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Revisión / Review

Resveratrol as an anti-asthmatic agent: could this stilbenoid help against COVID-19 in any way? A meta-analysis

[Resveratrol como agente antiasmático: ¿podría este estilbenoide ayudar contra el COVID-19 de alguna manera? Un metaanálisis]

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Abstract: Resveratrol is a phenolic phytoconstituent found in many plants. This molecule has always caught the attention of scientists because of biological potentials such as inhibition of inflammation, oxidative stress and platelet aggregation as well as to prevent/protect against cardiovascular and neurodegenerative disease/disorders. Literature search have been conducted over resveratrol in covid-19 and asthma studies published in Pubmed and Google Scholars until 30 September 2020. The criteria used in the literature review were determined and were reviewed works on resveratrol including 368 articles and 47 articles on covid-19 and asthma, respectively. As a result of meta-analysis, TNF-α values of the studies showed a significant difference (heterogeneity) of I2=68.39% from each other in total (Cochran Q:6.33, $p<0.0423$). This study shows that resveratrol would have a potential to reduce ARDS symptoms, by suppressing the cytokine storm and severe inflammation caused by SARS-CoV-2, and by showing strong activity against various types of DNA/RNA viruses.

Keywords: Resveratrol; COVID-19; Asthma; Novel coronavirus; Meta analysis.

Resumen: El resveratrol es un fitoconstituyente fenólico que se encuentra en muchas plantas. Esta molécula siempre ha llamado la atención de los científicos debido a sus potenciales biológicos como la inhibición de la inflamación, el estrés oxidativo y la agregación plaquetaria, así como para prevenir/proteger contra enfermedades/trastornos cardiovasculares y neurodegenerativos. Se han realizado búsquedas bibliográficas sobre resveratrol en covid-19 y estudios sobre asma publicados en Pubmed y Google Scholars hasta el 30 de septiembre de 2020. Se determinaron los criterios utilizados en la revisión bibliográfica y se revisaron trabajos sobre resveratrol que incluyen 368 artículos y 47 artículos sobre covid-19 y asma, respectivamente. Como resultado del metanálisis, los valores de TNF-α de los estudios mostraron una diferencia significativa (heterogeneidad) de I2=68,39% entre sí en total (Cochran Q: 6,33, $p<0{,}0423$). Este estudio muestra que el resveratrol podría reducir los síntomas del ARDS al suprimir la tormenta de citocinas y la inflamación severa causada por el SARS-CoV-2, y al mostrar una fuerte actividad contra varios tipos de virus de ADN/ARN.

Palabras clave: Resveratrol; COVID-19; Asma; Nuevo coronavirus; Metanálisis.

ABBREVIATIONS

Middle East Respiratory Syndrome Coronavirus - MERS-CoV; airway hyperresponsiveness - AHR; interferon-γ - IFN-γ; transforming growth factor beta - TGF-β; toll-like receptor - TLR; nuclear factor kappa-light-chain-enhancer of activated B cells - NF-κB; angiotensin-converting enzyme 2 - ACE2; herpes simplex virus - HSV; early growth response gene product - EGR; long terminal repeat - LTR; human T-cell lymphotrophic virus - HIV; Acute Respiratory Distress Syndrome, ARDS; lipopolysaccharides - LPS; house dust mites - HDM; interleukin - IL; immunoglobulin - Ig; malondialdehyde - MDA; myeloperoxidase - MPO; bronchoalveolar lavage fluid - BALF; white blood cells - WBC; tumor necrosis factor alpha - TNF-α; nonsteroidal anti-inflammatory drugs - NSAID; ovalbumin - OVA.

INTRODUCTION

Traditional herbal medicines from which mankind has taken benefits since ancient times, remain in force and are increasingly popular despite the advancement and development of modern medicine. One of the reasons for its high acceptability is related to the fact that people are looking for other/new/~~novel~~ alternatives (environmentally friendly) for the treatment of both physical diseases and psychological disorders, due to the unwanted side effects of some drugs, as well as how affordable and accessible these drugs are (Hodgson, 2015).

Many phytochemicals (e.g., polyphenols) ingested through the diet can act as nutraceuticals, decreasing the risk or preventing the progression of certain diseases including respiratory (e.g., asthma). Among these phytoconstituents, resveratrol, a natural phenolic stilbene (C_6-C_2-C_6 scaffold), found in many fruits such as grapes, peanuts (Chang *et al*., 2006), blackcurrant, raspberry, cranberry, chokeberry, blackberry (Lin *et al*., 2017; Kim, 2018) and vegetables (Martinez *et al*., 2020), plays an important role as a therapeutic and chemopreventive agent in the treatment of various diseases; it was first isolated from *Veratrum grandiflorum* in 1940, and later it was also identified in a traditional Japanese and Chinese medicine called Ko-jo-kon (*Polygonum cuspidatum*) (Takaoka, 1940).

Although many modern medications (e.g., anticholinergics, β-adrenergic agonists, steroids, antihistamines, antileukotrienes, and phosphor-diesterase inhibitors) through direct therapy are used to treat asthma to date, a significant number of patients experience repeated asthmatic attacks (Janssen & Killian, 2006). In addition, long-term and excessive use of some of these drugs, especially nonsteroidal anti-inflammatory drugs (NSAID) and corticosteroids, can cause undesirable side effects such as gastrointestinal toxicity, addiction, drug resistance, and induction of Cushing´s syndrome (Hodgson, 2015), which would limit the use of current therapies in related patients, and accordingly, new therapeutic agents are needed that target both inflammation and pathways of airway smooth muscle contraction (Fanta, 2009; Lam *et al*., 2018). In this sense, use of active ingredients (e.g., shikimic acid) from plants (*Illicum verum, I. religiosum* - star anise) to obtain intermediates/pro-drugs/drugs (oseltamivir - Tamiflu®) for the treatment of respiratory diseases (e.g., H1N1 influenza, avian flu, influenza types A/B) (Alhajj *et al*., 2020; Singh *et al*., 2020) has become a valuable alternative for pharmaceutical companies, due to both its high effectiveness and relatively few side effects.

Since the first outbreak reported in the Chinese city of Wuhan in December 2019, the world has witnessed the pandemic spread of the recently identified SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2, related to a β-coronavirus), which is responsible for coronavirus disease 2019 (COVID-19) (Fei *et al*., 2020; Lu *et al*., 2020; Zhu *et al*., 2020), and since early 2020, it has broadcast rapidly in Europe first and later in America to date, causing approximately 400 thousand deaths and 6.5 million infections, according to reports (June 2020) from Johns Hopkins University and the European Centre for Disease Prevention and Control (Thiery, 2020). The new coronavirus pandemic is a major challenge to health systems worldwide, with 144.5 million people infected and almost 3.100.000 deaths (as of April 21, 2021) (Worldometer, 2021). The most common mode of SARS-CoV-2 transmission is from human to human through respiratory droplets or direct contact, having an average incubation period of 5.1 days and an estimated basic reproduction number of 2.24-3.58 per each infected individual (Jackowska *et al*., 2020; Rajwa *et al*., 2020).

On the other hand, referring to asthma as a respiratory disorder, this is a chronic inflammatory disease that affects more than 300 million people in the world and its prevalence has continuously increased; children are the group with the highest percentage of the disease compared to the other age groups (Kudo *et al*., 2013). Asthma is characterized by airway inflammation, hyper responsiveness, and reversible airflow obstruction (D'Amato *et al*., 2016);

it also produces symptoms of chest tightness, wheezing, and cough (Zhai *et al*., 2018). The pathogenesis of asthma is very complex due to various factors such as cytokines (e.g., interleukins, chemokines), growth factors, reactive oxygen species, inflammatory and T cells (e.g, eosinophils, lymphocytes, neutrophils) (Pelaia *et al*., 2008).

MATERIAL AND METHODS

This meta-analysis, Systematic Reviews, was conducted on the model of the Preferred Reporting Elements for Meta-Analyzes (PRISMA) statement by Liberati *et al*. (2009).

Search strategy

The words "Resveratrol", "Sars", "Asthma" and "Covid-19" were searched separately in Scopus, MEDLINE/Pubmed and Google Scholar (Up to September 10, 2020). The research was limited to English-language, human and animal studies, and reviews, including clinical studies only. The "criteria for inclusion" included randomized, controlled trials comparing only different interventions with key words. If other interventions were given, it was considered that they should be the same in all treatment groups. Also, only articles published in peer-reviewed journals Iran J Pharm Res. Chin J Pharmaceut Anal Med Plant Commun and some others were included in this study. Since covid-19 is so new, the resveratrol literature search was conducted independently of covid-19, while a literature search was performed together with asthma-covid19 and asthma-resveratrol. see fonts The reference list was designed using the "Mendeley" program.

Data extraction

All articles to be accepted as reference were reviewed by all authors. Articles for which double-blind peer-review was not evaluated were excluded. Extracted data included information about the study design, characteristics, amount of resveratrol, other compounds, the ratio of resveratrol to other compounds. For meta-analysis, articles measuring the level of TNF-α were searched.

Statistical analysis

Data tables were created after all the combined literature was carefully read and the data were extracted according to the requirements of the meta-analysis. Further analysis GraphPad Prism 7.01 (San Diego, CA 92108) was used and p values less than 0.05 were considered significant.

Meta-analysis was performed using Medcalc 19.5.3. MedCalc uses the Hedges g statistic as a formulation for the standardized mean difference under the fixed effects model. Next the heterogeneity statistic is incorporated to calculate the summary standardized mean difference under the random effects model.

RESULTS

As a result of the literature search about "resveratrol" as described above, 13,571 and 37,000 articles were found in pubmed and google scholar respectively. Moreover, as a result of the search for the keywords "asthma" together with "resveratrol" in the same databases, 47 and 17,700 articles were found respectively. The keyword "covid-19" reached 58,155 and 1,320,000 results, respectively. However, as a result of searching these three main words together, no articles were found. As illustrated in Figure No. 1, only 47 studies were found to investigate the relationship between resveratrol and asthma patients' outcomes.

In the articles related to asthma and resveratrol, 5 articles examining the level of TNF-alpha were reviewed. Accordingly, the statistical data of the test are given in Figure No. 2.

As a result of the meta-analysis, it was found that the heterogeneity of the TNF-α values of the studies was significant (Cochran Q: 6.33, $p<0.0423$) and the degree of heterogeneity was I2 = 68.39 %. The results of these studies differ from each other by a total of 68.39%.

The phenol resveratrol (3,4´,5-trihydroxy-trans-stilbene, 5-[(1E)-2-(4-hydroxyphenyl) ethenyl]-1,3-benzenediol - Figure No. 3a) is a phytoalexin biosynthesized in plant sources against causing-disease or damage/stress agents; this molecule occurs in two isomeric forms (E and Z) along with its glycosylated derivatives [E-/Z-piceid (E-/Z-resveratrol-3-O-β-ᴅ-glucopyranoside) - Figure No. 3b] and it is also a powerful antioxidant. Many studies have been conducted/documented in cell and animal trials on resveratrol and its ability to prevent cardiovascular diseases (Jang *et al*., 1997; Sahebkar *et al*., 2015) and cancer (Carbó *et al*., 1999; Parlar & Arslan, 2019), along with its potential to reduce inflammation (Guzman *et al*., 2018), inhibit high glucose-induced cell damage (Hu *et al*., 2016), inhibit antioxidant capacity (Guzman *et al*., 2018; Muñoz *et al*., 2020), inhibit the oxidation of low-density lipoproteins, inhibit platelet aggregation (Frémont *et* *al*., 1999), protect against neurodegenerative disorders (Pourhanifeh *et al*., 2019), decreasing cardiometabolic risk factors (Stivala *et al*., 2001) and even prolong life (McMichael *et al*., 2020).

Covid-19 is the most serious disease that has affected the planet almost completely (Guo *et al*., 2017), and it is well known that all coronaviruses affect the respiratory system; nevertheless, SARS-CoV-2 adheres more efficiently to the lower airways (e.g., bronchi, lungs, bronchioles, alveoli) than other coronaviruses (Sarzi-Puttini *et al*., 2020), causing eventually severe respiratory failure and acute respiratory distress syndrome (ARDS) in some patients with comorbidities (e.g., hypertension, diabetes, immunosuppressed) (Guo *et al*., 2020; Reiner *et al*., 2020). Into the bargain, this coronavirus can cause serious cardiovascular and liver problems (Banach *et al*., 2020; South *et al*., 2020).

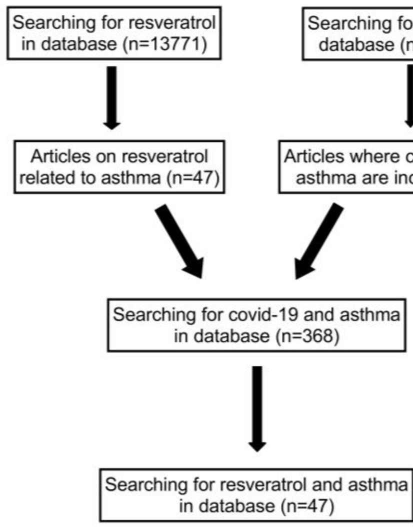

Figure No. 1
Article selection process

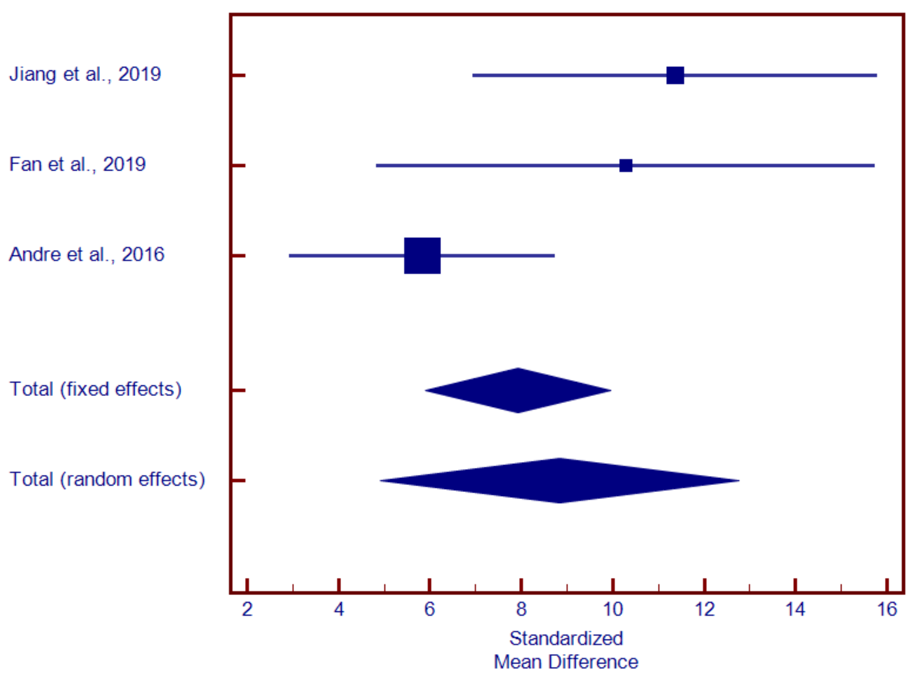

Figure No. 2
Meta-analyses of three case-control studies relating TNF alpha. Summary compare means calculated by random and fixed effects method. Heterogeneity: Q:6,33, *p*<0.0423, I2=68,39%, 95% CI for = 0,00 to 90,82 (André *et al*., 2016; Fan *et al*., 2019; Jiang *et al*., 2019)

Figure No. 3
***E*-Resveratrol; *E/Z*-Piceid**

This new pandemic is a great challenge for health systems worldwide (Worldometer, 2020). In all countries, the treatment of patients affected by COVID-19 has been prioritized, and all resources have been focused on finding and/or expanding more clinical resources to serve the population where the increase in Covid-19 cases seems to go hand in hand with falling temperatures. Ways to prevent and/or delay the progress of infections have been established/assumed differently by each country. In this way, local decrees have arisen in the countries themselves as well as other more specialized documents for large groups (Cunningham *et al*., 2020).

While big pharmaceutical companies/laboratories around the world are searching for new drugs that can directly or indirectly combat Covid-19, comorbidities such as hypertension, diabetes and respiratory disorders (such as asthma), among others, in patients with Covid-19 would rapidly increase their critical states to impending doom (Tian & Liu, 2020).

The purpose of this review is to report how the phytoconstituent resveratrol has been effective against asthma and thus, hypothetically it could have an impact on the decrease of comorbidity (asthma) in patients with Covid-19 and therefore, an improvement in life expectancy of critically ill patients. The manuscript will mention the effect of resveratrol and its mechanism of action on asthma.

Plants containing resveratrol

Some plants containing resveratrol are included in Table No. 1. Thus, 111 species belonging to 71 genera and 34 families have been included in this Table No. 1.

Table No. 1

Study	Research type	measurement method	Quantification of resveratrol	Family	Species
Tian & Liu, 2020	Review	--	--		*Alnus* spp., *Aster tataricus* L. f., *Syneilesis aconitifolia* (Bge.) Maxim, *Vaccinium dendrocharis* Hand. -Mazz., *Vaccinium chaetothrix* Sleumer, *Vaccinium moupinense* Franch., *Vaccinium sikkimense* C. B. Clarke, *Euphorbia humifusa* Willd. ex Schlecht., *Poa annua* L, *Festuca ovina* L. *Stipa tianschanica* (Roshev.) Norl, *Stipa tianschanica* (Roshev.) Norl
Da Silva *et al*., 2014	Chemical research	Chemical analysis	0.56 x 10^{-2} ng/mL	Bromeliaceae	*Ananas comosus* (L) Merr.
Suzuki *et al*., 1987	Chemical research	Spectroscopic analysis	--	Cyperaceae	*Carex fedia* var. *miyabei* (Franchet) T. Koyama
Ito *et al*., 2003	Chemical research	Spectroscopic analysis	--	Dipterocarpaceae	*Vatica pauciflora* (Korth.) Bl.
Lyons *et al*., 2003	Chemical research	LC-MS/MS	36 ng/g	Ericaceae	*Vaccinium myrtillus* Linn.
Rimando & Barney, 2005	Chemical research	GC/MS	0.26-4.67 µg/g	Ericaceae	*Vaccinium haitangense* Sleumer
Borowska *et al*., 2009	Chemical research	HPLC	712.3 ng/g	Ericaceae	*Vaccinium microcarpum* (Turcz. ex Rupr.) Schmalh.
Česoniene & Daubaras, 2015	Chemical research	HPLC	533.4 ng/g	Ericaceae	*Vaccinium oxycoccos* Linn.
Tanaka *et al*., 2001	Chemical research	Spectroscopic analysis	429.6 ng/g	Gnetaceae	*Gnetum parvifolium* (Warb.) C. Y. Cheng ex Chun
Xiang *et al*., 2002	Chemical research	chromatography	16.3 ng/g	Gnetaceae	*Gnetum montanum* Markgr
Huang *et al*., 2000	Chemical research	UV spectra	161.7 ng/g	Gnetaceae	*Gnetum hainanense* C. Y. Cheng
Powell *et al*., 1994	Chemical research	GC/MS	2300 ppm	Poaceae	*Lolium perenne* L.

Ehala *et al*., 2005	Chemical research	capillary zone electrophoresis	97.8%	Grossulariaceae	*Ribes nigrum* L.
Muangthai & Sutiono, 2014	Chemical research	HPLC	76.82 g/L	Lauraceae	*Cinamomum* spp.
Irnidayanti *et al*., 2019	Chemical research	TLC, HPLC	65.15-55.35 %	Fabaceae	*Glycine max* (Linn.) Merr.
Anjaneyulu *et al*., 1984	Chemical research	X-rays	6.79-2H, d, J=8Hz		*Bauhinia racemosa* Lam.
Chukwumah *et al*., 2009	Chemical research	HPLC	9.49 mg/mL		*Arachis hypogaea* Linn.
Liu *et al*., 2004	Chemical research	X-rays	6.33 (1H, d, J2.5 Hz) this is not a quantification!		*Caragana stenophylla* Pojark.
Kineman *et al*., 2010	Chemical research	HPLC	0.1 ± 0.08 nmol/g tissue		*Medicago sativa* L.
Tian *et al*., 2008	Chemical research	X-rays	7.46 (dd, J ¼ 6.5, 2.0 Hz, 2 H)		*Ammopiptanthus mongolicus* (Maxim. ex Kom.) Cheng f.
Ning *et al*., 2013	Chemical research	HPLC	62.89 g/L		*Vigna umbellata* (Thunb.) Ohwi et Ohashi
Takaoka, 1940	Review	--	--		*Veratrum grandiflorum* (Maxim.) Loes. *f*
Zhao *et al*., 1998	Review	--	--		*Veratrum nigrum* L. var. *ussuriense* Nakai
Zhou *et al*., 1999	Chemical research	Enzyme assay	30 µM		*Veratrum taliense* Loes. *f*.
Wu *et al*., 2018	Chemical research	HPLC	0.478 mg/g		*Veratrum maackii* Regel
Yuan *et al*., 2018	Chemical research	HPLC	0.549 mg/g		*Ornithogalum caudatum* Jacq
Wang *et al*., 2013	Abstract	Chromatography			*Smilax scobinicaulis* C. H. Wright
Li *et al*., 2007	Chemical research	HPLC	0.288 mg/mL		*Smilax glabra* Roxb
Shu *et al*., 2002	Chemical structure	Ultraviolet spectra	7.65, d, J=15.9 Hz		*Smilax bracteata* Presl
Sagar *et al*., 2006	Chemical research	HPLC	20%	Magnoliaceae	*Magnolia officinalis* Rehd. et Wils.
Xu *et al*., 2004	Chemical structure	Ultraviolet spectra	1H, d, J=1.5 Hz, H-6	Myrcinaceae	*Aegiceras corniculatum* (Linn.) Blanco
Rajkumari *et al*., 2018	Animal research	Anti-oxidant activity	8000 IU		*Syzygium jambos* (L.) Alston
Hillis & Inoue, 1967	Chemical structure	HPLC	62.1 %	Nothofagaceae	*Nothofagus fusca* Hook.*f*.
Li *et al*., 2009	Chemical structure	MS/MS	0.529.6 mg/g		*Pinus sylvestris* L.

Lee *et al.*, 2016	Chemical structure	HPLC	0.322 mg/mL		*Pinus koraiensis* Sieb. et Zucc.
Aritomi *et al.*, 1965	Chemical research	UV spectra	--		*Rumex japonicus* Houtt.
Kim *et al.*, 2002	Chemical research	HPLC	59 mg/0.18 g	Ranunculaceae	*Paeonia suffruticosa* Andr.
Sarker *et al.*, 1999	Chemical research	HPLC	ED_{50} = 10 to 50 μM *vs.* 5 × 10^{-8}M 20-hydroxyecdysone)		*Paeonia suffruticosa* (Andr.) Kerner
Yu *et al.*, 2019	Review		--	Rosaceae	*Rubus chingii* Hu
Gadani *et al.*, 2017	Animal research	Antioxidants activity	51.0 ± 7.6 *vs* 29.6 ± 11.3 µM	Theaceae	*Camellia sinensis* (L.) Kuntze
Soural *et al.*, 2015	Chemical research	LC/MS	6030 ± 680 µg/g	Vitaceae	*Vitis vinifera* L.
Ji *et al.*, 2014	Chemical research	HPLC	0.009 µg/mL		*Vitis amurensis* Rupr.
Kim *et al.*, 2007	Chemical research	HPLC	5.2 mg/500 mg		*Ampelopsis japonica* (Thunb.) Makino
Adesanya *et al.*, 1999	Chemical structure	UV spectra it is impossible identify only by UV!	6.21, 2H, d, J=2 Hz		*Cissus quadrangularis* L.
Lins *et al.*, 1991	Chemical structure	UV spectra	7.30, 3H, d, J=8.5 Hz		*Parthenocissus tricuspidata* (S. et Z.) Planch.
Tanaka *et al.*, 1998	Chemical structure	UV spectra	1H, d, J = 2.0 Hz		*Parthenocissus quinquefolia* (L.) Planch.
Syah *et al.*, 2000	Chemical structure	UV spectra	7.23 1H, d, J=16.4 Hz		*Morus macroura* Miq.
Choi *et al.*, 2013	Chemical research	NMR spectral analysis	23.7 to 105.5 mg % in six different mulberry cultivars.		*Morus alba* L.
Abbas *et al.*, 2014	Chemical structure	NMR spectral analysis	2H, d, J=2.0 Hz.		*Morus nigra* L.
Chen *et al.*, 2015		CD spectra	6.30 (1H, dd, J=8.0, 2.0 Hz, H-8		*Cudrania cochinchinensis* Lour.
Borah *et al.*, 2017		Ultraviolet-visible	85.00 mg/kg		*Artocarpus lakoocha* Roxb.

Asthma

Asthma is a reversible airway obstruction that increases sensitivity in the lungs, mucus production, and inflammation in the airway (James *et al*., 2009). It includes pathophysiological condition, epithelial fibrosis, metaplasia and hyperplasia of goblet cells, hypersecretion of mucus (Shinagawa & Kojima, 2003). Asthma is a disease with different phenotypes but does not have a standard way of defining them (Wenzel, 2006), and to determine them not only are the clinical parameters sufficient, but other biomarkers are also needed to find genetic/phenotypic differences (Hesselmar *et al*., 2012). In establishing the specific phenotypes of asthma, several particular models of asthma have been suggested and demonstrated in animal models.

DISCUSSION

This work is a review that seeks to correlate the therapeutic effects of resveratrol and certain plants containing it against some respiratory diseases such as ARDS and asthma, which are caused by many pathogens, including SARS-CoV-2, as well as provides information to researchers in these areas.

Isolation of viruses from the upper airway of asthmatic patients during clinical exacerbations suggested that viruses may play an important role in asthma (Johnston *et al*., 1995), and therefore, they are common triggers for these exacerbations (Kumar *et al*., 2020). In most people with asthma, Th2 mediators increase, as well as when a viral infection arises (Contoli *et al*., 2006); such Th2 mediators like IL-4 and IL-13 can inhibit epithelial production of type I interferon (Contoli *et al*., 2015). Furthermore, interferon α can suppress the polarization of Th2 cells in T cells and, consequently, can attenuate the expression of GATA3, IL-4 and IL-5 (Huber *et al*., 2010; Pritchard *et al*., 2012). Evidence for this is that type 2 inflammation occurs in mice with type I IFN receptor deficiency in response to pulmonary eosinophilia and influenza infection in mice (Duerr *et al*., 2016). Additionally, the results of a series of previous *in vitro* and *in vivo* studies in humans and animals for various asthma-related viruses, e.g., rhinovirus, influenza, and respiratory syncytial virus, promote this hypothesis (Chen *et al*., 2019; Han *et al*., 2019; Lee *et al*., 2019).

Previous studies on T-cell lymphotrophic virus 1 (HIV-1) showed that resveratrol led to the activation of the lytic cycle of HIV-1, attenuation of the HIV-1 Tat-induced long terminal repeat (LTR) transactivation and inhibition of HIV-1 replication when used synergistically with nucleoside analogues by activating the early growth response gene product 1 (EGR-1) and sirtuin 1 and prolonging the S-phase of the cell cycle, respectively (Heredia *et al*., 2000; Krishnan & Zeichner, 2004; Wang *et al*., 2004; Zhang *et al*., 2009). In addition, Faith *et al*. (2006) and Docherty *et al.* (2006) demonstrated that resveratrol, by suppressing activation of the NF-κB pathway, inhibited the replication of varicella-zoster virus (VZV) and herpes simplex virus 1 and 2 (HSV-1 and HSV-2). Similarly, Palamara *et al*. (2005), established (both *in vivo* and *in vitro* assays) that resveratrol inhibited the replication of influenza A virus by causing inhibition of protein kinase C activity.

SARS-CoV-2 binds to respiratory epithelial cells via angiotensin-converting enzyme 2 (ACE2) (Kim *et al*., 2020) and the virus links to the host serine protease TMPRSS2, which cleaves the viral spike protein in S1/S2 allowing the fusion of viral and cell membranes (Hoffmann *et al*., 2020). In a study investigating the *in vitro* and *in vivo* translation and budding process of SARS-CoV-1 and MERS viruses, the infection caused by SARS-CoV-1 can be detected by various intercellular sensors (e.g., RIG I/MDA5/MAVS/TRAF3/IRF3/IRF7) and pathways (e.g., TLRs/TRIF/MyD88/IkB/NF-kB/MAPK/AP-1). Thus, the blocking of the IRF3 and RIG I pathways by the SARS virus produces the inhibition of the antiviral response and the inefficient production of type 1 interferons (Siu *et al*., 2009). As a result of all this process, cell death can lead to increased hyperinflation and cytokine storm.

IL-1β and IL-18, which cause exacerbation of symptoms of SARS-CoV-2 infection, are generated by NF-κB pathway; these proinflammatory cytokines play a role in pathogenic inflammation and are activated through the detection of viral RNA using toll-like receptors (e.g., TLR-3, TLR7, TLR8 and TLR9) (Conti *et al*., 2020). Based on the report by Wang *et al*. (2020b), SARS-CoV-2 infects human T cell lines in a new way from the CD147 spike protein located on the surface of T lymphocytes.

The excess immune response caused by COVID-19, especially in the airway mucosa, can be suppressed by Treg cells (Loebbermann *et al*., 2013). While eosinophils, which contain and produce molecules with antiviral activity, serve as antigen-presenting cells as demonstrated *in vitro* and *in vivo* against some respiratory viruses, including respiratory syncytial virus and influenza (Flores-Torres *et al*., 2019).

The vast majority of patients with COVID-19 survive the disease without symptoms, while some of them with mild to moderate symptoms recover within a week (Dong *et al*., 2020; Huang *et al*., 2020). Nonetheless, some patients develop severe pneumonia in the second week, followed by excessive cytokine storm, acute respiratory distress syndrome, multiple organ dysfunction disorder, and disseminated intravascular coagulation in the third week (Azkur *et al*., 2020). Referring to the cytokine storm, it is a process characterized by the activation of large numbers of white blood cells, such as monocytes, neutrophils, macrophages, and NK, B and T cells, as well as the release of great amounts of pro-inflammatory cytokines (Behrens & Koretzky, 2017; Zinovkin & Grebenchikov, 2020). Among the causes of cytokine storm, cases such as Ebola, bacterial sepsis and other hemorrhagic fevers could be tied to some infectious and non-communicable diseases (e.g., flu and blunt trauma) (Liu *et al*., 2016; Channappanavar & Perlman, 2017; Younan *et al*., 2017).

According to Lo Muzio *et al*. (2020), reported that natural purified polyphenols prevented pneumonitis caused by coronavirus. In another study conducted by Marinella (2020), showed that two potential anti-inflammatory agents include indomethacin, which has been shown in experimental models to decrease canine coronavirus levels in dogs and exhibit antiviral activity against several other viruses and the polyphenol, resveratrol, a potent antioxidant that has shown antiviral activity against several viruses.

According to Dennis and Norris (2015), the proinflammatory cytokines and eicosanoids play a key role in the inflammatory process caused by SARS-CoV-2, in the same way as TNF-α, IL-6, IL-12, IL-17, IL-1β, and IFN-γ (Chousterman *et al*., 2017). Meanwhile, IL-10 limits the expansion of tissue lesions in experimental models (Savarin & Bergmann, 2018; Ashrafizadeh *et al*., 2020). Considering as described by Huang *et al*. (2005), high levels of monokine were detected in the serum of patients with SARS in the acute phase, and these monokines are induced by IL-6, IL-8, IL-18, interferon-γ-inducible protein-10 (CXCL10 or IP-10), monocyte chemoattractant protein-1 (MCP-1), IFN-γ, and TGF-β (Huang *et al*., 2005; Savarin & Bergmann, 2018).

Another important feature of asthma is airway hyperresponsiveness (AHR), and it was evaluated by Parlar and Arslan using unrestrained whole-body plethysmography, which is a method that can detect breathing patterns (Parlar & Arslan, 2020). Furthermore, in human studies, SARS is known to cause acute inflammatory lung injury, characterized by bilateral alveolar opacities and decreased pulmonary compliance with acute hypoxemic respiratory failure on chest X-ray (Peiris *et al*., 2003; Fan *et al*., 2018). ARDS develops in patients within 3 weeks after SARS infection, whereas ARDS progresses in COVID-19 patients between 8-9 days after disease onset (Huang *et al*., 2020). Reports show that some diseases and factors such as bronchitis, diabetes, Parkinson´s disease, ischemic disease of the central nervous system, hypertension, and coronary artery disease increase the severity of ARDS caused by SARS-CoV-2 and even cause the death of patients (Wujtewicz *et al*., 2020).

Since some herbal medicines suppress type 2 inflammation (Lee *et al*., 2018), resveratrol can lead to the beneficial effect of secondary restoration of impaired antiviral immunity in the exacerbation related to SARS-CoV-2 (Lin *et al*., 2017; Filardo *et al*., 2020). Thus, Lin et *al*. (2017) demonstrated that resveratrol is a potent anti-Middle East Respiratory Syndrome coronavirus (MERS-CoV) agent *in vitro* by down-regulating the apoptosis induced by MERS-CoV and decreasing the expression of nucleocapsid (N) protein essential for MERS-CoV replication (Lin *et al*., 2017). Other research carried out on Vero E6 cell culture showed that the derived stilbene protects against SARS-CoV-induced cytopathy (Li *et al*., 2006). In addition, Zhao *et al.* (2016), reported that resveratrol inhibited viral replication and mortality in ducklings infected with the duck enteritis virus. One more report by Zhao *et al.* (2017), always on the pseudorabies virus, which affects pigs causing fatal encephalitis and lung inflammation, evidenced that resveratrol inhibits intracellular viral proliferation by blocking the activity of IκB kinase; this enzime is the key regulator in NF-κB activation. But despite the high antiviral potential of resveratrol, its oral bioavailability is low, which would constitute an apparent disadvantage. Nonetheless, Some researchers suggest that to improve its bioavailability, resveratrol can be combined in nanoparticle formulations or with modified beta-glucan in aqueous solutions (Baldassarre *et al*., 2020). In another example of reliability of the therapeutic effect of resveratrol against SARS-CoV-2, Cui *et al*. (2018), added resveratrol to the piglets´ diet for 21 days, and they found that resveratrol reduced both TNF-α levels and diarrhea due to rotavirus.

Besides all the health benefit effects listed above, resveratrol has adverse effects (Shaito *et al*., 2020). Some references have reported that resveratrol has hormetic effects, including pro-oxidant effects associated with high dose (Dai *et al*., 2007: Dei *et al*., 2009; Gadacha *et al*., 2009; Rocha *et al*., 2009; Guha *et al*., 2010; Posadino *et al*., 2019; Shaito *et al*., 2020). Moreover, resveratrol has been reported to have an immune toxic effect (Bolton & Dunlap, 2017).

Recent studies have shown that some bioactive compounds found in dietary fruits could be active in suppressing SARS-CoV infection, among which resveratrol is found (Lin *et al*., 2017; Wang *et al*., 2020b).

CONCLUSION

This study shows that resveratrol would have the potential to reduce ARDS symptoms, both by suppressing the cytokine storm and severe inflammation caused by SARS-CoV-2, and by showing strong activity against various types of DNA and RNA viruses. Although the antiviral activity of resveratrol is known, the cell pathways leading to its protective activity in asthma have not yet been elucidated. Interestingly, some molecular pathways regulated by resveratrol, e.g., IFN-γ, TGF-β, NF-κB, TNF-α, IL-6, IL-12, IL-17, or IL-1β, also play an important role in the control of virus infection. Therefore, resveratrol can improve respiratory distress symptoms caused by covid-19 in patients with asthma.

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