Antiviral potential of turmeric longa (Curcuma longa L.)

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SUMMARY

Long turmeric (Curcuma longa L.) and its biologically active substances curcuminoids have pleiotropic activity, including anti-inflammatory, antioxidant, antitumor, antibacterial and antiviral activity. Numerous studies have shown that the antiviral activity of extracts of turmeric rhizomes and curcuminoids has a wide range of biological and pharmacological properties against various viruses, such as influenza virus, hepatitis B and C viruses, human immunodeficiency virus, etc. The mechanisms of curcumin's antiviral action are either direct intervention in viral reproduction, or in suppression of cellular signaling pathways necessary for viral replication. This review summarizes the current data and prospects for the use of the antiviral activity of curcumin.

Key words: long turmeric, curcumin, antiviral effect, viruses.

RESUME

Curcuma longa L. and its compound curcuminoids have pleiotropic activity, including anti-inflammatory, anti-oxidant, anti-tumor, antimicrobial and antiviral activities. Numerous studies have shown that antiviral activities for rhizome extracts of C. longa and curcuminoids possesses a wide spectrum of biological and pharmacological properties against different viruses like the influenza virus, hepatitis B and C viruses, HIV etc. Mechanisms of antiviral activity of curcuminoids involve either a direct of interference of viral replication or suppression of cellular signaling pathways essential for viral replication. This review summarizes the current knowledge and future perspectives of the use of the antiviral effects of curcumin.

Keywords: curcuma, curcumin, anti-infective properties, viruses.

INTRODUCTION

Viruses (kingdom Virae) are strict intracellular parasites and are widelydistributed among vertebrates and invertebrates, plants, protozoa, fungi, bacteria, archaea [3]. Viral infections have existed throughout human history. Viruses are the etiological factor of about 90% of human infectious pathology. At least 300 known viruses belonging to 51 genera of 30 families are capable of causing pandemics (influenza A, smallpox, HIV infection, poliomyelitis), epidemics (Dengue fever, yellow fever, Ebola, Zika, Chikungunya, West Nile), epidemic outbreaks and sporadic diseases. The problem of antiviral therapy is of global importance. And the current situation with the COVID-19 pandemic caused by the SARS-CoV-2 coronavirus confirms this position. The population of our planet turned out to be defenseless from this new viral infection.

The absence or insignificant arsenal of prophylactic and therapeutic agents for many viral infections, the emergence of antiviral drug resistance, the high cost of some types of antiviral therapy necessitate the search for new antiviral agents, which is an extremely important and urgent task. Along with the search for new antiviral drugs among synthetic compounds, research is being carried out for antiviral agents of plant origin.

Biologically active substances (BAS) are contained in rapidly dividing plant cells (an evolutionary analogue of mammalian embryonic and stem cells) and have unique regulatory properties [4]. Various kinds of extracts from medicinal plant materials have a wide spectrum of pharmacological activity, including antiviral activity. Medicinal plants and biologically active substances from them are a constant source of new medicines [5]. For more than half a century of production (to date), half of all drugs in the United States were natural products or their derivatives directly related to them [51].

1. Turmeric and Curcuminoids

Plants as a rich source of phytochemicals with various biological activities, including antiviral ones, are of great interest for the search and creation of new antiviral drugs. Numerous studies have been carried out to study the antiviral potential of natural biologically active substances. One plant that has been extensively studied for this purpose is turmeric.

Turmeric (Curcuma longa L.) (syn.: Homemade turmeric (Curcuma domestica), turmeric) refers tofamily of ginger (Zingiberaceae) and is native to India and Southeast Asia. Many species of the genusCurcuma is cultivated as a spice and medicinal plant. The most widespread as a spice is long turmeric (Curcuma longa), dried root powder of whichknown as the spice turmeric [1]. Turmeric has been traditionally used for centuries and is still widely used in Ayurveda, siddhi medicine and traditional Chinese medicine [77].

The rhizomes of many types of turmeric contain essential oils, curcuminoids, sesquiterpenes, and steroids [53]. Curcuminoids include curcumin, dimethoxycurcumin, and bis-dimethoxycurcumin. They are the main BAS in turmeric. It is thanks to the curcuminoids that the turmeric root has its characteristic yellow color. Of the curcuminoids, curcumin is the main component of the yellow pigment and the main BAS.

Chemically, curcumin is diferuloylmethane, a diarylheptanoid belonging to the class of naturally occurring polyphenols. Its chemical structure was described already in 1910 as a symmetrical molecule of two phenolic rings connected by α, β-unsaturated carbonyl groups [45].

Curcumin has various therapeutic properties due to antioxidant, anti-inflammatory, antiseptic and anticarcinogenic activities [17].

Numerous studies on the antiviral potential of natural biologically active substances in turmeric have shown that curcumin has antiviral activity against various viruses, including hepatitis B and C viruses, influenza A viruses, human immunodeficiency virus, Zika virus, Chikungunya virus, herpes simplex virus types 1 and 2. human papillomavirus, etc. Several reviews are devoted to these studies [43, 47, 56].

The pleiotropic antiviral activity of curcumin is due to its ability to modulate numerous molecular targets that contribute to various cellular events, such as regulation of transcription and activation of cellular signaling pathways (inflammation and apoptosis) [30, 58].

Studies have shown that curcumin interacts with proteins such as DNA polymerase [71], focal adhesion kinase [37], thioredoxin reductase [21], protein kinase [60], lipoxygenase [68], and tubulin [24]. In addition to modulating cellular events, curcumin affects viral infection at all stages of the viral reproduction cycle, including viral adsorption [14] and genome replication [49, 66].

However, curcumin as a therapeutic agent has low bioavailability and is insoluble in water. The problem of overcoming the low bioavailability of curcumin is solved in different ways, which are described in the section "Bioavailability of curcumin".

2. ANTI-VIRAL ACTIVITY OF TUMBER AND CURCUMIN

Table 1 provides a summary of antivirus activityCurcuma longa and curcumin,as well as the possible mechanisms of their action underlying the inhibitory effects.

2.1. Curcumin inhibits human immunodeficiency virus

In the review by Yu.A. Smirnova et al. [6] provides general information about HIV infection, summarizes scientific data on the antiviral activity of biologically active substances in medicinal plants, including turmeric biologically active substances. These biologically active substances act directly at different stages of HIV reproduction or by activating the immune system.

Table 1

Antiviral activity of turmeric and curcumin

Viruses	Family	Mechanism of action	Links
Virus immunodeficiency human (HIV)	Retroviridae	Inhibitor of HIV-1 integrase	25, 26
Hiv	Retroviridae	Inhibition of HIV transcription and replication	49
Hiv	Retroviridae	Degradation of the viral protein TAT	eight
Hiv	Retroviridae	Inhibition of proteases	70
Hiv	Retroviridae	Inhibition of integrase and reverse transcriptase	63, 73
Influenza A virus	Orthomyxoviridae	Inhibition of virus adsorption	14, 54
Hepatitis B virus	Hepadnaviridae	Replication inhibition Circular cccDNA inhibitor	31, 33, 59, 74
Hepatitis C virus	Flaviviridae	Inhibition of virus entry	9, 15
Herpesvirus type 1	Herpesviridae	Inhibition of gene expression	36, 76
Herpesvirus type 2	Herpesviridae	Protecting mice from infection	12
Cytomegalovirus human	Herpesviridae	Early antigen expression (MEA) and UL83A	40, 41
Epstein-Barr virus	Herpesviridae	BZLF-1 lytic protein inhibitor	22, 28
Herpesvirus large cattle 1	Herpesviridae	Inhibition of virus entry	78
Coxsackie Virus B3	Picornaviridae	Inhibition of viral reproduction	66
Japanese virus encephalitis	Flaviviridae	Inhibition of virus entry	16, 55
Chikungunya virus	Togaviridae	Inhibition of virus adsorption on cells	50
Virus hemorrhagic ebola fever	Filoviridae	Interaction with the protein of the VP30 replicative complex	64, 69
Respiratory-syncytial virus	Pneumoviridae	Virucidal effect (virus inactivation)	52, 75
Enterovirus type 71	Picornaviridae	Inhibition of viral replication	29
Fever virus Rift valleys	Bunyaviridae	Inhibition of viral replication	50
Papilloma virus human	Papilomaviridae	Inhibition of gene expression	36
Fever virus Dengue	Flaviviridae	Inhibition of virus entry	16, 55
Zika virus	Flaviviridae	Inhibition of virus adsorption on cells	48

Several studies have shown that curcumin has anti-HIV activity by binding directly to viral proteins. In 1993 Z. Sui et al. [70] reported inhibition of HIV-1 and HIV-2 proteases by curcumin. The authors found that curcumin binds to several sites of the enzyme and suppresses its activity. Model studies have confirmed that curcumin is well suited to the active site of the protease [73].

In addition to inhibiting protease, curcumin has been found to be a potent inhibitor of HIV integrase. It was shown that curcumin binds acid residues in the domain of the catalytic nucleus of integrase [44].

Another HIV protein that curcumin binds to is the trans-activator of transcription (TAT), a regulator of viral transcription. Upon infection, TAT is secreted and absorbed by uninfected cells, which promotes the growth of HIV-induced tumors and apoptosis of T cells [13]. Inhibition of TAT prevents efficient transcription of viral genes, as well as the development of infection. It was shown that in TAT-transduced HEK293T cells the level of TAT protein

decreases when incubated with curcumin in a dose-dependent manner. Curcumin causes proteasomal degradation of TAT [8]. In addition, it was reported that curcumin inhibits HIV proliferation by inhibiting TAT acetylation in SupT1 cells [10], effectively inhibits TAT-induced transactivation of long terminal repeats of the HIV-1 genome in HeLa cells [11].

Curcumin binds to the reverse transcriptase enzyme, inhibits the reverse transcription of HIV RNA and thereby suppresses the reproduction of the virus [63].

Recently, new derivatives of curcumin have been developed against HIV - drugs with increased bioavailability and stability [34, 39, 65]. Curcumin pretreatment of human genital epithelial cells has been shown to block HIV-mediated cytokine induction [22]. Clinical trials will show if these new curcumin variants are effective. Attempts to use curcumin as an anti-HIV drug continue.

2.2. Curcumin inhibits hepatitis viruses

Aqueous turmeric extracts have been found to inhibit the production of hepatitis B virus (HBV) and inhibit the development of hepatocellular carcinoma [31, 33]. As a result of these studies, the assumption arose about the antiviral effect of curcumin against hepatitis viruses. It was shown that curcumin actually inhibits the expression and replication of HBV genes [59]. Curcumin has also been shown to reduce the amount of covalently closed circular HBV DNA (cccDNA)in vitro [74].

Curcumin has also been found to be effective against the hepatitis C virus (HCV). Curcumin inhibits the infection of all HCV genotypes in hepatoma cells and primary human hepatocytes [9]. The authors found that curcumin, especially its α, β-unsaturated ketones, affect the fluidity of the viral membrane and thereby prevent its binding and fusion with the plasma membrane of cells, as well as the intercellular spread of the virus. It has also been shown that curcumin inhibits HCV replication [15, 32]. Curcumin acts synergistically with clinically used HCV inhibitors such as α-interferon, boceprevir, and cyclosporin [9, 32].

2.3. Curcumin inhibits influenza A virus

When studying the action of curcumin on various subtypes of influenza A virus (HAV) in vitro wasit was found that curcumin inhibits the adsorption and penetration of the virus into cells, the replication of viral RNA and the production of virions [15, 18, 27]. It has been shown that curcumin prevents the binding of the viral glycoprotein hemagglutinin to the corresponding cellular receptor [15, 54]. Recent researchhave shown in vivo that curcumin prevents the development of pneumonia, caused by HAV in mice, and increases the immune response to HAV in turkeys [27, 72]. Thus, it is suggested that curcumin can be used to fight the flu.

2.4. Curcumin inhibits herpes viruses

Several studies have found that curcumin reduces the infectivity of herpes simplex viruses type 1 (HSV-1) and type 2 (HSV-2) in vitro and in vivo [12, 36, 76]. It was shown that curcumin significantly reduces the expression of early viral HSV-1 genes, which is due to a decrease in the use of RNA polymerase II to the promoters of these genes [36]. Pretreatment of human genital epithelial cells with curcumin reduced the release of HSV-2 from these cells [22].

Curcumin also reduces the expression of early genes of human cytomegalovirus [41]. It is assumed that curcumin interacts with the cellular heat shock protein 90, which is necessary for the expression of the early gene of this virus [42].

2.5. Curcumin inhibits human papillomaviruses

The effect of curcumin on human papillomavirus (HPV) infections and on the growth of HPV-associated tumors has been extensively studied [62]. It was assumed that curcumin binds to the site of interaction of the p53 protein with the viral gene E6, preventing their interaction [42]. Researchin vitro showed that curcumin inhibited the expression of genes E6 and E7 [46].

Topical curcumin-containing creams and capsules have been developed to prevent or treat HPV infections, thus circumventing the problem of curcumin's low bioavailability. These creams suppressed the growth of HPV-positive cells and cervical tumors and even induced apoptosis of cervical cancer cells.in vitro and in vivo [17]. Clinical studies have confirmed that topical cervical application of curcumin, which is not toxic

action, increased the rate of HPV clearance [23]. Thus, bioavailable curcumin preparations have the potential to be used to prevent sexually transmitted HPV infections or to treat cervical dysplasia caused by the virus.

2.6. Curcumin inhibits respiratory syncytial virus

Curcumin blocks the reproduction of respiratory syncytial virus (RSV) and its release from human epithelial cells. However, it does not affect RSV in human lung cells [52]. Recently, two types of silver nanopreparations loaded with curcumin have been developed, which have shown good bioavailability and effective action on RSV reproduction in experiments.in vitro [75]. Nanoparticles appear to directly bind RSV, inhibiting virus adsorption, resulting in a significant reduction in infected cells. Further research is needed to clarify whether the use of curcumin-loaded nanoparticles is feasible and effectivein vivo.

2.7. Curcumin inhibits arboviruses

For most arboviruses, there are no vaccines and no specific prophylactic or drug treatment. Therefore, the search for remedies against arbovirus infections is especially relevant.

Recently, it was shown that curcumin blocks the penetration of the Chikungunya virus by inhibiting its adsorption on host cells [48]. Incubation of cells with curcumin by the same mechanism significantly reduced their infection with Dengue virus, Japanese encephalitis virus, and Zika virus [16, 48]. In addition to inhibiting the penetration of the virus into cells, treatment with curcumin of cells infected with the Dengue virus or Japanese encephalitis virus resulted in a decrease in the production of virions [20, 55].

Reproduction of Rift Valley Fever virus has also been shown to be inhibited by curcumin [50]. This data was obtained asin vitro and in vivo. Survival of mice treatedcurcumin was 60% compared to untreated animals.

3. Bioavailability of curcumin

Numerous studies have shown the effectiveness of curcumin against various viral infections. However, a limitation of its use is its low bioavailability; therefore, the development of effective dosage forms of curcumin in order to increase its bioavailability is an important task. In Ayurveda, biologically active substances from plants have long been used as enhancers of the action of turmeric: pepper (Piper longum Linn.), Common ginger (Zingiber officinale Rosc.) And smooth licorice (Glycyrrhiza glabra Linn.).

Scientists have proposed various methods to improve the bioavailability of curcumin. Currently, new formulations of curcumin have been developed based on biocompatible organic substances and delivery systems such as liposomes, polyethylene glycols, biopolymers, cellulose, corn oil, hydrogels, etc. [35, 38]. In the review by N.A. Solovyova et al. [7] describes in detail the existing methods of overcoming the bioavailability of curcumin. To increase the bioavailability of curcumin, bioavailability enhancers (enhancer) are used - genetic regulatory elements that can block the metabolism of curcumin. It is included in the composition of nanoparticles, liposomes, micelles and phospholipid complexes, which provide better permeability and resistance to metabolic processes. Many pharmaceutical companies are trying to develop a modified version of turmeric with maximum absorption. Clinical trials are underway to measure plasma levels of turmeric in patients. Japanese scientists have partly solved this problem by reducing the particle size of turmeric to nano-size. Nanoparticles do not precipitate in a liquid for a long time. Such a preparation of turmeric is called teracurmin [61]. Mesoporous silicon nanoparticles are used to create nanosystems to improve the bioavailability of drugs poorly soluble in water. It was shown that curcumin binds covalently to silicon nanoparticles [57]. Gold nanoparticles are used for drug delivery, cancer diagnostics and treatment, and in other areas of biology and medicine [67]. Various methods are used to obtain gold nanoparticles: dispersive (based on the dispersion of metals) and condensation (reduced metal nanoparticles are formed from the ions of the corresponding salts) [2]. Silver nanoparticles are also used [65, 75]. Increased bioavailability of curcumin in the near future,

will probably allow it to be used as a herbal preparation for the treatment of human viral infections.

CONCLUSION

Numerous studies in vitro and in vivo have shown that curcumin is active againstvarious viruses, even highly pathogenic, new and drug-resistant. The mechanism of anti-viral action of curcumin is complex and differs from body to body. The broad spectrum antiviral activity of curcumin makes it a promising antiviral drug candidate. However, the poor solubility of curcumin, its low bioavailability and rapid metabolism have not shown a noticeable therapeutic effect in many clinical trials. However, topical oral or cervical administration of curcumin has been shown to be effective against human viruses. Formulating curcumin in various nanocarrier systems can help overcome the barriers to systemic use of curcumin.

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