Journal of Functional Foods 40 (2018) 692–699

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

Antiviral potential of curcumin

Dony Mathew, Wei-Li Hsu*

Graduate Institute of Microbiology and Public Health, College of Veterinary Medicine, National Chung Hsing University, 145 Xingda Road, Taichung 40227, Taiwan

ARTICLE INFO

Keywords:
Curcumin
Antiviral
PI3K/Akt
NF-κB
Molecular mechanisms

ABSTRACT

The use of synthetic drugs has increased over the recent years, but plant-based drugs are more suitable in terms of least side effects. Since ancient times mankind has been dependent on plants for the treatment of various ailments, among them widely used is curcumin, the principal polyphenol extracted from turmeric. Their medicinal and useful properties are mentioned in Indian Veda's and Chinese medicine. Curcumin has been studied extensively for its pleiotropic activity, including anti-inflammatory, anti-oxidant and anti-tumor activity. Accumulated evidence indicated curcumin plays an inhibitory role against infection of numerous viruses. These mechanisms involve either a direct interference of viral replication machinery or suppression of cellular signaling pathways essential for viral replication, such as PI3K/Akt, NF-κB. This review summarizes the current state of knowledge with a focus on the anti-viral effect of curcumin, and their possible molecular mechanisms.

1. Introduction

Curcumin is the major active compound in the rhizome of turmeric (*Curcuma longa*). Curcuminoids mainly comprise of curcumin I (77%), curcumin II (17%), curcumin III (3%) and cyclocurcumin (Lee et al., 2013), isolated by Vogel and Pelletier (1815) and its chemical structure and synthesis confirmed by Lampe and Miłobędzka (1913). Among the four curcuminoids found in turmeric, curcumin is known to be the most active phytochemical (Zhou, Beevers, & Huang, 2011).

Curcumin has been used extensively in Ayurveda, Siddha medicine and traditional Chinese medicine (Zhou et al., 2016) for centuries, as it has a variety of therapeutic properties including antioxidant, analgesic, anti-inflammatory, antiseptic activity, and anticarcinogenic activity (Çıkrıkçı, Mozioglu, & Yılmaz, 2008). It is generally recognized as safe (GRAS) by Food and Drug Administration (FDA). A healthy dose up to 12 g/day of curcumin was known to be safe for human consumption during the clinical trials without eliciting side effects (Gupta, Patchva, et al., 2013). A Phase I trial of curcumin in patients with high risk or premalignant lesion concluded that curcumin even at higher doses does not appear to be toxic (Cheng et al., 2001), while various clinical trials conducted in humans for various cancers and other health conditions have provided with a promising results suggesting low toxicity of curcumin (Dhillon et al., 2008; Lal et al., 1999; Lao et al., 2006; Satoskar, Shah, & Shenoy, 1986; Sharma et al., 2004). Besides all the beneficial role of curcumin, some studies are inconsistent and don't paint a rosy picture. It has been indicated high concentrations of curcumin triggers nuclear DNA fragmentation in lung cancer cell lines (Ting et al., 2015) as well as mitochondrial DNA damage in human hepatoma G2 Cells (Cao, Jia, Zhou, Liu, & Zhong, 2006), while treatment of curcumin at low doses had no effect on DNA integrity, indicating curcumin-induced DNA damage represents a dose-dependent manner. In addition, some clinical trials have shown that in order to accomplish killing of cancer cells, high concentration of curcumin is required (Syng-Ai, Kumari, & Khar, 2004), due to the poor availability of curcumin that leads to the low plasma concentration. To circumvent the drawbacks of limited systemic bioavailability and rapid metabolism, efforts were made to developing novel synthetic curcumin formulations and drug delivery systems, etc., and some of which have achieved promising results.

The role of curcumin as an anticancer agent has been studied extensively throughout the years. The underlying mechanisms of these effects appear to be diverse and it likely owns to the modulation of cell survival. Curcumin has been known to interfere with various biochemical pathways involved in cancer cell proliferation and survival. The molecular targets modulated by curcumin include, but is not limited, to activator protein (AP)-1 (Arnott et al., 2002), nuclear factor Kappa B (NF-κB) (Sethi & Tergaonkar, 2009), signal transducer and

Abbreviations: BEC, human buccal epithelial cells; CVB3, , coxsackievirus B3; DNV-2, dengue virus type 2; EV71, enterovirus; FIPV, feline infectious peritonitis virus; FHV, flock house virus; HN, haemagglutinin-neuraminidase; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; HSC-71, heat shock cognate; HO-1, heme oxygenase-1; HuNoV, human norovirus; IAV, influenza type A virus; JEV, Japanese encephalitis virus; LOX, lipoxygenase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphatidylinositol-3-kinase; PK, protein kinase; PTM, post-translational modifications; RSV, respiratory syncytial virus; RVFV, rift valley fever virus; SOCS, suppressor of cytokine signaling; UPS, ubiquitinproteasome system; VSV, vesicular stomatitis virus; VHSV, viral hemorrhagic septicemia virus; RTase, reverse transcriptase

* Corresponding author.
E-mail address: wlhsu@dragon.nchu.edu.tw (W.-L. Hsu).

https://doi.org/10.1016/j.jff.2017.12.017
Received 12 September 2017; Received in revised form 8 December 2017; Accepted 8 December 2017

activator of transcription (STAT) (Taub, 2003), tumor necrosis factor-alpha (TNF-α) (Aggarwal, Gupta, & Kim, 2012), interleukins, Cyclin D1 (Mukhopadhyay et al., 2002), p53 (Dey, Tergaonkar, & Lane, 2008), and growth factor induced signaling cascades (Starok et al., 2015). By suppression of NF-κB and STAT3 activation, curcumin regulates expression of many genes involved in growth regulation, inflammation, carcinogenesis and apoptosis, which play key roles in cancer development and progression (Bowman, Garcia, Turkson, & Jove, 2000; Gupta, Sundaram, Reuter, & Aggarwal, 2010; Kasdagly, Radhakrishnan, Reddivari, Veeramachaneni, & Vanamala, 2014; Sen & Baltimore, 1986). STAT3 is one of the major mediators of carcinogenesis and their activation has been involved in the induction of resistance to apoptosis, presumably through the expression of Bcl-xL and cyclin D1 (Catlett-Falcone et al., 1999; Gamero, Young, & Wiltrout, 2004). The failure of cells to undergo apoptosis might result in diseases like autoimmune disease, neurological disorder, cardiovascular disorders and cancer (Favaloro, Allocati, Graziano, Di Ilio, & De Laurenzi, 2012).

Several studies were conducted with curcumin against various forms of cancers like colorectal cancer (Cruz-Correa et al., 2006; He et al., 2011), multiple myeloma (Golombick, Diamond, Badmaev, Manoharan, & Ramakrishna, 2009; Vadhan-Raj et al., 2007), pancreatic cancer (Dhillon et al., 2008; Kanai et al., 2011), chronic myeloid leukaemia (Ghalaut et al., 2012), prostate cancer (Ide et al., 2010; Kim et al., 2011) and breast cancer (Bayet-Robert et al., 2010), and were deemed to have a potential role in negative regulation of tumor initiation, progression and metastasis.

In addition to anti-carcinogenic activity, curcumin appears to be a potent agent against various microbes. It restraints growth of a plethora of bacteria like *S. epidermis*, *Klebsiella pneumoniae*, *E. coli*, *Bacillus subtilis*, *Staphylococcus aureus* (Ungphaiboon et al., 2005) (Niamsa & Sittiwet, 2009), and pathogenic bacteria's found in shrimp, mice and chicken like some *Vibrio*, *Bacillus*, *Salmonella*, *Staphylococcus* and *Helicobacter pylori* species (De et al., 2009; Lawhavinit, Kongkathip, Kongkathip, & Kasetsart, 2010). The bactericidal role of curcumin was based on the fact, that it causes the leakage of bacterial membrane (Tyagi, Singh, Kumari, Kumari, & Mukhopadhyay, 2015), while a similar mechanism was also described against fungi. Curcumin exerts an *in vitro* inhibitory effect on the adhesion of *Candida* species to human buccal epithelial cells (BEC) (Martins et al., 2009) as a result it forms an electrostatic or hydrophobic interaction with the fungal cell membrane and cell wall causing membrane disruption (Kumar et al., 2014; Peter, Shirtliff, & Jabra-Rizk, 2010).

Curcumin's antiviral effects were observed against viruses like Parainfluenza virus type 3 (PIV-3), Feline infectious peritonitis virus (FIPV), vesicular stomatitis virus (VSV), herpes simplex virus (HSV), flock house virus (FHV) and respiratory syncytial virus (RSV) (Moghadamtousi et al., 2014).

The hallmark of this review is to discuss current understanding of the anti-viral aspects of curcumin and their underlying action mechanisms.

2. An overview of curcumin as an anti-viral drug

Combating viral diseases, especially those caused by the emerging viruses or variants have always been a challenge. Viral RNA polymerase possesses a high mutation rate (Elena & Sanjuan, 2005), owing to the lack of the proofreading capability, and evidently this trait helps viral pathogens with RNA genome to evolve resistance against pre-existing antiviral drugs. However, cost, time and effort to develop an antiviral drug takes its toll (Bolken & Hruby, 2008), as when a new mutated variant of a RNA viral pathogens emerges. Furthermore, long-term administration of antiviral drugs is known to elicit side effect like nausea, vomiting, mitochondriaxicity and insomnia depending upon the antiviral drug (Carr, 2003; Dolin et al., 1982; Fontana, 2009; Hima Bindu & Naga Anusha, 2011; Reust, 2011; Treanor et al., 2000; Winquist, Fukuda, Bridges, & Cox, 1999).

Curcumin's pleiotropic activities against virus's emanate from its ability to modulate numerous molecular targets that contribute to various cellular events, such as transcription regulation, and the activation of cellular signaling pathways such as inflammation, and apoptosis (Joe, Vijaykumar, & Lokesh, 2004; Ravindran, Prasad, & Aggarwal, 2009) likely via intermolecular interactions. Previous researches concluded that curcumin interacts directly with almost 30 proteins, such as, DNA polymerase (Takeuchi et al., 2006), focal adhesion kinase (FAK) (Leu, Su, Chuang, & Maa, 2003), thioredoxin reductase (Fang, Lu, & Holmgren, 2005), protein kinase (PK) (Reddy & Aggarwal, 1994), lipoxygenase (LOX) (Skrzypczak-Jankun, Zhou, McCabe, Selman, & Jankun, 2003), and tubulin (Gupta, Bharne, Rathinasamy, Naik, & Panda, 2006). Moreover, in addition to modulating cellular events, curcumin limits viral infection by interfering with critical steps in their replication cycle, including but not limited to, viral attachment (Chen et al., 2010a, 2010b), and genome replication (Narayan et al., 2011; Si et al., 2007).

Curcumin's role as an antiviral agent has been studied thoroughly in the case of viruses like HIV, Herpes simplex virus (HSV), Hepatitis viruses, influenza type A virus (IAV), and Ebola virus. Since curcumin's positive effects outweigh the negative effects and their role in targeting various cellular pathways, further inhibiting the growth and replication of viruses make it a candidate for an anti-viral drug.

3. Curcumin targets critical steps of virus replication cycle

As a single unit, a virus cannot equip all the enzymes required for their replication. They commandeer cellular machinery for their efficient reproduction and metabolic processes. However, an antiviral agent must stop the viral growth in infected cells, without affecting surrounding normal cells. Hence, specific processes of the virus replicative cycle, which include attachment/penetration, uncoating, genome replication, gene expression, assembly and release, have been attractive targets for chemotherapeutic intervention.

One of the bio-functions of curcumin is revoking the infection of viruses, by targeting the viral entry, or solely attacking the viral components essential for viral replication (Fig. 1). Correspondingly, curcumin's antiviral activity through mechanisms involving interference with viral replication step(s) has been summarized in Table 1 and described in the following sessions.

3.1. Viral attachment/penetration

Attachment is the initial event that brings viruses to the cell membrane surface. As previously indicated when curcumin was added to cells prior to or upon infection, it blocks the infectivity of a series of enveloped viruses, including members of poxvirus, flavivirus, herpesvirus, and orthomyxovirus, while plaque formation ability of the non-enveloped enterovirus 71 (EV71) was not affected (Chen et al., 2013). In addition, curcumin incubated directly with viruses abrogates the function of viral envelope proteins, i.e. haemagglutinin-neuraminidase (HN) protein of New Castle disease virus and haemagglutinin (HA) protein of IAV (Chen et al., 2013). Similarly, a recent study indicated curcumin inhibits two arthropod-borne viruses zika and chikungunya virus infections by blocking binding of viruses on the cell surface (Mounce, Cesaro, Carrau, Vallet, & Vignuzzi, 2017).

A variety of studies have identified curcumin as a membrane-modulating agent; in short, the association of curcumin on lipid bilayer causes a non-linear membrane thinning and weakens the elasticity of the membrane (Hung et al., 2008; Ingolfsson et al., 2014). In MDBK cells, curcumin increased lipid raft formation, which affected the bovine herpesvirus type 1 entry process and indeed reducing their overall viral yield in a dose-dependent manner (Zhu et al., 2015). Consistently, the entry of all major genotypes of hepatitis C virus (HCV) was affected by curcumin. In membrane fluidity experiments the impairment of viral entry involved two events, which are viral binding and membrane