



Natural polyphenols: potential in the prevention of sexually transmitted viral infections

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Sexually transmitted viral infections represent a major public health concern due to lack of effective prevention strategies. Efforts are ongoing to develop modalities that can enable simultaneous prevention of multiple sexually transmitted infections. In the present review, we discuss the potential of natural polyphenols to prevent sexually transmitted viral infections. The review gives an account of various *in vitro* and *in vivo* studies carried out on epigallocatechin gallate, theaflavins (black tea polyphenols), resveratrol, genistein and curcumin to highlight their potential to prevent sexually transmitted infections caused by HIV (human immunodeficiency virus), HSV (herpes simplex virus) and HPV (human papilloma virus).

Introduction

As detailed in World Health Organization (WHO) data, sexually transmitted infections (STIs) are one of the top five disease categories treated by healthcare professionals (<http://www.who.int/mediacentre/factsheets/fs110/en/>). It is estimated that more than 1 million individuals contract STIs every day (<http://www.who.int/mediacentre/factsheets/fs110/en/>). More specifically, sexually transmitted viral infections (STVIs) caused by HIV (human immunodeficiency virus), HPV (human papilloma virus) and HSV (herpes simplex virus) pose significant fear and anxiety due to lack of effective prevention and treatment strategies. Globally, more than 530 million individuals are infected with HSV-2, 290 million females suffer from an HPV infection and more than 35 million people are infected with the HIV (<http://www.who.int/mediacentre/factsheets/fs110/en/>). It has been observed that HIV-1 and HSV-2 (predominant serotype responsible genital herpes) exhibit synergy wherein infection of an individual with one virus facilitates the acquisition and transmission of the other virus [1]. Sexually transmitted HPV infections typically result in genital warts that are highly transmissible. Moreover, HPV infections account for 530 000 cases of cervical cancer and 275 000 cervical

cancer related deaths annually (<http://www.who.int/mediacentre/factsheets/fs110/en/>). A recent meta-analysis study concluded that there is a positive correlation between high risk HPV infection oncogenic group and HIV acquisition although the biological mechanisms need further exploration [2]. Taken together, STVIs represent a major global healthcare problem. Typically, development of vaccines is the most sought after strategy for prevention of infectious diseases. To date, effective vaccines to prevent infection from various strains of HPV (serotypes HPV 6, 11, 16, and 18) have been developed [3]. However, no effective vaccination strategy is available for the prevention of HSV and HIV infections. Hence, there is a clear need for the development of approaches that can enhance prophylaxis of STVIs.

Owing to lack of effective vaccines and failure of behavioral modifications to curb the incidences of STVIs, the focus has been shifted to chemoprophylaxis; especially for HIV prevention. Several clinical trials have been carried out to explore the potential of antiretroviral drugs for enhanced HIV pre-exposure prophylaxis [4]. CAPRISA-004 trial showed that pre- and post-coital topical application of 1% tenofovir gel led to almost 40% reduction in the HIV infections (close to 60% in the high adherence group) [5]. Further analysis showed that there was a 51% reduction in the HSV-2 incidences in the women applying topical 1% topical tenofovir gel [6]. This interesting observation engendered development of multi-purpose prevention technologies (MPTs) that can enable prevention of multiple infections (intersecting viral and/or

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bacterial infections) with a single modality [3,7]. MPTs are primarily female-controlled modalities (although they can be employed by men in some cases) that can concomitantly diminish the incidences of the sexual acquisition or transmission of HIV, other bacterial and/or viral infections and unintended pregnancy [3,7]. At present, various delivery systems like vaginal rings and gels [3,8] that can co-deliver antiretroviral and anti-herpetic drugs and anti-HPV drugs are being evaluated in pre-clinical and clinical trials (<http://mpts101.org/mpt-database/mpts-topical-rings>; <http://mpts101.org/mpt-database/mpts-topical-gel>). Due to their potential to control multiple STIs, there is a great interest in development of novel MPTs. The MPTs that are currently under development employ 2 to 3 modalities (mainly drugs) aimed at preventing different viral infections [3].

Since ancient times, natural products have played a great role in the healthcare. Even today, natural phytochemicals (or the modified forms of the natural phytochemicals) are being used in the modern medicine [9]. This review aims to highlight that some of the commonly known natural phytochemicals (polyphenols) (Fig. 1) have potential in prevention and/or treatment of STVIs and can be employed for MPTs.

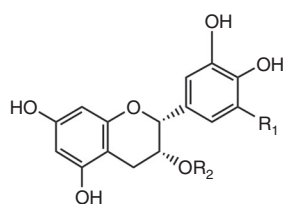
Natural polyphenols for prevention of (STVIs)

Due to excellent antioxidant properties, natural polyphenols have been a topic of medical research for several decades. Herein, we will describe potential of some important natural polyphenols against STVIs (Table 1).

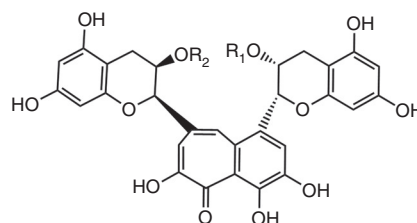
Epigallocatechin gallate

Epigallocatechin gallate (EGCG) is one of the main polyphenolic components of green tea (*Camellia sinensis*) [10]. EGCG belongs to 'catechins' class of the natural polyphenols. Catechins account for the 30–40% of the solid content in the green tea. Green tea mainly contains 4 different types of catechins viz. (–)-epicatechin (EC), (–)-epicatechin-3-gallate (ECG) (–)-epigallocatechin (EGC), (–)-epigallocatechin-3-gallate (EGCG) [10]. Among catechins, EGCG accounts for almost 59%, EGC accounts for around 19%, followed by ECG (13.6%) and EC, at 6.4% [10]. Studies suggest that presence of galloyl moiety is responsible for various physiological functions of EGCG including its activity against viruses such as HIV and HSV. EGCG is stable at the acidic pH of vagina and it has GRAS (generally regarded as safe) status as per US FDA [11].

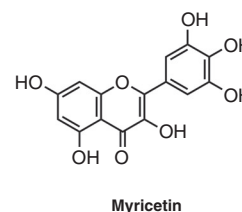
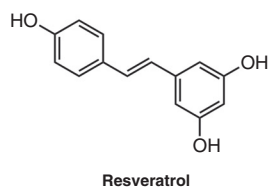
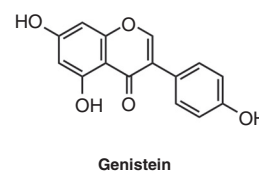
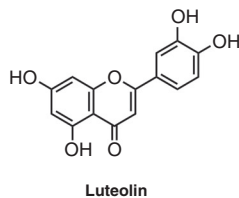
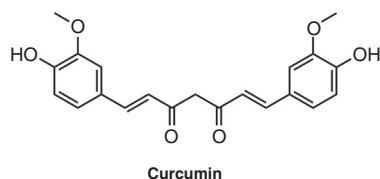
It has been established that semen discharge from a HIV-1 infected male is the primary reason for the sexual transmission



- $R_1 = H, R_2 = H ::$ Epicatechin
 $R_1 = H, R_2 = \text{galloyl} ::$ Epicatechin gallate (ECG)
 $R_1 = OH, R_2 = H ::$ Epigallocatechin
 $R_1 = OH, R_2 = \text{galloyl} ::$ Epigallocatechin gallate (EGCG)



- $R_1 = H, R_2 = H ::$ Theaflavin (TF₁)
 $R_1 = \text{galloyl}, R_2 = H ::$ Theaflavin monogallate (TF_{2A})
 $R_1 = H, R_2 = \text{galloyl} ::$ Epitheaflavin monogallate (TF_{2B})
 $R_1 = \text{galloyl}, R_2 = \text{galloyl} ::$ Theaflavin digallate (TF₃)



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FIGURE 1

Structure of some important natural polyphenols which have potential to become a modality for MPTs.

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