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Review Article

Antiviral properties of chalcones and their synthetic derivatives: a mini review

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Abstract

Chalcones (natural or synthetic derivatives) are aromatic ketones possessing a central backbone that form a core for variety important compounds with different substitutions. Recent scientific advances show that chalcones exhibit different bio-medical activities, including antiviral, which is related to the variety substitutions. This review provides general information on the origin, sources, virucidal and direct antiviral properties of chalcones *in vitro*, as well as a brief overview of the possible application and molecular modes of action of these compounds. The antiviral effect of chalcones probably results from the disruption of the different stage of viral replication cycle, inhibition of viral or cell enzymes, induction of apoptosis and others. Structural requirements for antiviral activities vary according to the mechanisms of action. Based on the published information, it could be considered that synthetic chalcones are very perspective antiviral candidates and deserve further studies for elucidating of their pharmacological potential.

Keywords

antiviral effect, chalcones, *in vitro*, synthetic derivatives

1. Phytochemicals and their application in the "world of viruses"

Medicinal plants represent the main source of bioactive compounds and secondary metabolites, such as phenolic, nitrogen and sulfur compounds, carotenoids, terpenoids, alkaloids, anthocyanins and other (Manach et al. 2004; Bucar et al. 2013; Harvey et al. 2015; Fierascu et al. 2020). Phytochemicals possess great structural diversity, for instant the majority of them are heterocyclic, although some are aliphatic (noncyclic) with different substituents in the main backbone chain (Newman and Cragg 2007; Lafay and Izquierdo 2008). These substances have attracted the attention of scientist centuries because for their diverse bio-pharmacological activities and medicinal properties (Hartmann 2007; Savoia 2012; Wink 2012; Pusztahelyi et al. 2015; Fridlender et al. 2015; Kapoor et al. 2017; Bulliyya 2017). Recently, it is clearly known that they play a crucial role for preventing against different types of diseases and promoting human health (Hamburger and Hostettmann 1991; Pretorius 2003; Dai and Mumper 2010).

In traditional medicine, large number of candidate substances such as phytochemicals and their synthetic

derivatives were found to be useful in the treatment and prevention of some diseases with viral origin (Abad et al. 2000; Novakova et al. 2018; Dhama et al. 2018; Akram et al. 2018). Alarmingly, the number of patients, regardless of gender, age and geographical location, diagnosed with viral infections is increasing dramatically every year. Some of these viruses that attack humans and animals are very aggressive with high infective potential such as Ebola, influenza, SARS (severe acute respiratory syndrome), COVID-19 (severe acute respiratory syndrome coronavirus 2), AIDS (acquired immunodeficiency syndrome) and other (Feldmann et al. 2003, 2012; Benvenuto et al. 2020).

2. Viral infection control and therapy

Viruses are obligate intracellular parasites, which contain either RNA or DNA, and some of them could be surround by a lipid-containing envelope. Consequently, viruses have adapted to all life organisms and conditions resulting in different diseases ranging from self-limiting to pandemics (Wagner and Hewlett 1999). Viruses have numerous invasion strategies and for their replication use the normal cellular metabolic pathways. This strategy makes it difficult to find a specific treatment and to attack the virion directly, or some steps of its replication, without to make adverse effects on the host-cells (Wagner and Hewlett 1999). Moreover, the major difficulty in developing of specific and targeted therapy is due to viral variations (He et al. 2009; Haagmans et al. 2009). Ninety antiviral drugs available today treat some viruses, included HIV (human immunodeficiency virus), HBV (hepatitis B virus), HCV (hepatitis C virus), HSV (herpes simplex virus), VZV (varicella zoster virus), influenza virus and HCMV (human cytomegalovirus) (Gilks et al. 2006; Wilson et al. 2009; Ahmed 2011; Vigano et al. 2012). Currently, there is no approved specific therapy in preventing or treating the majority of viral infection, as well as safety and efficacy vaccine against all types of viruses (Hewson 2000; Rollinger and Schmidtke 2011; Small and Ertl 2011; Liu et al. 2015). However, systemic application of antivirals often possesses limited efficacy, serious side effects and led to development of resistance (Piret and Boivin 2011; Kristen et al. 2016; Aves et al. 2018). Based on that, phytochemicals and their synthetic derivatives are very promising and may be a proper alternative for treating and preventing these medical problems (Abad et al. 2000; Naithani et al. 2008; Novakova et al. 2018). At present, it is necessary to highlighting the possibility and challenges of applied strategies for the delivery of these biologically active substances to the right target in the host-cells and to overcoming the multiple biological barriers (Ben-Shabat et al. 2020; Watkins et al. 2015). A wide variety of active antiviral phytochemicals and their derivatives have been isolated, purified and investigated recently, including chalcones, which belongs to the flavonoids family (Dhar 1981; Gaonkar and Vignesh 2017). They are also intermediates in the synthesis of flavones (Chavan et al. 2016).

3. An overview of chalcones

The term "chalcones" have given from Stanisław Kostanecki and Josef Tamboror, who first perfomed the pilot synthesis of these coloring compounds in laboratory conditions (Rayees Ahmed et al. 2011). Naturally, chalcones are abundant in fruits, vegetables, tea, spices, ferns, and are often responsible for the yellow pigmentation in some plant species such as *Glycyrrhiza*, *Angelica*, *Coreopsis*, *Asteraceae*, *Ruscus*, *Piper*, which have been used in Asia, Africa and South America as medicine from the centuries (Rayees et al. 2011; Singh et al. 2014; Chavan et al. 2016). Pure chalcones have been an area of great interest and extensively studied for their pharmaceutical properties in recent years. Several chalcone-based substances were approved as a therapeutics in clinical practice. One of them is metochalcone ((1-(2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one), which use as a choleretic drug, the others sofalcone, (2- [5- [(3-methyl-2-buten-1-yl) oxy] -2- [3- [4- [(3-methyl-2-buten-1-yl)oxy] phenyl] -1-oxo-2-propen-1-yl] phenoxy] acetic acid) was previously used as an antiulcer and mucoprotective drug (Opletalova et al. 2000; Batovska and Todorova 2010). Clinical trials have shown that these compounds are not toxic, reached reasonable plasma concentration and are well tolerated.

Structurally, chalcones are aromatic compounds (1,3-diphenyl-2-propene-1-one), in which two aromatic rings (ring A and B), forms the central core and are linked by a three carbon α,β-unsaturated keton system (Rayees Ahmed et al. 2011; Zhou and Xing 2015). The most of the natural chalcones are polyhydroxylated in the aryl rings (Dimmock at al. 1999; Zhuang et al. 2017). Since the chalcone back bone is found to be very potent as intermediate for the preparation of substances with clinical potentials against various diseases. This has lead to the need for synthesizing chalcone derivatives, which possess different useful pharmacological activities, such as antimicrobial, antiviral, antifungal, anti-oxidant, antitumor, anti-inflammatory, antiulcerative, antiparasitic, antimalarial, immunomodulatory, antihyperglycemic, antiproliferative and others (Haraguchi et al. 2002; Wang et al. 2004; Go et al. 2005, Kumar et al. 2013; Matos et al. 2015; Karthikeyan et al. 2015; Caamal-Fuentes et al. 2015, Funakoshi et al. 2015). Chalcones are synthesized by two reactions: Claisen-Schmidt condensation and base-catalyzed aldol condensation between appropriately substituted aldehydes and ketones or acid catalyzed followed by dehydration (Claisen and Claparede 1881; Palaniandavar and Natarajan 1980; Morrison and Boyd 2004; Singh et al. 2014). The chalcones are characterized by an extensive structural diversity (Zhuang et al. 2017). The synthetically derived chalcones may also contain one or more aryl substituents, which contain halogens, alkyl, amino, nitro,

acetamido and carboxyl groups (Singh et al.2014; Zhuang et al. 2017). Actually, many chalcons and their synthetic analogs demonstrate broad spectrum of biological activities, which are highly appreciated in many areas of today's life such as medicine for the treatment of cancer, cardiovascular diseases, viral and parasitic infections, food industry as a food additives, in agriculture as a plant growth regulator and to control weeds and unwanted pests (Duke et al. 2000; Kang et al. 2004; Ni et al. 2004; Lee et al. 2004; Shen Jeu et al. 2005). Some chalcone derivatives have also abilities to inhibit several important enzymes in cells, such as xanthine oxidase, aldose reductase, epoxide hydrolase, protein tyrosine kinase and quinone reductase (Sogawa et al. 1994; Iwata et al. 1999; Miranda et al. 2000; Yang et al. 2001; Nerya et al. 2004). However, much of the pharmacological potential of chalcones is still not utilized and not clearly understood. For that reason, they are of great interest amongst the scientists.

The purpose of this mini review is to provide an overview especially of the in vitro and in vivo antiviral activities of naturally occurring and synthetic chalcones and to highlights their efficacy against some viruses, potential mechanism of action and relevant structure-activity relationships.

4. Activities of chalcones and their synthetic derivatives against selected viruses

Pure chalcones and their synthetic analogs have not been intensively studied for their potency as antivirals inhibitors. Therefore further research on their biosynthesis, mechanisms of the antiviral therapeutic effect and the development of successful target-drug delivery systems are of interest of many research groups worldwide. According to the published scientific literature, the antiviral properties of a number of chalcones have been studied on some plant and human viruses. However, experimental data show that the various antiviral activities of the studied chalcones depend on their specific substitution patterns (Table 1). *Antiviral effect of chalcones against some plant viruses*

Several numbers of studies have been done on the anti-infective effects of synthetic chalcones derivatives against the tobacco mosaic virus (TMV). This virus infects a wide range of plants, especially tobacco, vegetable and other members of the *Solanaceae* family and causes uncontrolled crop loss Bos (2000). Dong et al. 2017 have synthesized a series of novel chalcone derivatives containing the 1,1-dichloropropene moiety and studied them for anti-infective activity against TMV. The experimental data showed that the most of the tested chalcone derivatives exhibited moderate to good inactivation effect against TMV at 500 μg/mL except one that achieved a stronger effect *in vivo* at EC_{50} of 45.6 μg/mL (effective concentration 50%). The latter was similar to that of the common antiviral drug ningnanmycin (46.9 μg/mL) but higher as compared to that of ribavirin (145.1 μg/mL). In addition, fluorescence spectroscopy and the microscale thermophoresis (MST) showed that one of the tested compound strongly interacted with the TMV coat protein, but the mechanism of inactivation was not clear (Dong et al. 2017).

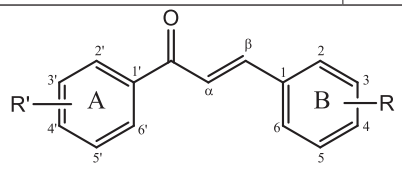
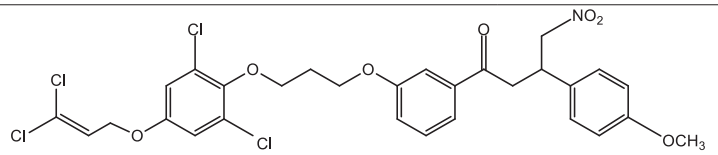
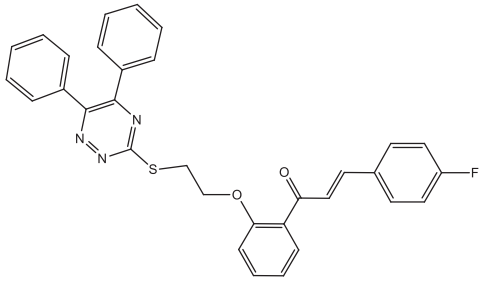
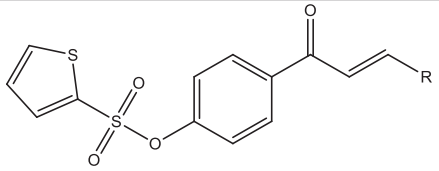
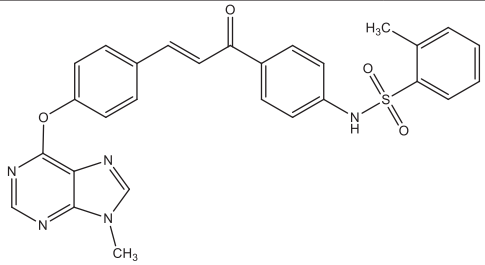
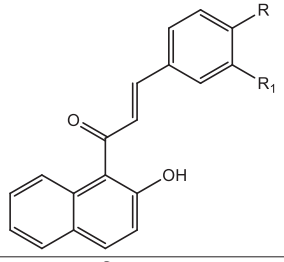
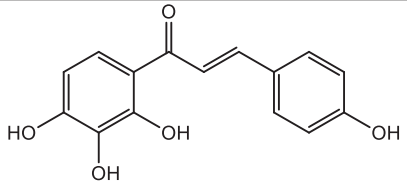
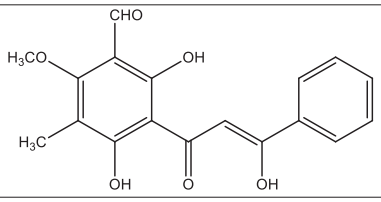
In addition, series of novel chalcone derivatives containing 1,2,4-triazine moiety were synthesized by Tang et al. (2009) for activity against TMV infection. Antiviral assays revealed that most of them possessed a curative, protective and inactivation potential against the virus at a concentration of 500 μg/mL^{-1} *in vivo*. The obtained results demonstrated notably that 1,2,4-triazine scaffold showed a better anti-TMV activity than that of ningnanmycin. Only one compound of the set had a significant protective effect with EC_{50} = 79.4 mg/mL^{-1} and dissociation constant (*K*d) value of 0.275 ± 0.160 μmol/L^{-1} to the TMV coat protein (TMV-CP). Molecular docking studies with TMV-CP showed that the compound was embedded well in the pocket between the two subunits of TMV-CP.

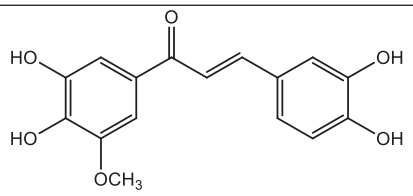
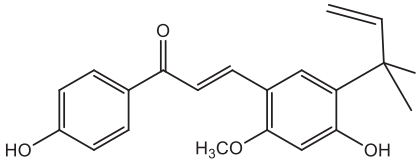
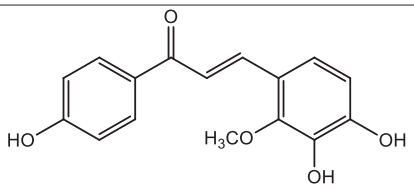
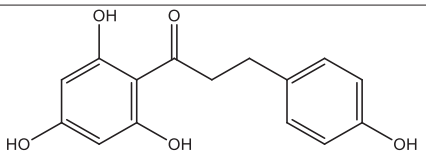
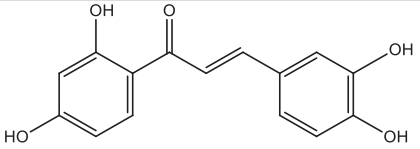
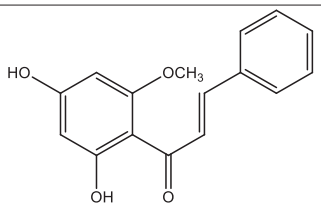
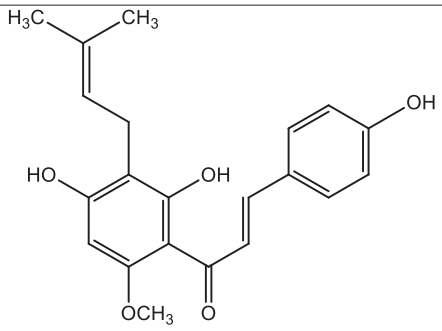
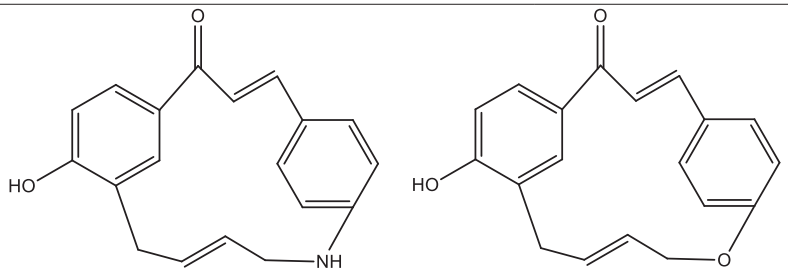
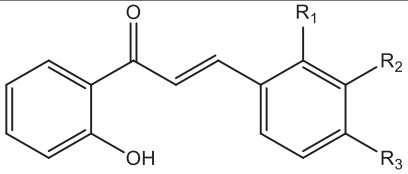
Other promising chalcone derivatives, containing a thiophene sulfonate group were synthesized and their antiviral efficacy against TMV was evaluated *in vivo* (Guo et al. 2019). Six compounds among them showed excellent curative activities against TMB. Microscale thermophoresis (MST) techniques for the biophysical analysis of interactions between biomolecules showed that the binding capacity of two of the chalcone derivatives to TMV-CP were better than that of the commercial ningnanmycin. It can be indicated from these results that some thiophene sulfonate chalcone derivatives could be further investigated in the area of the pesticide science as potential antiviral agents.

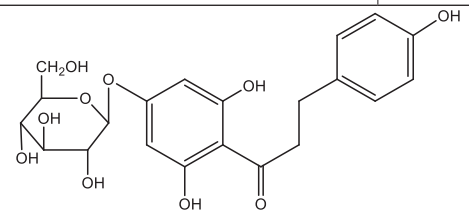
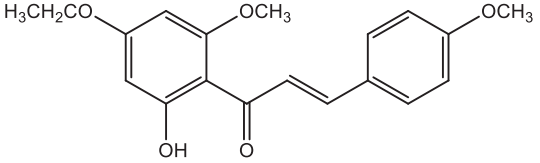
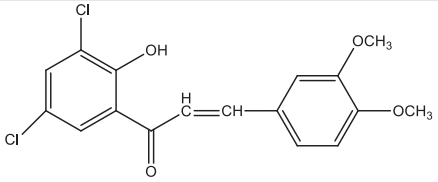
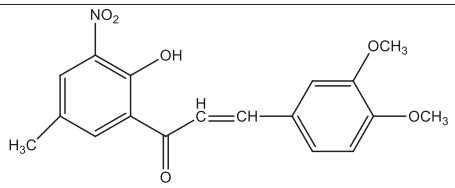
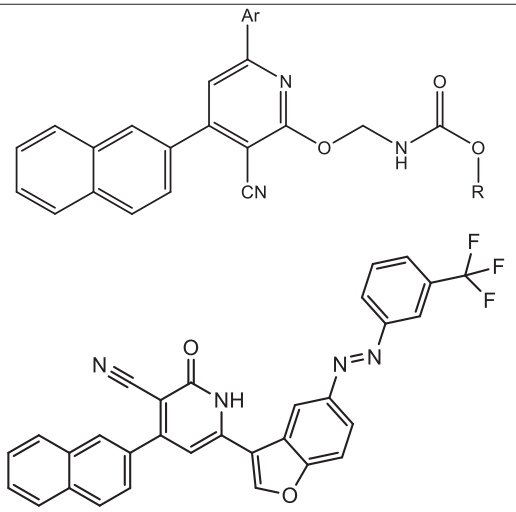
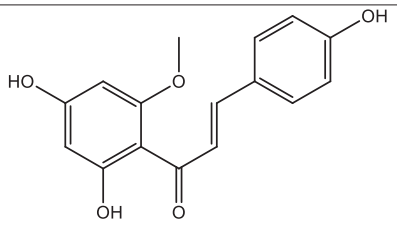
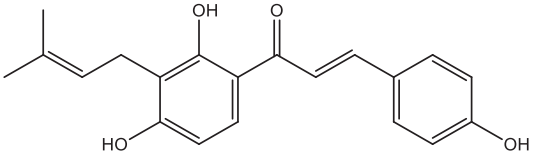
At about the same time, Zhou et al. (2018) studied the biological activity and the selectivity of novel chalcone derivatives containing a purine and benzenesulfonamide moiety against TMV and cucumber mosaic virus (CMV) *in vivo*. The obtained data indicated that several of the derivatives revealed significant anti-TMV and anti-CMV effect, which corresponded with a lower EC_{50} value (51.65 μg/mL) as compared to the antiviral agent ribavirin (150.45 μg/mL). In particular, one of the tested chalcone derivatives revealed a prominent inactivation activity against both viruses.

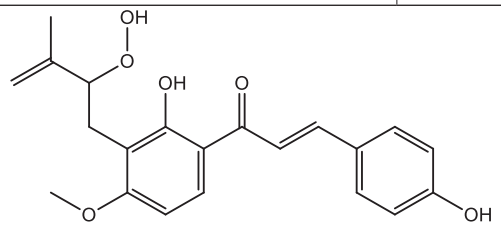
Other interesting research on plant viruses demonstrated that complexes of Cu(II), Ni(II) and Zn(II) with of 3-(phenyl)-1-(2'-hydroxynaphthyl)–2–propen–1–one (PHPO), 3-(4-chlorophenyl)-1-(2'-hydroxynaphthyl)–2–propen–1–one (CPHPO), 3-(4-methoxyphenyl)-1-(2'-hydroxynapthyl)-2-propen-1-one (MPHPO) and 3-(3,4-dimethoxyphenyl)–1-(2`-hydroxynaphthyl)–2-propen–1–one (DMPHPO) inhibited the tobacco ring spot virus (TRSV) growth on cowpea (*Vigna sinensis*) leaves indicating that they were more toxic to the virus than the respective ligands (Mallikarjun 2005). This effect can be ascribed to the property of the metal ions to interfere with normal cellular processes. It is evident from the mechanisms mentioned above that the toxic activity of a complex depend on the stability of the complex in solution. Complexes with higher stability and greater lipid

Table 1. Antiviral effect of chalcones and their derivatives against some plant and human viruses.

№	Chalcone derivatives		Antiviral activity	Reference
1	 Basic structure of chalcones			Dimmock et al. 1999
2	 5-((3,3-dichloroallyl)oxy)-2-(3-(3-(4-(4-methoxyphenyl)hex-1-en-2-yl)phenoxy)propoxy)-1,3-dimethylbenzene		Inactivation effect against tobacco mosaic virus (TMV) coat protein (CP)	Dong et al. 2017
	 (E)-1-(2-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(4-fluorophenyl)prop-2-en-1-one			Tang et al. 2019
	 **1.** R = Ph; **2.** R = 2-FPh; **3.** R = 2-Br-Ph; **4.** R = 2-NO_2-Ph; **5.** R = 3-CH_3-Ph; **6.** 3,4-di-OCH_3-Ph			Guo et al. 2019
3	 (E)-2-methyl-N-(4-(3-(4-((9-methyl-9H-purin-6-yl)oxy)phenyl)acryloyl)phenyl)benzenesulfonamide		Inactivation effect against TMV and cucumber mosaic virus (CMV)	Zhou et al. 2018
4		Complexes of Cu(II), Ni(II) and Zn(II) with the following ligands: 1. R = H, R1 = H (PHPO) 2. R = Cl, R1 = H (CPHPO) 3. R = OCH3, R1 = H (MPHPO) 4. R = OCH3, R1 = OCH3 (DMPHPO)	Inactivation effect against tobacco ringspot virus (TRSV)	Mallikarjun 2005
5		2',3',4',4-tetrahydroxychalcone	Inactivation effect against tomato ringspot virus (ToRSV)	Onyilagha et al. 1997
6		(*Z*)-2,4-dihydroxy-3-(3-hydroxy-3-phenylacryloyl)-6-methoxy-5-methylbenzaldehyde	Inhibition of human immunodeficiency virus (HIV) replication	Wu et al. 2003

№	Chalcone derivatives		Antiviral activity	Reference
6		(*E*)-1-(3,4-dihydroxy-5-methoxyphenyl)-3-(3,4-dihydroxyphenyl)prop-2-en-1-one	Inhibition of human immunodeficiency virus (HIV) replication	Uchiumi 2003
		(*E*)-3-(4-hydroxy-2-methoxy5-(2-methylbut-3-en-2-yl)phenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one		
		(*E*)-3-(3,4-dihydroxy-2-methoxyphenyl)-1-(4-hydroxyphenyl) prop-2-en-1-one		
7		3-(4-hydroxyphenyl)-1-(2,4,6-rihydroxyphenyl) propan-1-one, Phloretin	Inhibition of HIV-1 protease activity	Xu et al. 2000
		(*E*)-1-(2,4-dihydroxyphenyl)-3-(3,4-dihydroxyphenyl)prop-2-en-1-one, Butein		
		(*E*)-1-(2,4-dihydroxy-6-methoxyphenyl)-3-phenylprop-2-en-1-one, Cardamonin		Cheenpracha et al. 2006
8		(*E*)-1-(2,4-dihydroxy-6-methoxy-3-(3-methylbut-2-en-1-yl)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one, Xanthohumol	Inhibition of HIV-1 reverse transcriptase and p24 antigen	Wang et al. 2004
9	 stilben derivatives		Inhibition of human influenza A virus replication and neuraminidase	Bizzarii et al. 2019
		1. R1 = H, R2 = NO2, R3 = H 2. R1 = H, R2 = H, R3 = OCH3		Pradip et al. 2016

№	Chalcone derivatives		Antiviral activity	Reference
10	 1-(2,6-dihydroxy-4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)-3-(4-hydroxyphenyl)propan-1-one		Inhibition of herpes simplex virus (HSV) replication	Stompor et al. 2019
11	 (E)-1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one		– Anti-rubella virus effect – Anti – human poliovirus effect – Anti-rhinovirus effect	– Ahmad et al. 2008 – Ishltsuka et al. 1982 – Ninomiya Y. et al. (1984)
12		1-(3,5-dichloro-2-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one	Antiviral effect against hepatitis C virus (HCV)	Mateeva et al. 2017
		3-(3,4-dimethoxyphenyl)-1-(2-hydroxy-5-methyl-3-nitrophenyl) prop-2-en-1-one		
13	 4-(Naphthalen-2-yl)-2-oxo-6-(5-((3-(trifluoromethyl)phenyl)diazenyl)benzofuran-3-yl)-1,2-dihydropyridine-3-carbonitrile	1. R = C_6H_5 2. R = 4-$NH_2C_6H_4$	Antiviral effect against hepatitis A virus (HAV)	Gouhar et al. 2018
14		(*E*)-1-(2,4-dihydroxy-6-methoxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one, Helichrysetin	Inhibition of Middle East respiratory syndrome-related coronavirus (MERS-CoV) protease	Jo et al. 2019
	 (*E*)- 1- (2,4-dihydroxy-3-(3-methylbut-2-en-1-yl)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one, Isobavachalcone			

№	Chalcone derivatives	Antiviral activity	Reference
15	 (E)-1-(3-(2-hydroperoxy-3-methylbut-3-en-1-yl)-2-hydroxy-4-methoxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one, Xanthoangelol E	Inhibition of severe acute respiratory syndrome-related coronavirus (SARS-CoV) protease	Park et al. 2016

solubility are more toxic towards the virus and inhibit more effectively the virus growth.

Other examples for naturally occurring chalcones that can protect the crop as eco-friendly pesticides and weed control agents has been reported from Malhotra et al. (1996). For the first time, they found out that a 2-hydroxychalcone slightly inhibits the tomato ringspot virus (ToRSV) replication in *Chenopodium quinoa*. A hydroxy and methoxy substituted chalcone derivatives were investigated by Onyilagha et al. (1997) against ToRSV infection. This study demonstrated that the antiviral activity was activated by hydroxylation of the A-ring at 2‘,3‘,4‘ positions and B-ring at C-4‘, suppressed by hydroxylation at C-5‘, and reduced by methoxylation of the B-ring.

4.1. Antiviral effect of chalcones and their derivatives against some viruses relevant to the human pathology

There are 219 virus species that can infect humans. More than two-thirds of the human viruses can also infect mammals and sometimes birds (Woolhouse et al. 2012). Considered as precursors of flavonoid family, chalcones and their analogs display a diverse spectrum of pharmacological properties, including anti-viral activities against human viruses.

According to World Health Organization (WHO) data, human immunodeficiency virus (HIV)/AIDS has killed more than 25 million people worldwide and today is one of the major threats to human health and effective drug therapies are required to treat the infected people. The present highly active antiretroviral therapy (HAART) finds its limitations in the emergence of multidrug resistance and side effects, especially in persons undergoing long-term treatment (Valenti 2001). Recently, an enormous potential for isolation of some secondary metabolites or phytochemicals for treatment of HIV and management of AIDS has been found by investigating different plant species.

A recent report by Wu et al. (2003) demonstrated that a compound belonging to the group of chalcones and isolated from the genus Desmos (*Annonaceae*) which is distributed in southern Asia countries showed a potent anti-HIV activity (EC_{50} = 0.022 μg/mL) with good therapeutic index (TI = 489). It was suggested, that a C-2 methoxy group in the chalcone skeleton may be essential for the anti-HIV activity.

The inhibitory activity of butein and phloretin on HIV-1 protease was evaluated by Xu et al. (2000). The data demonstrated that butein applied at a concentration of 50 mg/mL caused more than 50% inhibition of HIV-1 protease, whereas phloretin lead to only 27% inhibition.

Other interesting fact was that licochalcones A and B (Uchiumi 2003), as well as 3,4-tetrahydroxy-2-methoxychalcone suppressed the 12-*o*-tetra-decanoyl phorbol-13-acetate (TPA)-induced HIV promoter. These antiviral effects were thought to result from multiple biological effects such as inhibition of poly(ADP-ribose) glycohydrolase PARG and superoxide radical-scavenging (Tewtrakul et al. 2003). The chalcone cardamonin exhibited an appreciable anti-HIV activity by inhibiting the HIV-1 protease by 75.1% at the IC_{50} value of 31 $\mu g/mL^{-1}$ (Cheenpracha et al. 2006). Trivedi et al. (2007) synthesized two structurally related coumarins, 4-hydroxy-8-isopropyl-5-methylcoumarin and 4-hydroxy-6-chloro-7-methylcoumarin, which were acylated at C-3 and further converted to the respective chalcones. Biological assessments were carried out against HIV-I (III B) and HIV-2 (ROD). However, no specific antiviral effects were noted for any of the compounds against any of the viruses evaluated.

Wang et al. (2004) reported that xanthohumol was an effective and selective inhibitor of HIV-1 and may represent a novel promising therapeutic agent for HIV-1 infection. The target of this substance probably was the step post reverse transcription. The EC_{50} of the compound on inhibiting HIV-1 p24 antigen was 1.28 $\mu g/mL^{-1}$.

Influenza viruses cause large epidemics and pandemics worldwide every year (Shaw and Palese 2013). Currently, three families of therapeutic drugs have been developed for treatment of influenza: 1) blockers of the ion-channel activity of the matrix (M2) protein (rimantadine and amantadine) (Gannagé et al. 2009); 2) neuraminidase inhibitors (oseltamivir and zanamivir) (Nabeshima et al. 2012) and compounds active against polymerase complex (favipiravir and baloxavir marboxil) (Furuta et al. 2017). However, there are certain well pronounced side effects associated with administration of these drugs, In addition, long-term systematic treatment can lead to multidrug-resistant influenza quasispecies (Hayden and Jong 2011). Therefore, new antiviral agents are required for the efficient inhibition of influenza viruses and combating the problems with the fast developing resistance. The scientific literature reports information about the

anti-influenza effect of some chalcones and their synthetic derivatives. For instance, Bizzarri et al. (2019) synthesized by self-, cross-, and ring-closing metathesis procedure stilbene and chalcone derivatives with efficacy against influenza A virus. Microscopic examination and trypan blue exclusion test demonstrated that most of the analyzed compounds exerted a toxic efect at the highest concentrations tested (20–50 μg/mL). The experiments were performed on influenza A/PR8/H1N1 virus. Stilbene and some chalcone derivatives were active against influenza A virus showing IC_{50} values of 15 μg/mL, whereby one of the analogs was characterized by a relatively high selectivity index (SI). Additionally, an appreciable antiviral activity against influenza A virus for some of the novel derivatives was observed, mainly involving the early stage of virus replication, probably during transcription or viral uncoating.

Pradip et al. (2016) focused on the anti-influenza neuraminidase effect of naturally occurring scaffold chalcone, derived from roots of *Glycyrrhiza* by incorporating various substituents based on their electronic and steric properties. With the help of computational drug design. All the compounds under study showed different mode of binding in the active cavity and almost all showed good antiviral activity.

Antiviral activity of chalcones and their derivatives was reported from Gomha et al. (2016). They synthesized a series of chalcones containing pyrazole moiety and utilized these chalcones in the preparation of pyrazolylpyrazoles, pyrazolylpyrimidine thiones, and pyrazolylpyridopyrimidine thiones. The results of the tested compounds showed various viral activity against herpes viruses. The anti-herpes effect showed was mostly moderate or low, except for three of the compounds which express high antiviral activity due to the presence of electron-donating groups in the p-position of the phenyl group (CH_3, OCH_3, and NMe_2). Dihydrochalcones (obtained by double bond reduction of chalcone) especially Trilobatin (effective in inhibiting HSV-2 at the concetration of 458 μM) derived from *Millettia leucantha* (*Leguminosae*) were shown also to possess anti-herpes simplex effect (Stompor et al. 2019).

The anti-rubella activity of 4-ethoxy-2-hydroxy-4, 6-dimethoxy-chalcone was studied *in vitro* in both tissue and organ culture. Rubella is a mild infection with teratogenic effect in pregnancy. Live vaccines which are safe and effective are available and have reduced the incidence of congenital rubella in young children (Reef et al. 2002). Ahmad et al. (2008) found that the above mentioned chalcone was nontoxic for the test cell cultures at a concentration of 8 μg/mL or less and had TI more than 100, therefore it was concluded that post probably this compound would not show side effect if used in humans. In particular, a concentration of 0.03 μg/mL or more was reported to inhibit the 100TCID50 of rubella virus.

Recently, the need for identifying new antiviral agents with different mechanisms of action is urgent. Michelli et al. (2018) evaluated the potential cytotoxic, antibacterial, antifungal and anti-dengue virus (DENV) effect of ten triazole chalcones *in vitro*. DENV cause mosquito-borne fever. Forty percent of the human population lives in areas with a risk of dengue (Halstead 2007). From 2016 an effective vaccine is available, but there is still no specific therapy. Although triazole chalcones showed low cytotoxicity and did not exhibite antimicrobial activity against Gram-positive and Gram-negative bacteria, except *S. epidermidis*, a poor antimicrobial effect was observed. However, none of tested compounds were able to reduce the cytopathic effect caused by DENV infection.

Based on the survey of Gouhar et al. (2018) a set of naphthalene-benzofuran chalcones was synthesized and evaluated for antiviral activity against hepatitis A virus (HAV). The results obtained suggested that all compounds possessed anti-HAV effect with TI ranging from 0 to 4.75 $\log_{10}TCID_{50}$. Only one of the substances had strong antiviral activity against HAV, reducing the virus titers by 3.75 $\log_{10}TCID_{50}$, when incubated with the virus before infection.

According to Mateeva et al. (2017) substituted chalcones, but not flavonoids showed inhibition of viral translation without significantly affecting viral replication in cells infected with hepatitis C virus (HCV). This virus represents an enveloped, single-stranded RNA virus from the family Flaviviridae. The structural proteins of the hepatitis C virus include core protein, E1 and E2, whereas the nonstructural proteins are NS2, NS3, NS4A, NS4B, NS5A and NS5B (Tang and Grisé 2009). NS5A is hydrophilic phosphoprotein which plays an important role in the viral replication (RNA replication, RNA translation and viral assembly), modulation of cell signaling pathways and the interferon response (Ross-Thriepland and Harris 2015). During viral translation NS5A activates the mammalian target of Rapamycin (mTOR) pathway by disrupting the interaction between FK506-binding protein 38 (FKB38) and mTOR (Peng et al. 2010; George et al. 2012). Activated mTOR increases the phosphorylation of ribosomal protein S6 kinase beta-1 (S6K1) protein, which eventually phosphorylates ribosomal protein 6 (rps6) and dampen HCV translation (Gingras et al. 2001). Unfortunately, the effective concentrations (5 μM) of chalcones studied in this work against HCV are relatively high.

A study of Ahmad A (2012) evaluated a new synergistic combination between the compounds dichloroflavan and chalcone against poliovirus *in vitro*. They found that the toxicity of both compounds on RD and L20B cells ranged between 16–32 μg/mL by single application. Both compounds possess similar modes of action which would suggest rather an additive effect. Interestingly, the investigation revealed that the combination is synergistic.

Ishltsuka et al. (1982) and Ninomiya et al. (1984) have investigated the anti-rhinovirus effect of Ro 09-0410 (4'-ethoxy-2'-hydroxy-4,6'-dimethoxychalcone). They suggested that Ro 09-0410 bound to a structure on the surface of the tested human rhinoviruses and inactivated them at minimal inhibitory concentration (MIC) ranging from 0.003 to 3.0 $\mu g/mL^{-1}$. The authors concluded that Ro 09-0410 binds to the rhinovirus virion and prevents viral replication in the cell.

4.2. Antiviral properties of chalcones against human coronaviruses (HCoVs)

Members of family *Coronaviridae* cause diseases in a variety of domestic and wild animals as well as in humans. They are large, positive sense, single-stranded RNA viruses, lipid-enveloped (Fehr and Perlman 2015). Human coronaviruses represent a major group and were associated with different respiratory diseases – from mild upper respiratory tract infections to more pathogenic with high mortality rate such as SARS (Severe acute respiratory syndrome), MERS (Middle East respiratory syndrome), which cause outbreaks in 2003 and 2012 and according WHO pandemic COVID-19 (Coronavirus disease 2019) in 2020 (Heikkinen and Järvinen 2003;Tambyah 2004; Arabi et al. 2017; Lu et al. 2020). However, no vaccine or specific antiviral treatment is currently available. Jo et al. (2019) reported that isobavachalcone (2'4,4'-Trihydroxy-3'-(3-methyl-2-butenyl)chalcone) and helichrysetin (4,2',4'-trihydroxy-6'- methoxychalcone) were found to have prominent inhibitory activity to Middle East respiratory syndrome-related coronavirus (MERS-CoV). The antiviral effects of them due to the inhibition of the main viral protease MERS-CoV 3CLpro and thus nullify a process of virus peptides. The structural comparison of isobavachalcone indicated that the hydrophobic modification at the 3'-position of the acetophenone ring moiety of isobavachalcone improves its binding affinity to MERS-CoV 3CLpro. Additionally, the docking analys shows that the 4-hydroxyl group of helichrysetin forms a hydrogen bond with the hydroxyl group of Tyr54 of MERS-CoV 3CLpro (Puyvelde et al. 1989; Erbel et al. 2006; Kiat et al. 2006). The experimental study showed that chalcone derivatives are favorite scaffolds to bind with the catalytic site of MERS-CoV 3CLpro.

In order to confirm the antiviral effect of natural chalcones against HCoVs Park et al. (2016) by kinetic plots and molecular docking studies demonstrate that nine naturaly alkylated chalcones, isolated from leaves of *Angelica keiskei*, possess potential inhibitory effect against severe acute respiratory syndrome-related coronavirus (SARS-CoV) proteases, especially chymotrypsin-like protease ($3CL^{pro}$) and papain-like protease (PL^{pro}) (Chou et al. 2003; Ghosh et al. 2006). These two proteases catalyze their own release and liberate other nonstructural proteins (nsps) from the polyprotein for that both proteases are essential for the viral life cycle, and both enzymes are attractive targets for the development of antiviral drugs directed against SARS-CoV and other coronavirus infections (Anand et al. 2003; Harcourt et al. 2004; Ghosh et al. 2006).

Conclusions

In summary, chalcones are naturally coloring compounds with an unsaturated side chain found in various edible plant species, precursors of flavonoids and isoflavonoids. During the last decades, it was proven that the chalcone backbone is very effective, with an array of biological activities. This has given rise to the need for discovery and synthesis of new synthetical chalcones with different constituents as pharmaceutically important molecules. Synthetic and naturally occurring chalcones have been reported to possess various medical properties, including direct anti-viral and virucidal activities. A few numbers of studies were focused on the anti-infective activity of chalcones against plant and human viruses. This review provides information on the anti-viral effect of chalcones (whether natural and synthetic derivatives) *in vitro*, as well as an overview of the mechanisms of actions and possible medical applications of these compounds. In general, chalcones are versatile molecules with a broad range of biological activities, including anti-viral, and a wide variety of application areas. However, more investigations are needed to fully understand the molecular targets and mechanisms, in which they are involved.

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