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The Natural Product Eugenol is An Inhibitor of the Ebola Virus *In Vitro*

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Abstract

Since the 2014 Ebola virus (EBOV) outbreak in West Africa there has been considerable effort towards developing drugs to treat Ebola virus disease and yet to date there is no FDA approved treatment. This is important as at the time of writing there is an ongoing outbreak in the Democratic Republic of the Congo. We have evaluated a small number of natural products, some of which had shown antiviral activity against other pathogens. This is exemplified with eugenol, which is found in high concentrations in multiple essential oils, and has shown antiviral activity against feline calicivirus, tomato yellow leaf curl virus, Influenza A virus, Herpes Simplex virus type 1 and 2, and four airborne phages. Four compounds possessed EC_{50} values less than or equal to 11 μM. Of these, eugenol, had an EC_{50} of 1.3 μM against EBOV and is present in several plants including clove, cinnamon, basil and bay. Eugenol is much smaller and structurally unlike any compound that has been previously identified as an inhibitor of EBOV, therefore it may provide new mechanistic insights. This compound is readily accessible in bulk quantities, is inexpensive, and has a long history of human consumption, which endorses the idea for further assessment as an antiviral therapeutic. This work also suggests that a more exhaustive assessment of natural product libraries against EBOV and other viruses is warranted to improve our ability to identify compounds that are so distinct from FDA approved drugs.

Keywords

Antiviral; Drug discovery; Ebola; Eugenol; p-anisaldehyde

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Competing interests
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Supplementary data
Supplementary data related to this article can be found at:

The history of natural products as therapeutics is long and varied going back a millennia (1). For example, 175 anticancer drugs were approved between the 1940's and 2014 and 49% of these were natural products or derived from them (2). The anti-infective drug discovery area is still heavily dependent on natural products and their structures (2). Others have also suggested that approximately 50% of new chemical entities are based on natural products and derivatives. From 1981 to 2010, 64% of FDA approved drugs were natural products or analogs (3). For example, several natural product drugs have been important natural product drugs for decades (4, 5). Marine natural products alone have led to 8 drugs or cosmeceuticals (a product that is a drug, a cosmetic or both) approved by the FDA and EMA. These include FDA approved marine-derived drugs, namely cytarabine, depocyt, vidarabine and ziconotide and at least 10 candidates in clinical trials (6) as well as a large number of marine chemicals in the preclinical pipeline (7). Even scents represent a relatively untapped source of biologically active molecules (8) (e.g. menthol (9–16)).

Since the 2014 Ebola virus (EBOV) outbreak in West Africa responsible for over 11,000 deaths in ten countries (17), no vaccine or drug has been approved. With the most effort applied to EBOV, four other families of filovirus exist (18) therefore this calls for a broad-spectrum antiviral drug for such emerging viruses (19, 20). The 2018 EBOV outbreaks in the Democratic Republic of the Congo has to date led to over 500 deaths. It is likely, that sporadic outbreaks will continue to occur and treatments will be needed to prevent and stop the progression of the next pandemic even as vaccines continue to be tested during these outbreaks.

The search for small molecule drugs for the treatment of EBOV has involved multiple medium and high-throughput screens (HTS) which have identified hundreds of molecules potentially effective against EBOV *in vitro*. Some of the earliest drugs active against EBOV included clomiphene, toremifene, tamoxifen, and raloxifene and diethylstilbestrol (21). Many other research groups have performed HTS with varying success rates (22–32). The hits identified in these studies belong to several groups of drugs including GPCR antagonists (25), selective estrogen receptor modulators (21), antidepressants (33), L-type calcium channel inhibitors (34) and antimalarials (19, 20).

Our own previous effort in EBOV drug discovery used machine learning to identify three compounds; quinacrine, pyronaridine, and tilorone (35) with the latter showing 100% efficacy in a mouse model of EBOV infection at a dose of 30mg/kg/day (36). This work suggests that promising clinical stage compounds can be identified and progressed through preclinical disease models. A recent study has suggested there are at least 141 drugs with preliminary *in vitro* and / or *in vivo* data in animals, most of which are FDA approved drugs (37).

Relatively small molecules (MWT 100–200) and natural products have been tested as potential treatments for other viruses. For example nicotinamide (Vitamin B3) was evaluated for activity against HIV (38). Essential oils also have a rich history as potential antivirals and possess numerous pharmacological activities (8, 39).

Our recent research suggests that plant derived natural products and structurally similar small molecules are worthy of closer inspection as a source of novel leads for EBOV drug discovery and will provide more molecular diversity. Seven small natural compounds (MWT range 122.1–164.2) were selected for testing against EBOV (Supplemental Methods) based on their commercial availability and previous testing for biological activity against viruses or bacteria. Eugenol (EC_{50} = 1.3 μM) and *p*-anisaldehyde (EC_{50} = 2.8 μM) were the two most potent of the 7 compounds tested (Table 1 and Figure 1A). Benzyl acetate (EC_{50} = 10 μM) and phenethyl acetate (EC_{50} = 10 μM) were less active and L-menthol, nicotinamide and nicotinic acid were inactive (Table 1). The most active compounds did not show appreciable cytotoxicity in HeLa cells, with CC_{50}'s >50 μM (Figure 1B). No EBOV active compounds that were tested in this study had associated Pan Assay INterference compoundS (PAINS) or predicted promiscuity issues issues. *p*-anisaldehyde does however contain the potentially reactive (i.e., electrophilic) aldehyde (Table S1).

It is common for antivirals against one disease to be effective against another that may be closely related. Nicotinamide is active against HIV and HBV (40), but was found to be inactive against EBOV in this study, suggesting a potentially different mechanism for these other viruses. Extracts from plants have been found to contain varied pharmacological activities over the long history of medicine (41) and some suggest that the flora of various countries are still untapped sources for potential drugs or starting points for drug discovery (42). Surprisingly several of the very common essential oils are still finding new activities, such as acting as antimicrobials and antivirals, with the latter being demonstrated in this study.

Eugenol is one such essential oil commonly found in cloves, cinnamon, basil and Bay with diverse biological activities. Eugenol has shown promising activity against feline calicivirus (43), tomato yellow leaf curl virus (44, 45), Influenza A virus (46), Herpes Simplex virus type 1 (47), Herpes Simplex virus 2 (48, 49), four airborne phages (50) as well as larvicidal activity against Aedes Aegypti (51). Dai et al (46) showed that Eugenol inhibits autophagy and influenza A virus replication by interfering with the ERK, p38MAPK and IKK/NF-κB signal pathways. Eugenol also displays broad antimicrobial, antifungal and anti-inflammatory activity (52). it has also been shown to be antiproliferative and have anti-metastatic effects (53). It is likely bioactivated via O-dealkylation of the O-alkoxy group resulting in catechol which is further oxidized to o-quinone (54). To our knowledge this is the first time eugenol has been tested against EBOV, likely because it is very small, more like a drug-fragment (55–57) and therefore very structurally different to the many Ebola active compounds tested to date (22–32). Because it is so small, eugenol provides plenty of scope for medicinal chemistry optimization. It is also present in several foods and has a long history of use by humans, therefore it may represent a faster path to regulatory approval if it possesses *in vivo* activity in an animal model infected with EBOV.

A second promising compound we identified is *p*-anisaldehyde which is also present in fragrances and yet the literature is silent on its potential antiviral potential, although it has been used to deter pests (58, 59). Benzyl acetate is another essential oil widely used in perfumes and cosmetics as well as pesticide applications (60). Phenethyl acetate is a volatile flavor present in many fruits and other foods as well as in fungal infected honeybee larvae, where it induces hygienic behavior (61). Menthol was the only scent or essential oil that we tested that had no appreciable activity against EBOV.

The current assessment is admittedly far from an exhaustive analysis of all natural products with inhibitory activity against EBOV. Interestingly when we used our previously successful Ebola machine learning models they scored these small molecules poorly to borderline active according to these Bayesian models (0.33–0.54, Table S2, Supplemental References) which may be representative of the fact that there are few compounds like these natural products in the models tested to date and further indicative of the need for model retraining with smaller compounds before future virtual screening of natural product libraries. Interestingly, menthol clearly scores the poorest of these compounds. Very few of these smaller sized molecules have previously been identified with activity against EBOV. For example, a recent screen of compounds inhibiting the VP35-nucleoprotein interface identified a small drug (MWT 273.2) tolcapone (IC_{50} = 2μM) which is a catechol-O-methyltransferase inhibitor (62). It remains to be seen if eugenol and p-anisaldehyde are targeting VP35 as well.

Further efforts to characterize these natural product in vitro EBOV actives could include analyzing their effects on: virus and cellular protein levels, EBOV genomic RNA and mRNA, primary human cells like macrophages or dendritic cells. Time-course experiments to show at which stage of infection the two compounds are active as antivirals and assessment of their activity against other human pathogenic RNA viruses would also be of interest to discern their EBOV mechanism.

Serendipity has played an important role in drug discovery over its history (41, 63–70) but we cannot rely on this solely to discover drugs. We can utilize simple, abundant natural products, such as essential oils, as a starting point for new anti-EBOV drug discovery. While the discovery and development of new drugs and chemical probes from natural products is an active area (71), there are several well-known challenges, such as only small amounts of compound are available, analog development is difficult, complexity of synthesis, identification of potential targets/diseases, etc. (72) and avoiding re-isolating known compounds (73). Advantages of natural products include their high potency (74), predisposition to biological activity due to evolution and selection and history of therapeutic success. There has been much recent discussion of the importance of using natural products to increase the diversity of high throughput screens (71). Additionally, the need for further collaborations with chemists who focus on natural product isolation, characterization, and synthesis, cannot be underestimated in these efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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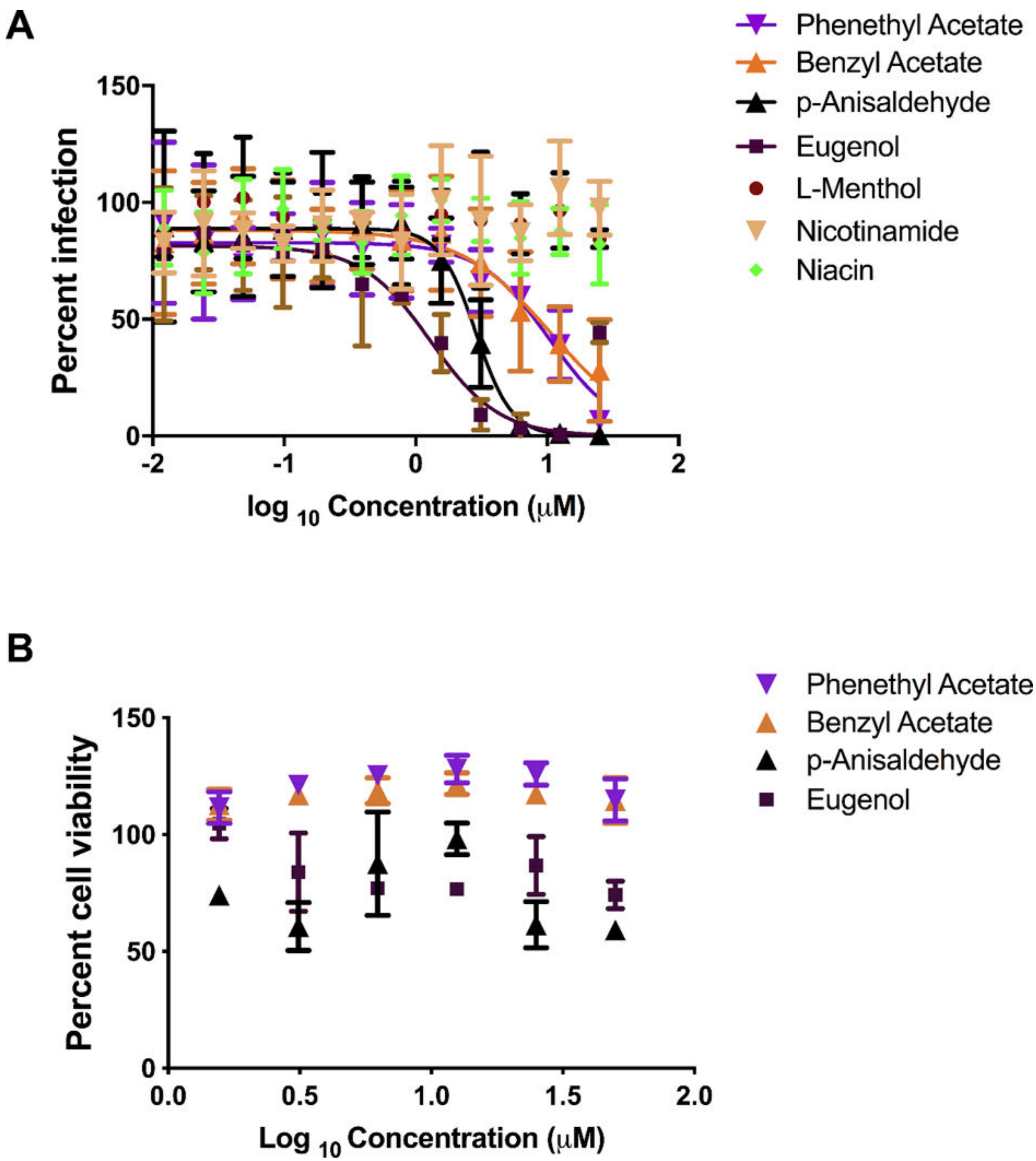
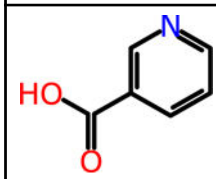
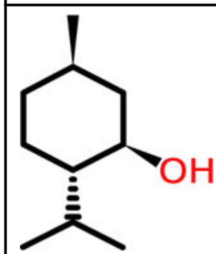
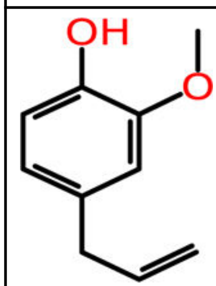


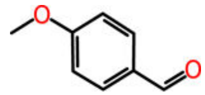
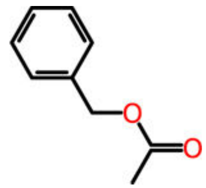
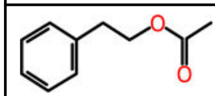
Figure 1.

A. EBOV activity of various compounds using EBOV infected HeLa cells 24 hours post infection. Error bars represent the SD. B. Cytotoxicity of natural product compounds using HeLa cells. Error bars represent the SD.

Table 1.

Natural products and other small molecules tested against EBOV. (NA = no activity).

Molecule	Name: Function	EC_{50} Activity (μM; ±SD; n=4)	HeLa CC_{50} (μM; n=2)	AlogP	MWT
	Nicotinamide: Active Form of Vitamin B3	NA	NA	−0.32	122.13
	Nicotinic acid: Vitamin B3	NA	NA	0.31	123.11
	L- menthol: Scent	NA	NA	2.78	156.27
	Eugenol: Used in Perfumeries, Flavorings, Essential Oils and in Medicine as a Local	1.3 ± 0.5	> 50	2.58	164.20

	P-anisaldehyde: Flavoring ingredient	2.9 ± 0.6	> 50	1.57	136.15
	Benzyl acetate: Perfumery and Flavorings	10.7 ± 5.0	> 50	1.60	150.17
	Phenethyl acetate: Perfumery and Flavorings	10.4 ± 3.4	> 50	1.93	164.20