantly lower than the number of antifungal and antibacterial compounds. Over the past few years, antiviral compounds have been produced from actinobacteria isolated from under studied/extreme ecosystems (Kim et al. 2016). Some reports on antiviral compounds from actinobacteria are given in Table 1.

Actinobacteria-derived drugs against coronaviruses

There are two important actinobacteria derived antibiotics, ivermectin and teicoplanin, which are found to be active against corona viruses. Colson and Raoult (2016) summarized the broad spectrum antiviral activities of these two actinobacterial antibiotics.

Ivermectin

Ivermectin is a semi-synthetic derivative of avermectin B1a (one of 8 natural avermectins) produced by *Streptomyces avermectinius* isolated by Omura and group of scientists at the Kitasato Institute, Japan in 1973. Ivermectin (Fig. 2) is already labelled as "wonder drug" essential to eliminate two

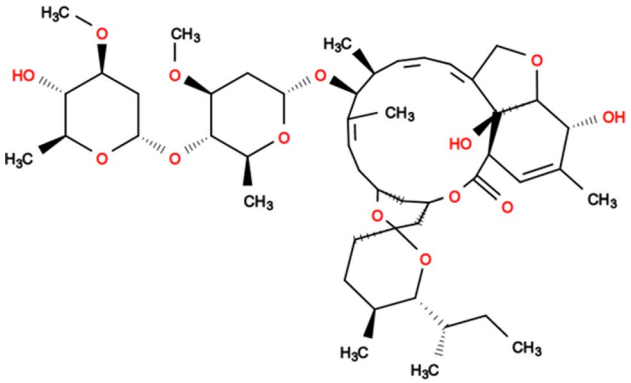

Fig. 2 Chemical structure of Ivermectin

devastating tropical diseases. Ivermectin has been approved by the FDA as antiparasitic agents. New uses for ivermectin are identified regularly, including possible antibacterial, antiviral and anticancer properties (Omura and Crump 2014). Recently, Heidary and Gharebaghi (2020) have critically reviewed the antiviral activity of ivermectin against a broad range of DNA and RNA human viruses. Primarily, it has been substantiated to act on the infections by RNA viruses such as VEEV (Venezuelan equine encephalitis

Table 1 List of some actinobacteria showing antiviral properties against different human viruses

Antiviral agents	Source	Target virus	References
Purified compounds	*Streptomyces*	Vaccinia virus	Thomson (1947)
Actinomycin	*Streptomyces*	Fowl pox virus	Jones et al. (1945)
Achromoviromycin	*Streptomyces*	Encephalitis virus	Umezawa et al. (1953)
Formycin	*Streptomyces*	Antiviral	Ishida et al. (1967)
Clazamycin B	*S. puniceus*	HSV	Dolak and Deboer (1980)
Benanomicins A & B	*Streptomyces*	HIV	Kondo et al. (1991)
Kijimycin	*Actinomadura*	HIV	Nakamura et al. (1991)
Bellanamine	*S. nashvillensis*	HIV	Ikeda et al. (1996)
Cycloviracin B & B2	*Kibdellosporangium albatum sp. nov.,*	HSV1	Tsunakawa et al. (1992)
Actinomycin D	*Streptomyces*	HIV 1	Guo et al. (1998)
Fattiviracins 1–13	*S. microflavus*	DNA viruses (HSV1 & VZV) and RNA viruses (Influenza A & B and HIV)	Uyeda et al. (2003)
Ivermectin	*S. avermetilis*	Newcastle disease virus, Coronavirus, Dengue virus, HIV, yellow fever virus	Omura and Crump (2004)
Methanolic fractions	*Streptomyces*	HSV1	Sacramento et al. (2004)
Antimycin A	*S. kavengensis*	Wide range of RNA viruses (Toga-, Bunya-, Picorna-, Flavi- and paramyxo-viridae	Raveh et al. (2013)
Purified methanol fractions	*S. chartreusis*	Bovine viral diarrhea virus	Padilla et al. (2015)
Xiamycin D	*Streptomyces*	Porcine epidemic diarrhea virus (PEDV)	Kim et al. (2016)
Hydroxy marilone C	*S. badius*	HINI virus	El Sayed et al. (2016)
Teicoplanin	*Actinoplanes*	Influenza, dengue, chickungunya, yellowfever, HIV and coronaviruses	Colson and Raoult (2016)
Salinomycin	*S. albus*	Influenza virus	Jang et al. (2018)

virus), DENV 1-4, West Nile and Influenza Virus. This wide array activity is considered to be because of the dependence by many different RNA viruses on IMPα/β1 during infection (Caly et al. 2012; Jans et al. 2019). A single stranded positive sense RNA virus, which is the causative agent of the current COVID-19 pandemic, is closely related to severe acute respiratory syndrome coronavirus (SARS-CoV). Reports on SARS-CoV proteins have demonstrated the potency of IMPα/β1 in the course of infection in signal-dependent nucleocytoplasmic shutting of the SARS-CoV nucleocapsid protein (Wulan et al. 2015). With this view, Caly et al. (2020) investigated ivermectin's activity of replication inhibition on SARS CoV-2 in vitro. The preliminary results showed that the ivermectin is able to cause approximately 500 fold reduction in viral RNA in 48 h of incubation. However, its mechanism of action is not clearly defined. But it can be acceptable that the same protein and molecular process outlined above portray that the nCoV-19 is a RNA virus.

Ivermectin, owing to its antiviral activity, could be of service as a potential candidate for the treatment of various types of viral infections including COVID-19 but only after adequate clinical trials. FDA issued a statement on April 10, 2020, regarding self-administration of ivermectin against COVID-19 (FDA Letter, 2020) (The FDA's Center for Veterinary Medicine) in reference to in vitro study published in recent times on this subject (Caly et al. 2020). FDA emphasized that this type of in vitro study is typically used in the initial stages of drug development. Besides, further trials are required to validate the safety and efficacy of ivermectin for human use against COVID-19 to uncover therapeutic or preventive window of opportunity.

Teicoplanin

A glycopeptide antibiotic, Teicoplanin (Fig. 3) is produced by an actinobacterium, *Actinoplanes teichomyceticus*. It is widely used for the treatment of multi drug resistant Gram positive bacterial infections such as *Enterococcus faecalis* and methicillin-resistant *Staphylococcus aureus* (MRSA) (Colson and Raoult 2016). Teicoplanin is widely known for its convenient administration, considerably lower toxic side

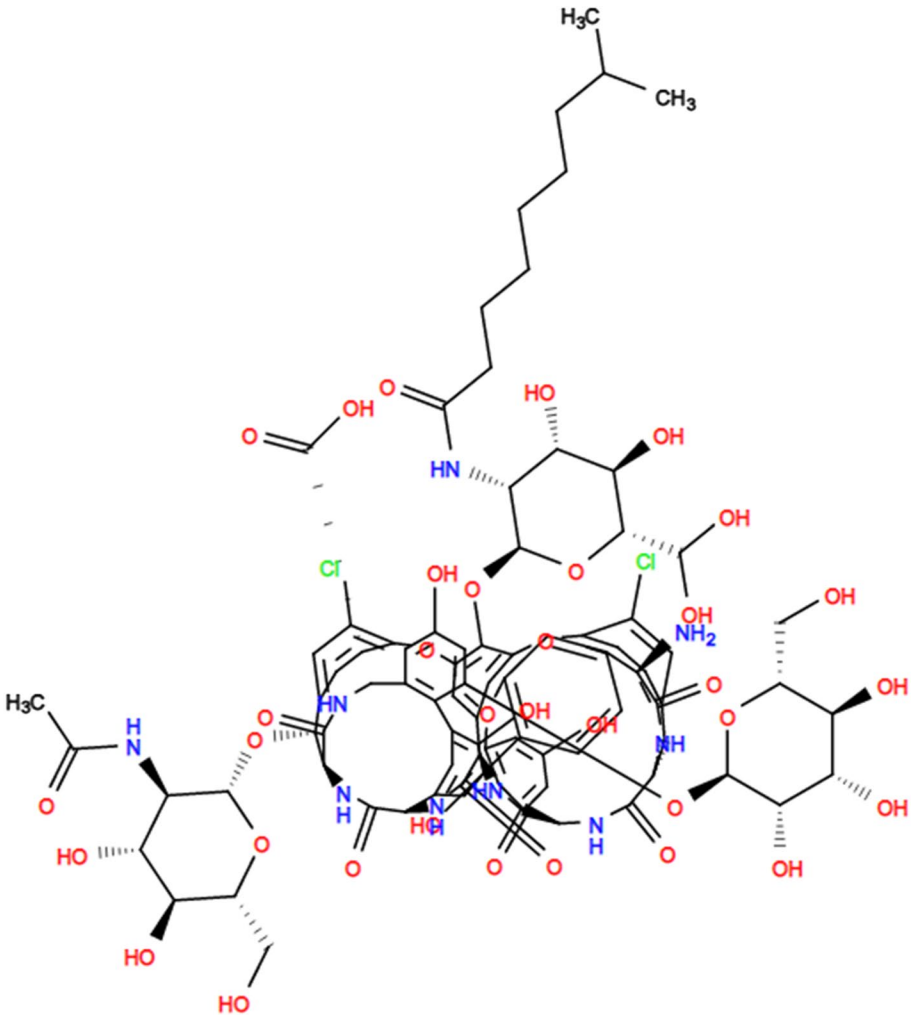

Fig. 3 Chemical structure of Teicoplanin

effects, safety when used in combination with other antibiotics, and long half life in blood plasma, consequently rendering it as a routinely used antibiotic.

In addition to well known antibacterial properties, some studies reported the antiviral properties of teicoplanin and their derivatives and analogues against a vast array of viruses, such as Ebola, Influenza, HIV, Dengue, Chickungunya, yellow fever, Hepatitis C, encephalitis and corona viruses (Colson and Raoult 2016). Zhang and his team from China investigated the antiviral properties of teicoplanin against corona viruses. Wang et al. (2015) observed that teicoplanin, could inhibit Ebola envelope pseudotyped viruses. Rationalistic studies on how teicoplanin block viral entry declared that teicoplanin specifically inhibit the activity of L-cathepsin that performs glycoprotein proteolysis needed for membrane fusion during the entry step of SARS-CoV, MERS-CoV and Ebola viruses (Zhou et al. 2016). This observation opened a new means for the exploitation of glycopeptides as potent inhibitors of cathepsin L-dependent viruses. In 2020, upon comparing nCoV-2019 and SARS-CoV for their cleavage site of L-cathepsin, Zhang et al., found that nCoV-2019 has a well conserved L-cathepsin cleavage site. Further, they also observed that teicoplanin potentially inhibited the entry of nCoV-2019 pseudovirus. This provides a plausible approach to nCoV-19 infection treatment and prophylaxis. Furthermore, other glycopeptide antibiotics, including telavancin, oritavancin, and dalbavancin, excluding vancomycin, turned out to be inhibitors for the entry of Ebolavirus, SARS-CoV and MERS-CoV transcription and replication competent virus like particles (Zhang et al. 2020).

Actinobacteria as future source for new drugs against nCoV 19: opportunities and challenges

The excellent track record of commercial antibiotics produced from actinobacteria evidenced that they are the promising resources for novel antibiotics. The handful of published literatures published from 1945 up to 2020 on antiviral properties of actinobacterial antibiotics, are very less when compared to the antibacterial and antifungal antibiotics produced by them, highlighted that members of actinobacteria also being a promising source for antivirals. Actinobacteria from under studied ecosystems and sources like marine and insect nest showed notable antiviral activity. However there is a long way to go to procure antiviral antibiotics from actinobacteria. Screening of actinobacterial extracts/compounds for antiviral properties need expertise, sophisticated BSL III facility to handle viral pathogens, cell lines and expensive consumables to perform assays. These factors limit the work on actinobacteria for antiviral screening and drug discovery. Apart from this, the preliminary results obtained with antibiotics like teicoplanin, ivermectin and some other closely related compounds, absolutely paved way for repurposing of commercially available antibiotics from actinobacteria for antiviral drug development even against nCov-2019 infection. In silico docking analysis of actinobacterial antibiotics against the potential targets of viral pathogens might well be a promising approach.

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Code availability Not applicable.

Declarations

Ethical approval This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors.

Conflict of interest Radhakrishnan Manikkam has no conflict of interest. Krupakar Parthasarathy has no conflict of interest. Abirami Baskaran has no conflict of interest. Lavanya Dellibabu has no conflict of interest.

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