

## **Nrf2-interacting nutrients, insulin resistance and COVID-19: Time for research to develop mitigation strategies**

Jean Bousquet (1-3), Jean-Paul Cristol (4), Wienczyslawa Czarlewski (5-6), Josep M Anto (7-10), Adrian Martineau (11), Tari Haahtela (12), Susana C Fonseca (13), Guido Iaccarino (14), Hubert Blain (15), Alessandro Fiocchi (16), G Walter Canonica (17), Joao A Fonseca (18), Alain Vidal (19), Hak-Jong Choi (20), Hyun Ju Kim (21), Vincent Le Moing (22), Jacques Reynes (22), Aziz Sheikh (23), Cezmi A Akdis (24), Torsten Zuberbier (1), and the ARIA group

1. Charité, Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Comprehensive Allergy Center, Department of Dermatology and Allergy, Berlin, Germany.
2. University Hospital Montpellier, France.
3. MACVIA-France, Montpellier, France.
4. Laboratoire de Biochimie et Hormonologie, PhyMedExp, Université de Montpellier, INSERM, CNRS, CHU, Montpellier, France.
5. Medical Consulting Czarlewski, Levallois, France.
6. MASK-air, Montpellier, France.
7. IMIM (Hospital del Mar Research Institute), Barcelona, Spain.
8. Universitat Pompeu Fabra (UPF), Barcelona, Spain.
9. CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain.
10. ISGlobal. ISGlobAL, Barcelona, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.
11. Institute for Population Health Sciences, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK.
12. Skin and Allergy Hospital, Helsinki University Hospital, and University of Helsinki, Helsinki, Finland.
13. GreenUPorto - Sustainable Agrifood Production Research Centre, DGAOT, Faculty of Sciences, University of Porto, Campus de Vairão, Vila do Conde, Portugal.
14. Department of Advanced Biomedical Sciences, Federico II University, Napoli, Italy.
15. Department of Geriatrics, Montpellier University hospital, Montpellier, France.
16. Division of Allergy, Department of Pediatric Medicine - The Bambino Gesù Children's Research Hospital Holy see, Rome, Italy.
17. Personalized Medicine Asthma & Allergy Clinic-Humanitas University & Research Hospital, IRCCS-Milano, Italy.
18. CINTESIS, Center for Research in Health Technology and Information Systems, Faculdade de Medicina da Universidade do Porto; and Medida, Lda Porto, Portugal.
19. World Business Council for Sustainable Development (WBCSD) Maison de la Paix, Geneva, Switzerland & AgroParisTech - Paris Institute of Technology for Life, Food and Environmental Sciences, Paris, France.
20. Microbiology and Functionality Research Group, Research and Development Division, World Institute of Kimchi, Seoul, Korea.
21. SME Service Department, Strategy and Planning Division, World Institute of Kimchi, Seoul, Korea.
22. Maladies Infectieuses et Tropicales, CHU Montpellier, France
23. The Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK.
24. Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland.

**Short title: Nrf2-interacting nutrients and COVID-19**

**Address for correspondence:**

Professor Jean Bousquet

273 avenue d'Occitanie, 34090 Montpellier, France    Tel +33 611 42 88 47, Fax +33 467 41 67 01

[jean.bousquet@orange.fr](mailto:jean.bousquet@orange.fr)

## Abstract

There are large between- and within-country variations in COVID-19 death rates. Some very low death rate settings such as Eastern Asia, Central Europe, the Balkans and Africa have a common feature of eating large quantities of fermented foods whose intake is associated with the activation of the Nrf2 (Nuclear factor (erythroid-derived 2)-like 2) anti-oxidant transcription factor. There are many Nrf2-interacting nutrients (berberine, curcumin, epigallocatechin gallate, genistein, quercetin, resveratrol, sulforaphane) that all act similarly to reduce insulin resistance, endothelial damage, lung injury and cytokine storm. They also act on the same mechanisms (mTOR: Mammalian target of rapamycin, PPAR $\gamma$ : Peroxisome proliferator-activated receptor, NF $\kappa$ B: Nuclear factor kappa B, ERK: Extracellular signal-regulated kinases and eIF2 $\alpha$ : Elongation initiation factor 2 $\alpha$ ). They may as a result be important in mitigating the severity of COVID-19, acting through the endoplasmic reticulum stress or ACE-Angiotensin-II-AT $_1$ R axis (AT $_1$ R) pathway. Interestingly, geographical areas with very low COVID-19 mortality are those with the lowest prevalence of obesity (Sub-Saharan Africa and Asia). It is tempting to propose that Nrf2-interacting foods and nutrients can re-balance insulin resistance and have a significant effect on COVID-19 severity. It is therefore possible that the intake of these foods may restore an optimal natural balance for the Nrf2 pathway and may be of interest in the mitigation of COVID-19 severity.

## Abbreviations

ACE: Angiotensin converting enzyme  
AKT: Protein kinase B Ang II: Angiotensin II  
AT $_1$ R: Angiotensin II receptor type 1  
COVID-19: Coronavirus 19 disease  
DNA: Deoxyribonucleic acid  
EGCG: Epigallocatechin gallate  
eIF2 $\alpha$ : Elongation initiation factor 2 $\alpha$   
ER: Endoplasmic reticulum  
ERK: Extracellular signal-regulated kinases  
GI: Gastro-intestinal  
HCV: Hepatitis C virus  
HIV: Human immunodeficiency virus  
IFN: Interferon  
IR: Insulin resistance  
Keap1: Kelch-like ECH-associated protein 1  
LAB: Lactic acid bacilli  
mTOR: Mammalian target of rapamycin  
mTORC: mTOR complex  
MAPK: Mitogen-activated protein kinases

NADPH: Nicotinamide adenine dinucleotide phosphate  
NF- $\kappa$ B: Nuclear factor kappa B  
Nox: NADPH oxydase  
Nrf2: Nuclear factor (erythroid-derived 2)-like 2  
PI3K: Phosphoinositide 3-kinase  
PPAR: Peroxisome proliferator-activated receptor  
PERK: Protein kinase R (PKR)-like endoplasmic reticulum kinase  
PKR: protein kinase R  
RAAS: Renin-Angiotensin-Aldosterone system  
ROS: Reactive oxygen species  
RSV: Respiratory syncytial virus  
SARS: Severe acute respiratory syndrome  
SARS-Cov-2: Severe acute respiratory syndrome coronavirus 2  
STING: Signalling effector stimulator of interferon genes  
T2D: Type 2 diabetes  
UPR: Unfolded protein response

**Key words :** COVID-19, Nrf2, foods, nutrients, insulin resistance, obesity

## Introduction

Large differences in COVID-19 death rates exist between countries and between regions of the same country. Some very low death rate geographical areas such as Eastern Asia, Central Europe, the Balkans and Africa have a common feature: the consumption of large quantities of fermented foods (1-3) in which lactic acid bacteria are important. Notwithstanding the fact that data from ecological studies need to be interpreted with caution, fermented vegetables or cabbage have been found to be associated with low COVID-19 death rates in European countries (3-5).

Reactive oxygen species (ROS) exert beneficial and toxic effects on cellular functions. Nrf2 is a pleiotropic transcription factor protecting against oxidative stress. It expresses a wide array of genes involved in immunity and inflammation, including antiviral actions (6). Several Nrf2-interacting natural compounds (e.g. berberine, curcumin, epigallocatechin gallate, genistein, quercetin, resveratrol, sulforaphane) and lactobacilli acting as antioxidants are effective against insulin resistance associated diseases (7). They may be important in the mitigation of COVID-19 (3, 7, 8), acting through the endoplasmic reticulum (ER) (9-11) or ACE-Angiotensin-II-AT<sub>1</sub>R axis (AT<sub>1</sub>R) pathway (2, 3) and leading to insulin resistance (IR), endothelial damage, lung injury and cytokine storm. They may also interact with SARS-CoV-2 by other pathways involved in IR that may be Nrf2-dependent or -independent (9-11).

Obesity is a very important risk factor for COVID-19 severity (12) and is often associated with diet. There may be interactions between obesity, diet and COVID-19, possibly linked with Nrf2 (13).

The present rostrum follows the first two papers on diet and COVID-19 (2, 3). Specifically, we seek to (i) expand discussion on the role of Nrf2-interacting natural nutrients in IR, (ii) assess the mechanisms on ER stress and the AT<sub>1</sub>R pathway, and (iii) understand how Nrf2-interacting nutrients can interplay to mitigate COVID-19.

### 1- Nrf2-interacting nutrients

**The most common Nrf2 nutrients** include berberine, curcumin, epigallocatechin gallate (EGCG), genistein, quercetin, resveratrol, sulforaphane mostly found in vegetables and fruits, and *Lactobacillus* in fermented foods (Table 1).

**Table 1: origin of Nrf2-interacting nutrients**

Nutrient		Foods containing nutrient
Berberine	benzylisoquinoline alkaloid	European barberry, goldenseal, goldthread, Oregon grape, phellodendron, goldenseal, poppy, and tree turmeric
Curcumin	Curcuminoid (phenol)	Turmeric
EGCG	Catechin (polyphenol)	Green and white tea
Genistein	Soy isoflavone	Soy-based foods including tofu, tempeh and miso
<i>Lactobacillus</i>	Lactic acid bacteria	Fermented foods
Quercetin	Flavonoid group of polyphenols	Found in many fruits (cranberries, lingonberries, black plums), vegetables (broccoli, capers, kale, red onion, radish, sorrel, watercress), leaves (fennel), seeds, and grains
Resveratrol	Stilbenoid (phenol)	Skin of grapes, blueberries, raspberries, mulberries and peanuts

Sulforaphane	Isothiocyanate	Cruciferous vegetables such as broccoli, Brussels sprouts, and cabbages
--------------	----------------	---

EGCG: Epigallocatechin gallate,

**Herbs, fruits or vegetables** such as garlic (14) or kiwi can also have antioxidant activities mediated by Nrf2 (7).

**Micronutrients** such as Zinc, Chromium, Selenium (15) and vitamin D (16) possess antioxidant activities associated, at least partly, with activation of Nrf2.

## 2- Cellular response to SARS-CoV-2

### 2-1- Endoplasmic reticulum stress response and Coronavirus

The coronavirus infection triggers ER stress responses in infected cells associated with increased levels of reactive oxygen species (ROS) and unfolded protein response (UPR) (17-19). As a general response, ER stress leads to PERK phosphorylation of the elongation initiation factor 2 $\alpha$  (eIF2 $\alpha$ ) and of Nrf2 (20). Activated PERK inactivates eIF2 $\alpha$ , leading to a decrease in overall protein synthesis. Phosphorylation of PKR and PERK has been observed in SARS-CoV-2-infected cells (21). ERK/MAPK and PI3K/AKT/mTOR signalling responses play important roles in Middle East respiratory syndrome coronavirus (MERS-CoV) infection (22). The key role in the synthesis of proteins essential for these mechanisms belongs to mTOR (mammalian target of rapamycin) complexes and signalling pathways involved in mTOR regulation including eIF2 $\alpha$  (23). mTOR is a serine/threonine protein kinase in the PI3K-related kinase (PIKK) family that forms the catalytic subunit of two distinct protein complexes, known as mTOR Complex 1 (mTORC1) and 2 (mTORC2). The mTOR pathway functions as a central regulator of cell metabolism, growth, proliferation, and survival. mTORC1 mainly functions as a nutrient/energy/redox sensor and controls protein synthesis, lipid metabolism, and organelle biogenesis (24). mTORC2 promotes the activation of insulin receptors and insulin-like growth factor 1 receptors. mTORC1 and C2 complexes are activated by nutrients, growth factors, and inflammatory mediators.

ER stress and sustained UPR signalling are major contributors to the pathogenesis of several diseases, including inflammatory disorders and viral infections (25) and can increase the severity of these events (26). ER stress has an important role in cardiovascular and metabolic disease, obesity and in diabetes (27, 28) and pancreatic  $\beta$ -cell dysfunction, often through mTOR (29). Oxidative stress is counter-balanced by complex antioxidant defence systems regulated by a series of multiple pathways, including the UPR, to ensure that the response to oxidants is adequate. Nrf2, interrelated with the UPR sensor called the pancreatic endoplasmic reticulum kinase, is a regulator of cellular resistance to oxidants (20, 30).

A recent study showed a disruption of mTOR signalling with increased levels of mTOR and a down-regulation of eIF2 signalling in multiple cellular compartments of severe COVID-19 patients when compared to patients who recovered (31).

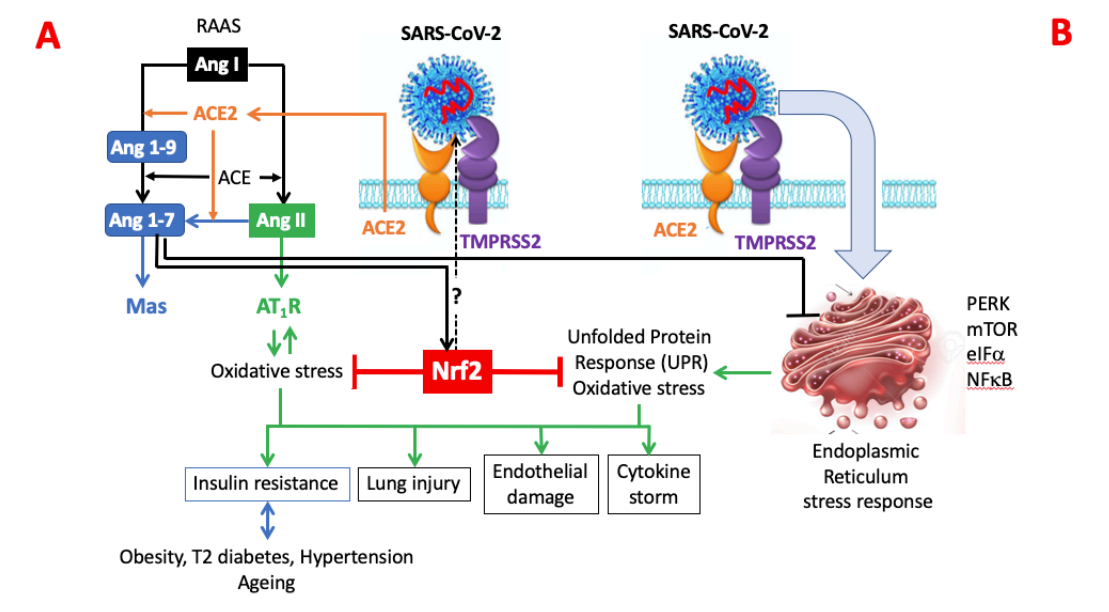
### 2-2- AT<sub>1</sub>R-associated effects

Angiotensin II (AngII) is the predominant Renin-Angiotensin-Aldosterone system (RAAS) component contributing to IR (32). The angiotensin-converting enzyme 2 (ACE2) receptor is part of the dual RAAS system consisting of an AT<sub>1</sub>R axis and an ACE-2-Angiotensin-(1-7)-Mas axis. AT<sub>1</sub>R is involved in most of the effects of Ang II, including oxidative stress generation (33), which in turn upregulates AT<sub>1</sub>R (34).

In metabolic disorders and with older age, there is an upregulation of the AT<sub>1</sub>R axis leading to pro-inflammatory, pro-fibrotic effects in the respiratory system, endothelial damage and IR (35). SARS-CoV-2 binds to its receptor ACE2 and exploits it for entry into the cell. The ACE2 downregulation, as a result of SARS-CoV-2 binding, enhances the AT<sub>1</sub>R axis (36) likely to be associated with IR (37, 38), but also with inflammation (39) and severe outcomes of COVID-19. Nrf2 is the most potent antioxidant in humans and can block the AT<sub>1</sub>R axis (6).

### 2-3- Cross-talk between the renin-angiotensin-aldosterone system (RAAS) and endoplasmic reticulum (Figure 1)

**Figure 1: Interactions between the renin-angiotensin-aldosterone system and the endoplasmic reticulum in COVID-19**



Several studies have shown an interaction of RAAS and ER in insulin resistance. Ang-II increases ER stress in adipose tissue (40). ACE2 regulates intramuscular fat by improving ER and mitochondrial function (41). On the other hand, Ang 1-7 protects against Ang II-induced ER stress and endothelial dysfunction via the Mas receptor (42). These mechanisms appear to be of great importance in COVID-19 and propose an interaction between ER stress and AT<sub>1</sub>R/Mas pathways with Nrf2 at the centre of the regulatory mechanism.

Moreover, in addition to reducing the production of infectious virions, the inhibition of ER glucosidases also impairs the entry of selected viruses via a post-receptor-binding mechanism (43).

### 2-4- Nrf2 in cytokine storm, endothelium and lung damage

The Nrf2 signalling pathway regulates anti-inflammatory gene expression and inhibits the progression of inflammation (44). In particular, the upregulation of Nrf2 signalling inhibits the overproduction of IL-6, pro-inflammatory cytokines, and chemokines as well as limiting the activation of NFκB.

Failure to protect against oxidative stress-induced cellular damage leads to endothelial dysfunction in cardiovascular diseases and other pathologies associated with metabolic syndrome. Several antioxidant

pathways are involved in cellular redox homeostasis, among which the Nrf2 signalling pathway is one of the most prominent (45).

Nrf2 induces cellular rescue pathways against oxidative pulmonary injury, abnormal inflammatory and immune responses, as well as apoptosis. The Nrf2 pathway can protect against various lung injuries including acute lung injury and acute respiratory distress syndrome (46).

## 2.5. Complexity of the anti-oxidant response

It is clear that Nrf2 is only one mechanism of the anti-oxidant stress and that multiple products can act on the anti-oxidant stress of COVID-19. As an example, sulforaphane protects against acetaminophen-induced hepatotoxicity (47). Its anti-oxidant and anti-inflammatory activity may be enhanced *in vitro* by combining it with some medications used in COVID-19 such as acetaminophen (48).

## 3- Nrf2-interacting nutrients and COVID-19

Obesity, possibly hypertension, type 2 diabetes (T2D) and ageing all represent risk factors for severe COVID-19 associated with cytokine storm and IL-6, endothelial damage in different organs and lung damage.

IR is a pathological condition in which cells fail to respond normally to the hormone insulin. Major mechanisms of IR include oxidative stress, inflammation, insulin receptor mutations, endoplasmic reticulum stress, and mitochondrial dysfunction (49). In COVID-19, IR can be induced by at least ER stress or the AT<sub>1</sub>R pathways. IR is a key component of the metabolic syndrome, a clustering of at least three of the five following medical conditions: abdominal obesity (50), high blood pressure (51), high blood sugar, high serum triglycerides, and low serum high-density lipoprotein (HDL) (52). The metabolic syndrome is associated with the risk of developing cardiovascular disease and T2D (53, 54). All nine Nrf2-interacting nutrients had some effect – although sometimes weak - against obesity, hypertension and T2D (Table 2).

**Table 2: Effect of Nrf2-interacting nutrients on diseases associated with oxidative stress**

<p><b>Search strategy:</b> For this table, in order to compare the mechanisms of action and properties of Nrf2-interacting nutrients, a PubMed search was initiated. This was not a systematic review, but an attempt to assess whether the impact on the disease has been described.</p> <ol style="list-style-type: none"> <li>1. We searched PubMed using the display option “best matches”.</li> <li>2. We first searched “systematic reviews” by PubMed for the different nutrients and we collected the first “best match” systematic review related to the question.</li> <li>3. If there was no systematic review, we searched for “reviews” and we collected the first “best match” review related to the question.</li> <li>4. If there was no review, we searched for papers and we collected the first “best match” paper related to the question.</li> </ol>								
---	--	--	--	--	--	--	--	--

	Insulin resistance						Lung injury	IL-6 cytokines
	AT1R	Obesity	HTA	T2D	Endothelium damage	Ageing		
Berberine		(55, 56)	(56)	(56-58)	(59)	(60)	(57)	(57)
Curcumin	(61)	(62, 63)	(64)	(65)	(66)	(67)	(68, 69)	(70)
EGCG	(71)	(63)	(72)	(73)	(72)	(67)	(74, 75)	(76)

Genistein	(77, 78)	(79)	(80)	(81)	(80)	(67)	(82)	(83)
<i>Lactobacillus</i>		(84, 85)	(86)	(87)	(88)	(89)	(90)	(91)
Quercetin		(62)	(92)	(93)	(72)	(67)	(94)	(95)
Resveratrol	(96)	(62, 63)	(97)	(98)	(99)	(67)	(100)	(101)
Sulforaphane		(102)	(103)	(103)	(104)	(67)	(105)	(106)

EGCG: Epigallocatechin gallate

IR is frequently associated with endothelial dysfunction and has been proposed to play a major role in cardiovascular (107), kidney (108) or cerebrovascular diseases (109). All nine Nrf2-interacting nutrients had an effect against endothelial damage.

Ageing is associated with IR (110) and all nine Nrf2-interacting nutrients had an effect on ageing. All nine Nrf2-interacting nutrients reduce IL-6 and cytokines.

#### 4- Mechanisms of Nrf2-interacting nutrients in COVID-19

Most Nrf2-interacting nutrients have an action on mTOR, PPAR $\gamma$ , NF $\kappa$ B, ERK and eIF2 $\alpha$  (Table 3).

**Table 3: Mechanisms involved in the antioxidant effects of Nrf2-interacting nutrients**

The **search strategy** used in Table 2 was applied in an attempt to assess whether a mechanism of action could be identified

	Nrf2	mTOR	PPAR $\gamma$	NF $\kappa$ B	ERK	eIF2 $\alpha$
Berberine	(57)	(60)	(59)	(111)	(60)	(112)
Curcumin	(67, 113)	(113, 114)	(113)	(113)	(113)	(115)
EGCG	(67)	(114)	(116)	(117, 118)	(118)	(119)
Genistein	(67)	(120)	(121)	(122) (123)	(124)	(125)
<i>Lactobacillus</i>	(126)	(127)	(128)	(126)	(129)	
Quercetin	(67)	(130)	(121)	(131)	(132)	(133)
Resveratrol	(67)	(114, 134)	(121)	(122)	(96)	(135)
Sulforaphane	(67)	(136, 137)	(103)	(103)	(138)	(139)

EGCG : Epigallocatechin gallate

##### 4-1- Anti-viral effects

Nrf2-interacting nutrients have large antiviral activities demonstrated in humans and animals (Table 4).

**Table 4: Antiviral effects of Nrf2-interacting nutrients**

The **search strategy** used in Table 2 was applied in an attempt to assess whether anti-viral or anti-COVID properties have been described

	Antiviral	COVID	STING
Berberine	(111)	(111)	
Curcumin	(140)	(141-144)	
EGCG	(145)	(146-149)	(150)
Genistein	(151)	(152)	



Lactobacillus	(153)	(153, 154)	
Quercetin	(155)	(156-160)	
Resveratrol	(161)	(162-166)	
Sulforaphane	(167)		(168)

Berberine through NF $\kappa$ B and MAPK pathways has an anti-viral activity on several viruses, and potentially against SARS-CoV-2 (111). Curcumin can block the entry of viruses into cells or its replication in the cell (140). It acts on NF $\kappa$ B (169) or MAPK (170). EGCG has multiple antiviral properties possibly through MAPK (171).

The suppressive effects of EGCG on viral replication were abolished in cells with knocked-down Nrf2 expression (172). siRNA-mediated depletion of Nrf2 boosted HIV infectivity in primary macrophages and reduced the anti-viral effects of sulforaphane (173). In a murine model, RSV-induced bronchopulmonary inflammation, epithelial injury, and mucus cell metaplasia as well as nasal epithelial injury were significantly greater in Nrf2(-/-) mice than in Nrf2(+/+) mice. Sulforaphane pre-treatment significantly limited lung RSV replication and virus-induced inflammation in Nrf2(+/+) but not in Nrf2(-/-) mice. This effect may be mediated through NF $\kappa$ B (174). Sulforaphane through Nrf2 significantly suppressed the hepatitis C virus (HCV) protein and RNA levels in HCV replicon cells and infectious system (175). Caffeic acid could modulate Keap1/Nrf2 interaction via increasing p62 expression, leading to the stabilization of Nrf2 and HO-1 induction, and an elicit IFN $\alpha$  antiviral response to suppress HCV replication (176). HCV genome replication was also suppressed in HCV sub-genomic replicon-bearing cells by bardoxolone methyl (BARD), an Nrf2 activator (177).

Type I IFNs (IFN $\alpha$  and - $\beta$ ) are central to immune-protection against viral infection (178). A balanced production of type I IFNs is needed for the protection against virus, but excessive production is a potent driver of pathology (178). Intracellular DNA and RNA sensors are essential in the innate immune response to viruses, causing the secretion of type I IFNs, cytokines and chemokines from infected cells. Viral cytosolic DNA is recognized by DNA sensors such as cyclic GMP-AMP synthase (cGAS) and its downstream signalling effector stimulator of interferon genes (STING) (179). Sulforaphane through Nrf2 activation decreases STING expression and responsiveness to STING agonists while increasing susceptibility to infection with DNA viruses (168). Reduction of STING expression by Nrf2 is mechanistically distinct from how Nrf2 reduces the release of the pro-inflammatory cytokines IL-1 $\beta$  and IL-6 (168). Nrf2 negatively regulates Type I INF responses and increases susceptibility to herpes genital infection in mice (180). Itaconate is a crucial anti-inflammatory metabolite that acts via Nrf2 to limit inflammation and modulate type I IFNs (181).

#### **4-2- mTOR and eIF2 $\alpha$**

Several Nrf2-interacting nutrients act through mTOR or eIF2 $\alpha$ . The insulin-sensitizing action of berberine was related to reducing ER stress in Hep G2 cells. The levels of phosphorylation both on PERK and eIF2 $\alpha$  were inhibited in cells pretreated with berberine (112). In an IR animal model, curcumin was found to act on eIF2 $\alpha$  (115). The induction of the ER stress pathway by green tea EGCG in colorectal cancer cells is mediated by the activation of PERK (182). The proteasome inhibitors Bortezomib (BZM) and MG132 trigger cancer cell death via induction of ER stress and UPR. EGCG antagonizes BZM toxicity by exacerbating the activation of autophagy and eIF2 $\alpha$  up-regulation (119). In rats, genistein protects against acute pancreatitis via the activation of an apoptotic pathway mediated through activation of multiple ER stress-related regulators like GRP78, PERK, and eIF2 $\alpha$  (125). Quercetin blocks airway epithelial cell chemokine expression through eIF2 $\alpha$  phosphorylation (133).

Pterostilbene (PT), a natural analogue of resveratrol, inhibits hepatocellular cell (HCC) growth without the induction of apoptosis in an ER stress- and autophagy-dependent manner through the eIF2 $\alpha$  pathway (135). Resveratrol modulates response against acute inflammatory stimuli in aged mouse brain. ER stress markers demonstrated significant changes in resveratrol-treated mice after LPS treatment, specifically in eIF2 $\alpha$  (183). Other studies have found an effect of resveratrol on eIF2 $\alpha$  (184, 185).

Sulforaphane exerts a neuroprotective effect involving Nrf2-dependent reductions in oxidative stress, mTOR-dependent inhibition of neuronal apoptosis, and the restoration of normal autophagy (186). Sulforaphane also inhibits mTOR in an Nrf2-independent manner (136).

Kimchi attenuates fatty streak formation in the aorta of low-density lipoprotein receptor knockout mice via the inhibition of ER stress (via several mechanisms including eIF2 $\alpha$ ) and apoptosis (187). Nutrients originating from Kimchi and its ingredients modulate the Nrf2/PERK signalling pathway to homeostasis in oxidative stress states. Kimchi and its bioactive compound ((3-4'-hydroxyl-3',5'-dimethoxyphenyl) propionic acid: HDMPPA), which is a metabolite result from fermentation, alleviate oxidative stress and inflammatory response not only via the Nrf2 pathway, but also via the PERK/CHOP pathway, which induced apoptosis of ER, in cardiovascular disease and ageing models (188-190). In addition, Arvelexin from *Brassica rapa* and anthocyanin-rich extract from red cabbage exert anti-inflammatory properties by the inhibition of NF- $\kappa$ B activation and by Nrf2-regulated HO-1 induction in macrophages and apolipoprotein E-deficient mice (191, 192), suggesting that Nrf2 activation during inflammation antagonizes the NF- $\kappa$ B pathway. It is possible that the intake of Kimchi may help to mitigate COVID-19 outcomes by maintaining or restoring the Nrf2 system.

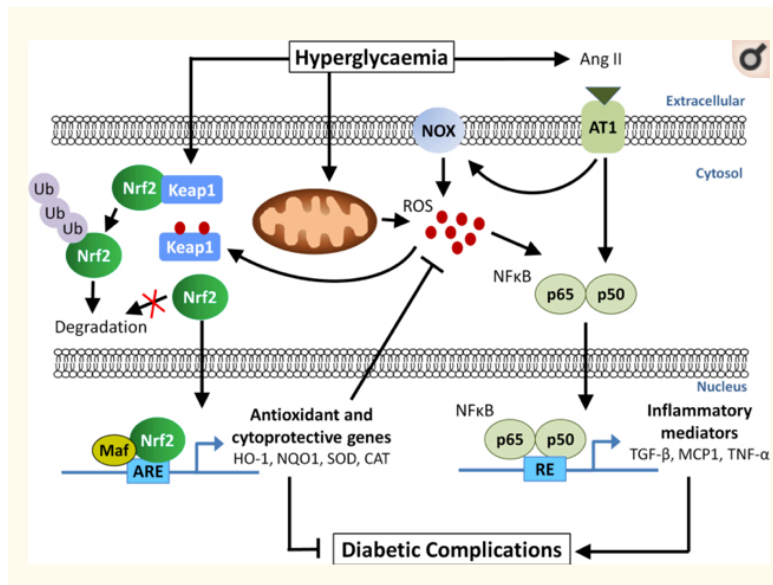
#### **4-3- AT<sub>1</sub>R**

Curcumin (61), EGCG (71), genistein (77, 78) and resveratrol (96) impact the AT<sub>1</sub>R pathway. NADPH oxidases of the Nox family are important sources of ROS and important agents in hypertension. They increase blood pressure in the presence of Ang II, an important and potent regulator of cardiovascular NADPH oxidase, via AT<sub>1</sub>R. Several natural compounds such as berberine, curcumin, quercitine, resveratrol and others are Nox inhibitors (193). Dietary curcumin supplementation can increase antioxidant activity through the induction of heme oxygenase-1, a scavenger of free radicals, and through the reduction of reactive oxygen species and Nox-2 (194). Sulforaphane reduces Ang II-induced vascular smooth muscle cells through Nrf2 signalling (195).

### **5- Complex interactions in oxidative stress**

IR induces oxidative stress either through the overproduction of superoxide by ER stress or the activation of Ang II-mediated upregulation of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase (NOX) activity, resulting in the cytosolic production of ROS (196) (Figure 2).

**Figure 2: Complex interactions leading to oxidative stress in diabetes** (from (196))



One of the key features of the complex interaction between nutrients and the oxidative stress/inflammatory response is the differential regulation of NFκB and Nrf2 by the cell redox status (197). Nrf2 and NFκB are present in an inactive form in the cytosol since they are linked to an inhibitory compound iNFκB or iNrf2 (Keap 1), both targets of reactive oxygen species (198-200). In the case of a large production of ROS, which would overwhelm the antioxidant defence, iNFκB is oxidized and catabolized. Furthermore, NFκB is translocated to the nucleus and initiates the expression of inflammatory proteins such as cytokines, chemokines, adhesion molecules, cytokine receptors, iNO synthases, lipoxygenases, cyclooxygenases and growth factors .... (201, 202). Once produced, cytokines are able to activate oxidant production by the NADPH oxidase complex, leading to an oxidative burst, which could in turn enhance the NFκB activation. Thus, NFκB activation results in a directional and synergistic linkage of inflammation and oxidative stress (199, 203).

The canonical pathway of Nrf2 activation also involves changes in the cell redox state (189). A weak or controlled ROS production results in the degradation of Keap 1. Thus, Nrf-2 could be translocated to the nucleus, binds to the antioxidant response element and activates an antioxidant enzyme such as Heme Oxygenase, SOD and catalase or cytoprotective genes (204, 205). It could also reduce the production of ROS (206). The increase in antioxidant defence maintains or restores the cellular redox state. In addition, Nrf2 stimulation could downregulate NFκB activation (207, 208). In fact, redox signalling appears as a black box, controlling both Nrf2 and NFκB activation and thus regulating inflammation and reparation. It is now recognized that the regulation of both pathways, NFκB and Nrf2, in part linked to the redox status, involved a cross talk to bring a coordinated inflammatory response (209, 210). The intensity of the ROS insult could be a key factor in the imbalance of the NFκB/Nrf2 system (211). In the case of oxidative stress, stimulation of NFκB (associated with a degradation of both Keap 1 and Nrf2) results in an amplification loop of inflammation. Thus, an imbalance between the NFκB and Nrf2 pathways has already been observed in T2D (195) or in multiple sclerosis. By contrast, an active and effective anti-oxidant system could result in a preventive loop leading to anti-oxidative and anti-inflammatory response. In this context, a positive modulation of Nrf2 by nutrients could act as an « oxidative pre-conditioning » system, and the resulting increase in the antioxidant enzyme could attenuate ROS deleterious effects and maintain cell integrity (212, 213).

This black box redox system could be effective in respiratory infection, particularly in COVID-19 (201). Indeed, COVID-19 activates RAAS and induces ER stress, resulting in ROS production (32, 33), which could be further enhanced by risk factors such as obesity, diabetes, and hypertension (214-216). Interestingly, RAAS activation seems related to COVID infection severity (39). If the ROS production overwhelms antioxidant defence, a vicious circle linking oxidative stress and inflammation is initiated leading to a cytokine storm, as well as lung and endothelial injury. On the other hand, if Nrf2 is activated via nutrients, the antioxidant response could maintain or restore an adequate redox status. This would lead to an antioxidant and anti-inflammatory response resulting in a pauci-symptomatic infection. Interestingly, very recently, a similar effect on the Nrf2/NfκB balance via redox signalling was hypothesized via ozone therapy (217).

However, although the therapeutic potential of Nrf2 raised great hopes in the early 2010s (218), Nrf2 levels vary significantly depending on the physiological and pathological context. Thus, a properly timed and targeted manipulation of the Nrf2 pathway is critical for an effective treatment (219). Surprisingly, only one Nrf2-based treatment has been approved: dimethyl fumarate (220), not devoid of side effects (221, 222). This suggests that the balance is difficult to reach in drug development. Nrf2 overexpression may also be associated with diabetic nephropathy or retinopathy (196). Recently, well-designed clinical trials with bardoxolone, an Nrf2 antagonist, were cancelled or stopped due to safety concerns (223). The Nrf2 system plays an important role in the body's natural defence against hyperglycaemia-induced damage. However, this initial adaptive response to counteract the diabetes-driven oxidative stress appears to be short-lived, after which the Nrf2 system becomes overwhelmed under chronic glucose stimulation (196).

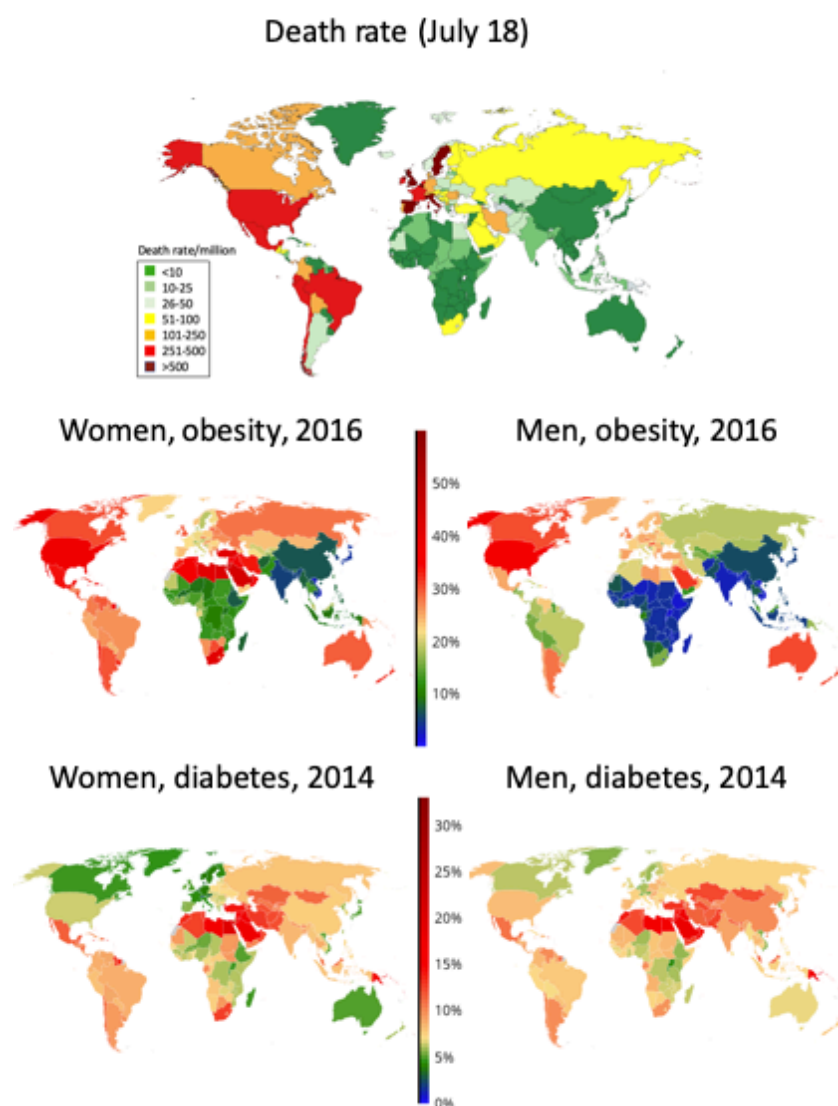
## **6- Obesity, diet, Nrf2 and COVID-19**

In general, T2D and obesity prevalence are associated and the following has been stated by the NCD Risk Factor Collaboration (NCD-RisC) “The upsurge of T2D reflects the global obesity epidemic” (224). However, many countries in Sub-Saharan Africa or Eastern Asia have a very low obesity prevalence that is not necessarily associated with a low diabetes prevalence (Figure 3). These countries have the lowest obesity prevalence as well as the lowest COVID-19 death rates. Obesity is lower in Canada than in the US and this may partly explain differences in COVID-19 severity between these two countries. Obesity is high in South Africa, possibly explaining the higher death rate in this country than in other Sub-Saharan African countries.

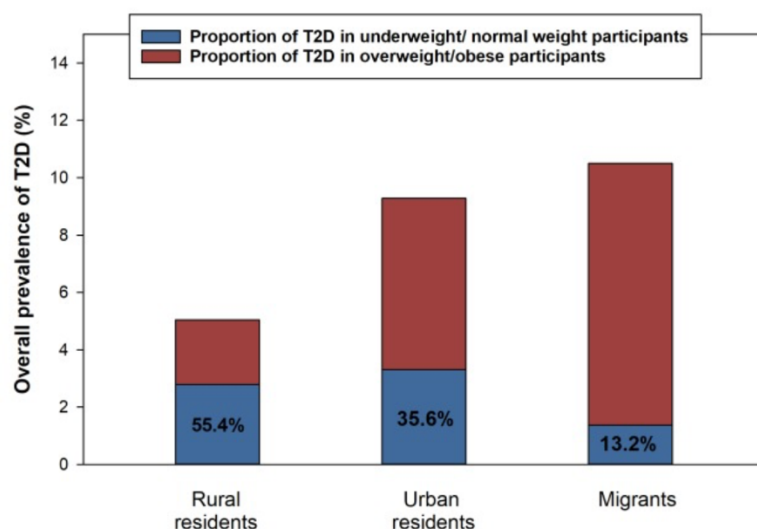
Many factors can explain this diabetes/obesity paradox. Genetic differences between countries are clear. However, the RODAM (Research on Obesity & Diabetes among African Migrants) study used a unique approach of comparing Ghanaians resident in the Netherlands, Germany, UK and Ghana to unravel the causes of obesity and T2D among African migrants and non-migrants. It showed striking differences suggesting that environmental factors are of great importance. Globally, one in 10 individuals is affected by T2D. In migrants, there is a higher T2D prevalence, the age of onset is younger and complications are more severe. One of the main determinants of T2D is obesity, which also disproportionately affects migrants (225-228). In rural Ghanaians, most T2D is independent of obesity (229) (Figure 4). Differences in food preferences were found across study sites: (i) in rural Ghana, diet concentrated on starchy foods (“roots, tubers, and plantain” diet) including cassava, (ii) in urban Ghana, nutrition was dominated by animal-based products, and (iii) in Europe, diet was highly diverse (230). The “roots, tubers, and plantain” diet was directly associated with increased 10-year cardiovascular disease risk (231) but the relationship between diet and T2D was unclear (232). In the national Korean cohort, obesity (50.4%) and abdominal obesity (47.8%) are associated with diabetes (233).

In COVID-19, obesity is a more severe risk factor than T2D (234). There is a dose-dependent association of obesity with worse COVID-19 morbidity requiring hospitalization and intensive care and with mortality. This particularly applies to patients younger than 50 to 60 years of age (235). Obesity is an important independent risk factor for serious COVID-19 disease (236, 237). The association between BMI and COVID-19-related mortality was U-shaped, both in type 1 diabetes and in T2D (lowest risk for those with a BMI of 25.0-29.9 kg/m<sup>2</sup>) (238). These data suggest differences between these two features of the metabolic syndrome for COVID-19 severity.

**Figure 3: Prevalence of obesity, diabetes** (NCD Risk Factor Collaboration (NCD-RisC, <http://ncdrisc.org>) **and the COVID-19 death rate** (Johns Hopkins Coronavirus Resource Center, <https://coronavirus.jhu.edu>)



**Figure 4: Links between obesity and diabetes in Ghanaians (229)**



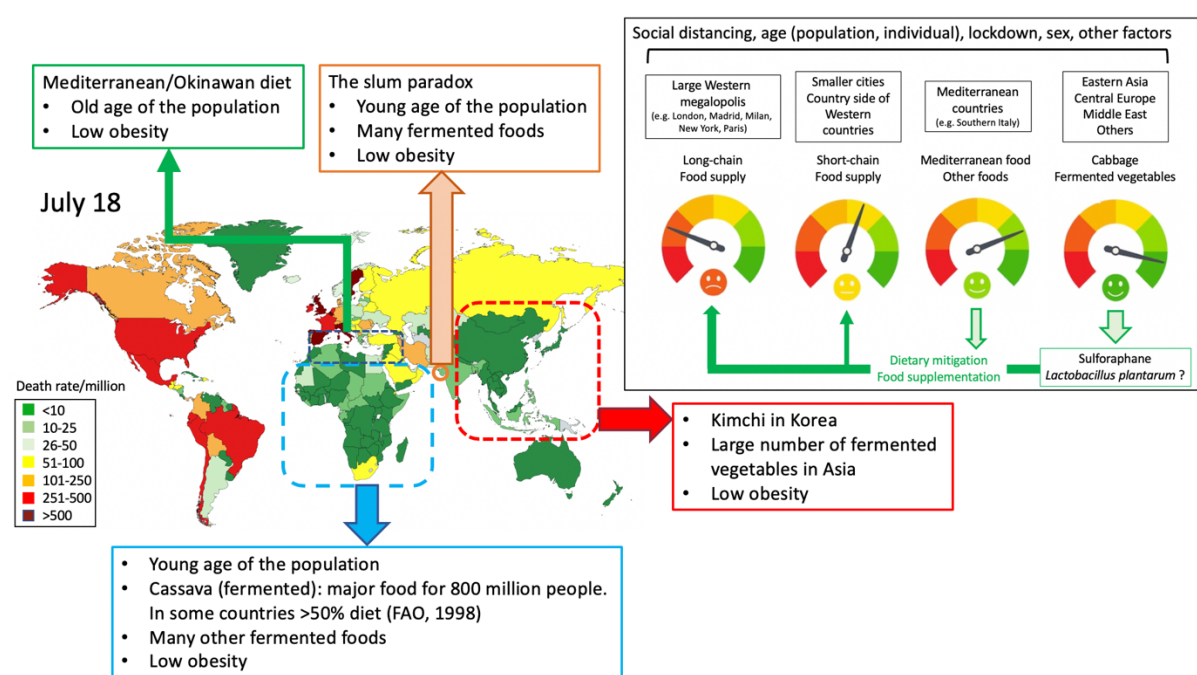
Nrf2 is also involved in complications of Type-1 diabetes (239). All nine Nrf2-interacting nutrients had an effect against obesity, often through IR (55, 56, 62, 63, 79, 84, 85, 102, 240, 241) (Table 2). In addition, Nrf2 may improve adipogenesis and adipocyte differentiation (242). Thus, diet may be important in the prevention/management of obesity and, at the same time, may reduce the impact of COVID-19.

## 7- Conclusions

Interestingly, all nutrients tested had a similar effect on IR, cytokine storm, lung injury and endothelial damage. They were all active on most of the tested Nrf2 pathways. These data strongly suggest a common mechanism of action for all nutrients. These effects appear to be highly conserved (243). However, we need to understand the differences between obesity and T2D in some countries with low obesity prevalence. These mechanisms may help to better appraise COVID-19 (Figure 5).

It is tempting to propose that Nrf2-interacting foods and nutrients can help re-balance IR, and that they can have a significant effect on COVID-19 severity, and possibly also on susceptibility to infection by SARS-CoV-2. It is therefore possible that an increasing intake of specific foods may achieve an optimal natural balance for the Nrf2 pathway, since COVID-19 death rates, used as a proxy of severity, are low or very low in some countries where Nrf2-interacting nutrients are largely used (Figure 5). Understanding the balance between Nrf2-interacting foods and nutrients would help to: (i) better understand the mechanisms of the oxidative stress in the IR diseases, (ii) develop optimal Nrf2-interacting nutrients and diets to reduce the prevalence and severity of IR diseases, (iii) optimize Nrf2 drug development and (iv) develop these strategies to mitigate COVID-19 severity.

**Figure 5: Geographic differences in COVID-19 death rates (Johns Hopkins Coronavirus center) and diet possibly explaining these differences**



There are still many unresolved questions requesting research on the time of onset of any efficacy of foods in COVID-19, the amount of the food to be administered and the interactions with the microbiome.

## References

1. Bousquet J, Czarlewski W, Blain H, Zuberbier T, Anto J. Rapid Response: Why Germany's case fatality rate seems so low: Is nutrition another possibility. *bmj*. 2020; <https://www.bmj.com/content/369/bmj.m1395/r-12>.
2. Bousquet J, Anto JM, Iaccarino G, Czarlewski W, Haahtela T, Anto A, et al. Is diet partly responsible for differences in COVID-19 death rates between and within countries? *Clin Transl Allergy*. 2020;10:16.
3. Bousquet J, Anto JM, Czarlewski W, Haahtela T, Fonseca SC, Iaccarino G, et al. Cabbage and fermented vegetables: from death rate heterogeneity in countries to candidates for mitigation strategies of severe COVID-19. *Allergy*. 2020.
4. Fonseca S, Rivas I, Romaguera D, Quijal M, Czarlewski W, Vidal A, et al. Association between consumption of fermented vegetables and COVID-19 mortality at a country level in Europe MEDRXIV/2020/147025 2020.
5. Fonseca S, Rivas I, Romaguera D, Quijal M, Czarlewski W, Vidal A, et al. Association between consumption of vegetables and COVID-19 mortality at a country level in Europe. *MedRxiv* 2020(10.1101/2020.07.17.20155846).
6. Tonelli C, Chio IIC, Tuveson DA. Transcriptional Regulation by Nrf2. *Antioxid Redox Signal*. 2018;29(17):1727-45.
7. Jimenez-Osorio AS, Gonzalez-Reyes S, Pedraza-Chaverri J. Natural Nrf2 activators in diabetes. *Clin Chim Acta*. 2015;448:182-92.
8. Pall ML, Levine S. Nrf2, a master regulator of detoxification and also antioxidant, anti-inflammatory and other cytoprotective mechanisms, is raised by health promoting factors. *Sheng Li Xue Bao*. 2015;67(1):1-18.
9. Iddir M, Brito A, Dingeo G, Fernandez Del Campo SS, Samouda H, La Frano MR, et al. Strengthening the Immune System and Reducing Inflammation and Oxidative Stress through Diet and Nutrition: Considerations during the COVID-19 Crisis. *Nutrients*. 2020;12(6).
10. Hassan SM, Jawad MJ, Ahjel SW, Singh RB, Singh J, Awad SM, et al. The Nrf2 Activator (DMF) and Covid-19: Is there a Possible Role? *Med Arch*. 2020;74(2):134-8.
11. Cuadrado A, Pajares M, Benito C, Jimenez-Villegas J, Escoll M, Fernandez-Gines R, et al. Can Activation of NRF2 Be a Strategy against COVID-19? *Trends Pharmacol Sci*. 2020.
12. Foldi M, Farkas N, Kiss S, Zadori N, Vancsa S, Szako L, et al. Obesity is a risk factor for developing critical condition in COVID-19 patients: A systematic review and meta-analysis. *Obes Rev*. 2020.
13. Mendonca P, Soliman KFA. Flavonoids Activation of the Transcription Factor Nrf2 as a Hypothesis



- Approach for the Prevention and Modulation of SARS-CoV-2 Infection Severity. *Antioxidants* (Basel). 2020;9(8).
14. Mocayar Maron FJ, Camargo AB, Manucha W. Allicin pharmacology: Common molecular mechanisms against neuroinflammation and cardiovascular diseases. *Life Sci*. 2020;249:117513.
  15. Schwarz M, Lossow K, Kopp JF, Schwerdtle T, Kipp AP. Crosstalk of Nrf2 with the Trace Elements Selenium, Iron, Zinc, and Copper. *Nutrients*. 2019;11(9).
  16. Berridge MJ. Vitamin D cell signalling in health and disease. *Biochem Biophys Res Commun*. 2015;460(1):53-71.
  17. Fung TS, Liao Y, Liu DX. Regulation of Stress Responses and Translational Control by Coronavirus. *Viruses*. 2016;8(7).
  18. Banerjee A, Czinn SJ, Reiter RJ, Blanchard TG. Crosstalk between endoplasmic reticulum stress and anti-viral activities: A novel therapeutic target for COVID-19. *Life Sci*. 2020;255:117842.
  19. Cui W, Li J, Ron D, Sha B. The structure of the PERK kinase domain suggests the mechanism for its activation. *Acta Crystallogr D Biol Crystallogr*. 2011;67(Pt 5):423-8.
  20. Cnop M, Toivonen S, Igoillo-Esteve M, Salpea P. Endoplasmic reticulum stress and eIF2alpha phosphorylation: The Achilles heel of pancreatic beta cells. *Mol Metab*. 2017;6(9):1024-39.
  21. Pfefferle S, Krahling V, Ditt V, Grywna K, Muhlberger E, Drosten C. Reverse genetic characterization of the natural genomic deletion in SARS-Coronavirus strain Frankfurt-1 open reading frame 7b reveals an attenuating function of the 7b protein in-vitro and in-vivo. *Virol J*. 2009;6:131.
  22. Kindrachuk J, Ork B, Hart BJ, Mazur S, Holbrook MR, Frieman MB, et al. Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome coronavirus infection as identified by temporal kinome analysis. *Antimicrob Agents Chemother*. 2015;59(2):1088-99.
  23. Rios-Fuller TJ, Mahe M, Walters B, Abbadi D, Perez-Baos S, Gadi A, et al. Translation Regulation by eIF2alpha Phosphorylation and mTORC1 Signaling Pathways in Non-Communicable Diseases (NCDs). *Int J Mol Sci*. 2020;21(15).
  24. Saxton RA, Sabatini DM. mTOR Signaling in Growth, Metabolism, and Disease. *Cell*. 2017;169(2):361-71.
  25. Oakes SA, Papa FR. The role of endoplasmic reticulum stress in human pathology. *Annu Rev Pathol*. 2015;10:173-94.
  26. So JS. Roles of Endoplasmic Reticulum Stress in Immune Responses. *Mol Cells*. 2018;41(8):705-16.
  27. Salvado L, Palomer X, Barroso E, Vazquez-Carrera M. Targeting endoplasmic reticulum stress in insulin resistance. *Trends Endocrinol Metab*. 2015;26(8):438-48.
  28. Villalobos-Labra R, Subiabre M, Toledo F, Pardo F, Sobrevia L. Endoplasmic reticulum stress and development of insulin resistance in adipose, skeletal, liver, and foetoplacental tissue in diabetes. *Mol Aspects Med*. 2019;66:49-61.
  29. Li M, Wang W, Dan Y, Tong Z, Chen W, Qin L, et al. Downregulation of amplified in breast cancer 1 contributes to the anti-tumor effects of sorafenib on human hepatocellular carcinoma. *Oncotarget*. 2016;7(20):29605-19.
  30. Cominacini L, Mozzini C, Garbin U, Pasini A, Stranieri C, Solani E, et al. Endoplasmic reticulum stress and Nrf2 signaling in cardiovascular diseases. *Free Radic Biol Med*. 2015;88(Pt B):233-42.
  31. Yao C, Bora SA, Parimon T, Zaman T, Friedman OA, Palatinus JA, et al. Cell type-specific immune dysregulation in severely ill COVID-19 patients. *medRxiv*. 2020.
  32. Underwood PC, Adler GK. The renin angiotensin aldosterone system and insulin resistance in humans. *Curr Hypertens Rep*. 2013;15(1):59-70.
  33. Wen H, Gwathmey JK, Xie LH. Oxidative stress-mediated effects of angiotensin II in the cardiovascular system. *World J Hypertens*. 2012;2(4):34-44.
  34. Bhatt SR, Lokhandwala MF, Banday AA. Vascular oxidative stress upregulates angiotensin II type I receptors via mechanisms involving nuclear factor kappa B. *Clin Exp Hypertens*. 2014;36(6):367-73.
  35. Dalan R, Bornstein SR, El-Armouche A, Rodionov RN, Markov A, Wielockx B, et al. The ACE-2 in COVID-19: Foe or Friend? *Horm Metab Res*. 2020;52(5):257-63.
  36. Sarzani R, Giulietti F, Di Pentima C, Giordano P, Spannella F. Disequilibrium between the Classic Renin-Angiotensin System and Its Opposing Arm in Sars-Cov-2 Related Lung Injury. *Am J Physiol Lung Cell Mol Physiol*. 2020.
  37. Bousquet J, Anto J, Czarlewski W, Haahtela T, Fonseca S, Iaccarino G, et al. Sulforaphane: from death rate heterogeneity in countries to candidate for prevention of severe COVID-19 Allergy. 2020;submitted.
  38. Ren H, Yang Y, Wang F, Yan Y, Shi X, Dong K, et al. Association of the insulin resistance marker TyG index with the severity and mortality of COVID-19. *Cardiovasc Diabetol*. 2020;19(1):58.
  39. Villard O, Morquin D, Molinari N, Raingeard I, Nagot N, Cristol JP, et al. The Plasmatic Aldosterone and C-Reactive Protein Levels, and the Severity of Covid-19: The Dyhor-19 Study. *J Clin Med*. 2020;9(7).
  40. Menikdiwela KR, Ramalingam L, Allen L, Scoggin S, Kalupahana NS, Moustaid-Moussa N. Angiotensin II Increases Endoplasmic Reticulum Stress in Adipose Tissue and Adipocytes. *Sci Rep*. 2019;9(1):8481.
  41. Cao X, Lu XM, Tuo X, Liu JY, Zhang YC, Song LN, et al. Angiotensin-converting enzyme 2 regulates endoplasmic reticulum stress and mitochondrial function to preserve skeletal muscle lipid metabolism. *Lipids Health Dis*. 2019;18(1):207.
  42. Murugan D, Lau YS, Lau CW, Mustafa MR, Huang Y. Angiotensin 1-7 Protects against Angiotensin II-Induced Endoplasmic Reticulum Stress and Endothelial Dysfunction via Mas Receptor. *PLoS One*. 2015;10(12):e0145413.
  43. Zhao X, Guo F, Comunale MA, Mehta A, Sehgal M, Jain P, et al. Inhibition of endoplasmic reticulum-resident glucosidases impairs severe acute respiratory syndrome coronavirus and human coronavirus NL63 spike protein-mediated entry by altering the glycan processing of angiotensin I-converting enzyme 2. *Antimicrob Agents Chemother*. 2015;59(1):206-16.



44. Ahmed SM, Luo L, Namani A, Wang XJ, Tang X. Nrf2 signaling pathway: Pivotal roles in inflammation. *Biochim Biophys Acta Mol Basis Dis.* 2017;1863(2):585-97.
45. Chen B, Lu Y, Chen Y, Cheng J. The role of Nrf2 in oxidative stress-induced endothelial injuries. *J Endocrinol.* 2015;225(3):R83-99.
46. Zhao H, Eguchi S, Alam A, Ma D. The role of nuclear factor-erythroid 2 related factor 2 (Nrf-2) in the protection against lung injury. *Am J Physiol Lung Cell Mol Physiol.* 2017;312(2):L155-L62.
47. Noh JR, Kim YH, Hwang JH, Choi DH, Kim KS, Oh WK, et al. Sulforaphane protects against acetaminophen-induced hepatotoxicity. *Food Chem Toxicol.* 2015;80:193-200.
48. Vuong LD, Nguyen QN, Truong VL. Anti-inflammatory and anti-oxidant effects of combination between sulforaphane and acetaminophen in LPS-stimulated RAW 264.7 macrophage cells. *Immunopharmacol Immunotoxicol.* 2019;41(3):413-9.
49. Yaribeygi H, Farrokhi FR, Butler AE, Sahebkar A. Insulin resistance: Review of the underlying molecular mechanisms. *J Cell Physiol.* 2019;234(6):8152-61.
50. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature.* 2006;444(7121):881-7.
51. Natali A, Ferrannini E. Hypertension, insulin resistance, and the metabolic syndrome. *Endocrinol Metab Clin North Am.* 2004;33(2):417-29.
52. Samson SL, Garber AJ. Metabolic syndrome. *Endocrinol Metab Clin North Am.* 2014;43(1):1-23.
53. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol.* 2010;56(14):1113-32.
54. O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. *Obes Rev.* 2015;16(1):1-12.
55. Asbaghi O, Ghanbari N, Shekari M, Reiner Z, Amirani E, Hallajzadeh J, et al. The effect of berberine supplementation on obesity parameters, inflammation and liver function enzymes: A systematic review and meta-analysis of randomized controlled trials. *Clin Nutr ESPEN.* 2020;38:43-9.
56. Li T, Yang GM, Zhu Y, Wu Y, Chen XY, Lan D, et al. Diabetes and hyperlipidemia induce dysfunction of VSMCs: contribution of the metabolic inflammation/miRNA pathway. *Am J Physiol Endocrinol Metab.* 2015;308(4):E257-69.
57. Ashrafizadeh M, Fekri HS, Ahmadi Z, Farkhondeh T, Samarghandian S. Therapeutic and biological activities of berberine: The involvement of Nrf2 signaling pathway. *J Cell Biochem.* 2020;121(2):1575-85.
58. Tabeshpour J, Imenshahidi M, Hosseinzadeh H. A review of the effects of *Berberis vulgaris* and its major component, berberine, in metabolic syndrome. *Iran J Basic Med Sci.* 2017;20(5):557-68.
59. Qiu H, Wu Y, Wang Q, Liu C, Xue L, Wang H, et al. Effect of berberine on PPAR $\alpha$ -NO signalling pathway in vascular smooth muscle cell proliferation induced by angiotensin IV. *Pharm Biol.* 2017;55(1):227-32.
60. Xu Z, Feng W, Shen Q, Yu N, Yu K, Wang S, et al. Rhizoma *Coptidis* and Berberine as a Natural Drug to Combat Aging and Aging-Related Diseases via Anti-Oxidation and AMPK Activation. *Aging Dis.* 2017;8(6):760-77.
61. Yao Y, Wang W, Li M, Ren H, Chen C, Wang J, et al. Curcumin Exerts its Anti-hypertensive Effect by Down-regulating the AT1 Receptor in Vascular Smooth Muscle Cells. *Sci Rep.* 2016;6:25579.
62. Zhao Y, Chen B, Shen J, Wan L, Zhu Y, Yi T, et al. The Beneficial Effects of Quercetin, Curcumin, and Resveratrol in Obesity. *Oxid Med Cell Longev.* 2017;2017:1459497.
63. Goktas Z, Zu Y, Abbasi M, Galyean S, Wu D, Fan Z, et al. Recent advances in nano-encapsulation of phytochemicals to combat obesity and its comorbidities. *J Agric Food Chem.* 2020.
64. Hadi A, Pourmasoumi M, Ghaedi E, Sahebkar A. The effect of Curcumin/Turmeric on blood pressure modulation: A systematic review and meta-analysis. *Pharmacol Res.* 2019;150:104505.
65. Pivari F, Mingione A, Brasacchio C, Soldati L. Curcumin and Type 2 Diabetes Mellitus: Prevention and Treatment. *Nutrients.* 2019;11(8).
66. Hallajzadeh J, Milajerdi A, Kollahdooz F, Amirani E, Mirzaei H, Asemi Z. The effects of curcumin supplementation on endothelial function: A systematic review and meta-analysis of randomized controlled trials. *Phytother Res.* 2019;33(11):2989-95.
67. Malavolta M, Bracci M, Santarelli L, Sayeed MA, Pierpaoli E, Giacconi R, et al. Inducers of Senescence, Toxic Compounds, and Senolytics: The Multiple Faces of Nrf2-Activating Phytochemicals in Cancer Adjuvant Therapy. *Mediators Inflamm.* 2018;2018:4159013.
68. Gouda MM, Bhandary YP. Acute Lung Injury: IL-17A-Mediated Inflammatory Pathway and Its Regulation by Curcumin. *Inflammation.* 2019;42(4):1160-9.
69. Lelli D, Sahebkar A, Johnston TP, Pedone C. Curcumin use in pulmonary diseases: State of the art and future perspectives. *Pharmacol Res.* 2017;115:133-48.
70. Mohammadi A, Blesso CN, Barreto GE, Banach M, Majeed M, Sahebkar A. Macrophage plasticity, polarization and function in response to curcumin, a diet-derived polyphenol, as an immunomodulatory agent. *J Nutr Biochem.* 2019;66:1-16.
71. Zhan XL, Yang XH, Gu YH, Guo LL, Jin HM. Epigallocatechin gallate protects against homocysteine-induced vascular smooth muscle cell proliferation. *Mol Cell Biochem.* 2018;439(1-2):131-40.
72. Yamagata K. Polyphenols Regulate Endothelial Functions and Reduce the Risk of Cardiovascular Disease. *Curr Pharm Des.* 2019;25(22):2443-58.
73. Khan N, Mukhtar H. Tea Polyphenols in Promotion of Human Health. *Nutrients.* 2018;11(1).
74. Favarin DC, de Oliveira JR, de Oliveira CJ, Rogerio Ade P. Potential effects of medicinal plants and secondary metabolites on acute lung injury. *Biomed Res Int.* 2013;2013:576479.
75. Wang J, Fan SM, Zhang J. Epigallocatechin-3-gallate ameliorates lipopolysaccharide-induced acute lung injury by suppression of TLR4/NF- $\kappa$ B signaling activation. *Braz J Med Biol Res.* 2019;52(7):e8092.

76. Martinez G, Mijares MR, De Sanctis JB. Effects of Flavonoids and Its Derivatives on Immune Cell Responses. *Recent Pat Inflamm Allergy Drug Discov.* 2019;13(2):84-104.
77. Malhotra A, Kang BP, Cheung S, Opawumi D, Meggs LG. Angiotensin II promotes glucose-induced activation of cardiac protein kinase C isozymes and phosphorylation of troponin I. *Diabetes.* 2001;50(8):1918-26.
78. Anandanadesan R, Gong Q, Chipitsyna G, Witkiewicz A, Yeo CJ, Arafat HA. Angiotensin II induces vascular endothelial growth factor in pancreatic cancer cells through an angiotensin II type 1 receptor and ERK1/2 signaling. *J Gastrointest Surg.* 2008;12(1):57-66.
79. Mukund V, Mukund D, Sharma V, Mannarapu M, Alam A. Genistein: Its role in metabolic diseases and cancer. *Crit Rev Oncol Hematol.* 2017;119:13-22.
80. Yamagata K. Soy Isoflavones Inhibit Endothelial Cell Dysfunction and Prevent Cardiovascular Disease. *J Cardiovasc Pharmacol.* 2019;74(3):201-9.
81. Weng L, Zhang F, Wang R, Ma W, Song Y. A review on protective role of genistein against oxidative stress in diabetes and related complications. *Chem Biol Interact.* 2019;310:108665.
82. Yi L, Chang M, Zhao Q, Zhou Z, Huang X, Guo F, et al. Genistein-3'-sodium sulphonate protects against lipopolysaccharide-induced lung vascular endothelial cell apoptosis and acute lung injury via BCL-2 signalling. *J Cell Mol Med.* 2020;24(1):1022-35.
83. Spagnuolo C, Moccia S, Russo GL. Anti-inflammatory effects of flavonoids in neurodegenerative disorders. *Eur J Med Chem.* 2018;153:105-15.
84. Crovesy L, Ostrowski M, Ferreira D, Rosado EL, Soares-Mota M. Effect of Lactobacillus on body weight and body fat in overweight subjects: a systematic review of randomized controlled clinical trials. *Int J Obes (Lond).* 2017;41(11):1607-14.
85. Lim S, Moon JH, Shin CM, Jeong D, Kim B. Effect of Lactobacillus sakei, a Probiotic Derived from Kimchi, on Body Fat in Koreans with Obesity: A Randomized Controlled Study. *Endocrinol Metab (Seoul).* 2020;35(2):425-34.
86. Lewis-Mikhael AM, Davoodvandi A, Jafarnejad S. Effect of Lactobacillus plantarum containing probiotics on blood pressure: A systematic review and meta-analysis. *Pharmacol Res.* 2020;153:104663.
87. Azad MAK, Sarker M, Li T, Yin J. Probiotic Species in the Modulation of Gut Microbiota: An Overview. *Biomed Res Int.* 2018;2018:9478630.
88. Skonieczna-Zydecka K, Kazmierczak-Siedlecka K, Kaczmarczyk M, Sliwa-Dominiak J, Maciejewska D, Janda K, et al. The Effect of Probiotics and Synbiotics on Risk Factors Associated with Cardiometabolic Diseases in Healthy People-A Systematic Review and Meta-Analysis with Meta-Regression of Randomized Controlled Trials. *J Clin Med.* 2020;9(6).
89. Malaguarnera G, Leggio F, Vacante M, Motta M, Giordano M, Bondi A, et al. Probiotics in the gastrointestinal diseases of the elderly. *J Nutr Health Aging.* 2012;16(4):402-10.
90. Khailova L, Petrie B, Baird CH, Dominguez Rieg JA, Wischmeyer PE. Lactobacillus rhamnosus GG and Bifidobacterium longum attenuate lung injury and inflammatory response in experimental sepsis. *PLoS One.* 2014;9(5):e97861.
91. Percopo CM, Ma M, Brenner TA, Krumholz JO, Break TJ, Laky K, et al. Critical Adverse Impact of IL-6 in Acute Pneumovirus Infection. *J Immunol.* 2019;202(3):871-82.
92. Marunaka Y, Marunaka R, Sun H, Yamamoto T, Kanamura N, Inui T, et al. Actions of Quercetin, a Polyphenol, on Blood Pressure. *Molecules.* 2017;22(2).
93. Eid HM, Haddad PS. The Antidiabetic Potential of Quercetin: Underlying Mechanisms. *Curr Med Chem.* 2017;24(4):355-64.
94. Gerin F, Sener U, Erman H, Yilmaz A, Aydin B, Armutcu F, et al. The Effects of Quercetin on Acute Lung Injury and Biomarkers of Inflammation and Oxidative Stress in the Rat Model of Sepsis. *Inflammation.* 2016;39(2):700-5.
95. Peluso I, Raguzzini A, Serafini M. Effect of flavonoids on circulating levels of TNF-alpha and IL-6 in humans: a systematic review and meta-analysis. *Mol Nutr Food Res.* 2013;57(5):784-801.
96. Gao Y, Kang L, Li C, Wang X, Sun C, Li Q, et al. Resveratrol Ameliorates Diabetes-Induced Cardiac Dysfunction Through AT1R-ERK/p38 MAPK Signaling Pathway. *Cardiovasc Toxicol.* 2016;16(2):130-7.
97. Bonnefont-Rousselot D. Resveratrol and Cardiovascular Diseases. *Nutrients.* 2016;8(5).
98. Ozturk E, Arslan AKK, Yerer MB, Bishayee A. Resveratrol and diabetes: A critical review of clinical studies. *Biomed Pharmacother.* 2017;95:230-4.
99. Li H, Xia N, Hasselwander S, Daiber A. Resveratrol and Vascular Function. *Int J Mol Sci.* 2019;20(9).
100. Conte E, Fagone E, Fruciano M, Gili E, Iemmolo M, Vancheri C. Anti-inflammatory and antifibrotic effects of resveratrol in the lung. *Histol Histopathol.* 2015;30(5):523-9.
101. Koushki M, Dashatan NA, Meshkani R. Effect of Resveratrol Supplementation on Inflammatory Markers: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Clin Ther.* 2018;40(7):1180-92 e5.
102. Martins T, Colaco B, Venancio C, Pires MJ, Oliveira PA, Rosa E, et al. Potential effects of sulforaphane to fight obesity. *J Sci Food Agric.* 2018;98(8):2837-44.
103. Patel B, Mann GE, Chapple SJ. Concerted redox modulation by sulforaphane alleviates diabetes and cardiometabolic syndrome. *Free Radic Biol Med.* 2018;122:150-60.
104. Cox AG, Gurusinghe S, Abd Rahman R, Leaw B, Chan ST, Mockler JC, et al. Sulforaphane improves endothelial function and reduces placental oxidative stress in vitro. *Pregnancy Hypertens.* 2019;16:1-10.
105. Zhao B, Gao W, Gao X, Leng Y, Liu M, Hou J, et al. Sulforaphane attenuates acute lung injury by inhibiting oxidative stress via Nrf2/HO-1 pathway in a rat sepsis model. *Int J Clin Exp Pathol.* 2017;10(8):9021-8.
106. Xie C, Zhu J, Jiang Y, Chen J, Wang X, Geng S, et al. Sulforaphane Inhibits the Acquisition of Tobacco Smoke-Induced Lung Cancer Stem Cell-Like

- Properties via the IL-6/DeltaNp63alpha/Notch Axis. *Theranostics*. 2019;9(16):4827-40.
107. Muniyappa R, Sowers JR. Role of insulin resistance in endothelial dysfunction. *Rev Endocr Metab Disord*. 2013;14(1):5-12.
  108. Artunc F, Schleicher E, Weigert C, Fritsche A, Stefan N, Haring HU. The impact of insulin resistance on the kidney and vasculature. *Nat Rev Nephrol*. 2016;12(12):721-37.
  109. Letra L, Sena C. Cerebrovascular Disease: Consequences of Obesity-Induced Endothelial Dysfunction. *Adv Neurobiol*. 2017;19:163-89.
  110. Costantino S, Paneni F, Cosentino F. Ageing, metabolism and cardiovascular disease. *J Physiol*. 2016;594(8):2061-73.
  111. Warowicka A, Nawrot R, Gozdicka-Jozefiak A. Antiviral activity of berberine. *Arch Virol*. 2020;165(9):1935-45.
  112. Wang ZS, Lu FE, Xu LJ, Dong H. Berberine reduces endoplasmic reticulum stress and improves insulin signal transduction in Hep G2 cells. *Acta Pharmacol Sin*. 2010;31(5):578-84.
  113. Patel SS, Acharya A, Ray RS, Agrawal R, Raghuvanshi R, Jain P. Cellular and molecular mechanisms of curcumin in prevention and treatment of disease. *Crit Rev Food Sci Nutr*. 2020;60(6):887-939.
  114. Zhou H, Luo Y, Huang S. Updates of mTOR inhibitors. *Anticancer Agents Med Chem*. 2010;10(7):571-81.
  115. Kobori M, Takahashi Y, Takeda H, Takahashi M, Izumi Y, Akimoto Y, et al. Dietary Intake of Curcumin Improves eIF2 Signaling and Reduces Lipid Levels in the White Adipose Tissue of Obese Mice. *Sci Rep*. 2018;8(1):9081.
  116. Babu PV, Liu D, Gilbert ER. Recent advances in understanding the anti-diabetic actions of dietary flavonoids. *J Nutr Biochem*. 2013;24(11):1777-89.
  117. Negri A, Naponelli V, Rizzi F, Bettuzzi S. Molecular Targets of Epigallocatechin-Gallate (EGCG): A Special Focus on Signal Transduction and Cancer. *Nutrients*. 2018;10(12).
  118. Dhatwalia SK, Kumar M, Dhawan DK. Role of EGCG in Containing the Progression of Lung Tumorigenesis - A Multistage Targeting Approach. *Nutr Cancer*. 2018;70(3):334-49.
  119. Modernelli A, Naponelli V, Giovanna Troglio M, Bonacini M, Ramazzina I, Bettuzzi S, et al. EGCG antagonizes Bortezomib cytotoxicity in prostate cancer cells by an autophagic mechanism. *Sci Rep*. 2015;5:15270.
  120. Tan HK, Moad AI, Tan ML. The mTOR signalling pathway in cancer and the potential mTOR inhibitory activities of natural phytochemicals. *Asian Pac J Cancer Prev*. 2014;15(16):6463-75.
  121. Wang L, Waltenberger B, Pferschy-Wenzig EM, Blunder M, Liu X, Malainer C, et al. Natural product agonists of peroxisome proliferator-activated receptor gamma (PPARgamma): a review. *Biochem Pharmacol*. 2014;92(1):73-89.
  122. Gupta SC, Kunnumakkara AB, Aggarwal S, Aggarwal BB. Inflammation, a Double-Edge Sword for Cancer and Other Age-Related Diseases. *Front Immunol*. 2018;9:2160.
  123. Pordanjani SM, Hosseinimehr SJ. The Role of NF-kB Inhibitors in Cell Response to Radiation. *Curr Med Chem*. 2016;23(34):3951-63.
  124. Dkhar B, Khongsti K, Thabab D, Syiem D, Satyamoorthy K, Das B. Genistein represses PEPCK-C expression in an insulin-independent manner in HepG2 cells and in alloxan-induced diabetic mice. *J Cell Biochem*. 2018;119(2):1953-70.
  125. Xia S, Wang J, Kalionis B, Zhang W, Zhao Y. Genistein protects against acute pancreatitis via activation of an apoptotic pathway mediated through endoplasmic reticulum stress in rats. *Biochem Biophys Res Commun*. 2019;509(2):421-8.
  126. Kong Y, Olejar KJ, On SLW, Chelikani V. The Potential of *Lactobacillus* spp. for Modulating Oxidative Stress in the Gastrointestinal Tract. *Antioxidants (Basel)*. 2020;9(7).
  127. Wang H, Cheng X, Zhang L, Xu S, Zhang Q, Lu R. A surface-layer protein from *Lactobacillus acidophilus* NCFM induces autophagic death in HCT116 cells requiring ROS-mediated modulation of mTOR and JNK signaling pathways. *Food Funct*. 2019;10(7):4102-12.
  128. Kim DH, Jeong D, Kang IB, Kim H, Song KY, Seo KH. Dual function of *Lactobacillus kefir* DH5 in preventing high-fat-diet-induced obesity: direct reduction of cholesterol and upregulation of PPAR-alpha in adipose tissue. *Mol Nutr Food Res*. 2017;61(11).
  129. Jeong M, Kim JH, Yang H, Kang SD, Song S, Lee D, et al. Heat-Killed *Lactobacillus plantarum* KCTC 13314BP Enhances Phagocytic Activity and Immunomodulatory Effects Via Activation of MAPK and STAT3 Pathways. *J Microbiol Biotechnol*. 2019;29(8):1248-54.
  130. Sanches-Silva A, Testai L, Nabavi SF, Battino M, Pandima Devi K, Tejada S, et al. Therapeutic potential of polyphenols in cardiovascular diseases: Regulation of mTOR signaling pathway. *Pharmacol Res*. 2020;152:104626.
  131. Chekalina N, Burmak Y, Petrov Y, Borisova Z, Manusha Y, Kazakov Y, et al. Quercetin reduces the transcriptional activity of NF-kB in stable coronary artery disease. *Indian Heart J*. 2018;70(5):593-7.
  132. Shaik Y, Caraffa A, Ronconi G, Lessiani G, Conti P. Impact of polyphenols on mast cells with special emphasis on the effect of quercetin and luteolin. *Cent Eur J Immunol*. 2018;43(4):476-81.
  133. Nana S, Zick SM, Andrade JE, Sajjan US, Burgess JR, Lukacs NW, et al. Quercetin blocks airway epithelial cell chemokine expression. *Am J Respir Cell Mol Biol*. 2006;35(5):602-10.
  134. Widlund AL, Baur JA, Vang O. mTOR: more targets of resveratrol? *Expert Rev Mol Med*. 2013;15:e10.
  135. Yu CL, Yang SF, Hung TW, Lin CL, Hsieh YH, Chiou HL. Inhibition of eIF2alpha dephosphorylation accelerates pterostilbene-induced cell death in human hepatocellular carcinoma cells in an ER stress and autophagy-dependent manner. *Cell Death Dis*. 2019;10(6):418.
  136. Zhang Y, Gilmour A, Ahn YH, de la Vega L, Dinkova-Kostova AT. The isothiocyanate sulforaphane inhibits mTOR in an NRF2-independent manner. *Phytochemistry*. 2019;153:062.
  137. Shawky NM, Segar L. Sulforaphane inhibits platelet-derived growth factor-induced vascular smooth muscle cell proliferation by targeting mTOR/p70S6kinase signaling independent of Nrf2 activation. *Pharmacol Res*. 2017;119:251-64.

138. Jo C, Kim S, Cho SJ, Choi KJ, Yun SM, Koh YH, et al. Sulforaphane induces autophagy through ERK activation in neuronal cells. *FEBS Lett.* 2014;588(17):3081-8.
139. Doudican NA, Wen SY, Mazumder A, Orlow SJ. Sulforaphane synergistically enhances the cytotoxicity of arsenic trioxide in multiple myeloma cells via stress-mediated pathways. *Oncol Rep.* 2012;28(5):1851-8.
140. Praditya D, Kirchhoff L, Bruning J, Rachmawati H, Steinmann J, Steinmann E. Anti-infective Properties of the Golden Spice Curcumin. *Front Microbiol.* 2019;10:912.
141. Rocha FAC, de Assis MR. Curcumin as a potential treatment for COVID-19. *Phytother Res.* 2020.
142. Roy A, Sarkar B, Celik C, Ghosh A, Basu U, Jana M, et al. Can concomitant use of zinc and curcumin with other immunity-boosting nutraceuticals be the arsenal against COVID-19? *Phytother Res.* 2020.
143. Zahedipour F, Hosseini SA, Sathyapalan T, Majeed M, Jamialahmadi T, Al-Rasadi K, et al. Potential effects of curcumin in the treatment of COVID-19 infection. *Phytother Res.* 2020.
144. Gupta H, Gupta M, Bhargava S. Potential use of turmeric in COVID-19. *Clin Exp Dermatol.* 2020.
145. Xu J, Xu Z, Zheng W. A Review of the Antiviral Role of Green Tea Catechins. *Molecules.* 2017;22(8).
146. Menegazzi M, Campagnari R, Bertoldi M, Crupi R, Di Paola R, Cuzzocrea S. Protective Effect of Epigallocatechin-3-Gallate (EGCG) in Diseases with Uncontrolled Immune Activation: Could Such a Scenario Be Helpful to Counteract COVID-19? *Int J Mol Sci.* 2020;21(14).
147. Mhatre S, Srivastava T, Naik S, Patravale V. Antiviral activity of green tea and black tea polyphenols in prophylaxis and treatment of COVID-19: A review. *Phytomedicine.* 2020;153286.
148. Nguyen TT, Woo HJ, Kang HK, Nguyen VD, Kim YM, Kim DW, et al. Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in *Pichia pastoris*. *Biotechnol Lett.* 2012;34(5):831-8.
149. Russo M, Moccia S, Spagnuolo C, Tedesco I, Russo GL. Roles of flavonoids against coronavirus infection. *Chem Biol Interact.* 2020;109211.
150. Tian Y, Bao Z, Ji Y, Mei X, Yang H. Epigallocatechin-3-Gallate Protects H2O2-Induced Nucleus Pulposus Cell Apoptosis and Inflammation by Inhibiting cGAS/Sting/NLRP3 Activation. *Drug Des Devel Ther.* 2020;14:2113-22.
151. Andres A, Donovan SM, Kuhlenschmidt MS. Soy isoflavones and virus infections. *J Nutr Biochem.* 2009;20(8):563-9.
152. Elfiky AA. Natural products may interfere with SARS-CoV-2 attachment to the host cell. *J Biomol Struct Dyn.* 2020;1-10.
153. Villena J, Kitazawa H. The Modulation of Mucosal Antiviral Immunity by Immunobiotics: Could They Offer Any Benefit in the SARS-CoV-2 Pandemic? *Front Physiol.* 2020;11:699.
154. Morais AHA, Passos TS, Maciel BLL, da Silva-Maia JK. Can Probiotics and Diet Promote Beneficial Immune Modulation and Purine Control in Coronavirus Infection? *Nutrients.* 2020;12(6).
155. Batiha GE, Beshbishy AM, Ikram M, Mulla ZS, El-Hack MEA, Taha AE, et al. The Pharmacological Activity, Biochemical Properties, and Pharmacokinetics of the Major Natural Polyphenolic Flavonoid: Quercetin. *Foods.* 2020;9(3).
156. Colunga Biancatelli RML, Berrill M, Catravas JD, Marik PE. Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19). *Front Immunol.* 2020;11:1451.
157. Glinsky GV. Tripartite Combination of Candidate Pandemic Mitigation Agents: Vitamin D, Quercetin, and Estradiol Manifest Properties of Medicinal Agents for Targeted Mitigation of the COVID-19 Pandemic Defined by Genomics-Guided Tracing of SARS-CoV-2 Targets in Human Cells. *Biomedicines.* 2020;8(5).
158. Pandey P, Rane JS, Chatterjee A, Kumar A, Khan R, Prakash A, et al. Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: an in silico study for drug development. *J Biomol Struct Dyn.* 2020:1-11.
159. Polansky H, Lori G. Coronavirus disease 2019 (COVID-19): first indication of efficacy of Gene-Eden-VIR/Novirin in SARS-CoV-2 infection. *Int J Antimicrob Agents.* 2020;55(6):105971.
160. Williamson G, Kerimi A. Testing of natural products in clinical trials targeting the SARS-CoV-2 (Covid-19) viral spike protein-angiotensin converting enzyme-2 (ACE2) interaction. *Biochem Pharmacol.* 2020;178:114123.
161. Abba Y, Hassim H, Hamzah H, Noordin MM. Antiviral Activity of Resveratrol against Human and Animal Viruses. *Adv Virol.* 2015;2015:184241.
162. Han YJ, Ren ZG, Li XX, Yan JL, Ma CY, Wu DD, et al. Advances and challenges in the prevention and treatment of COVID-19. *Int J Med Sci.* 2020;17(12):1803-10.
163. Hooper PL. COVID-19 and heme oxygenase: novel insight into the disease and potential therapies. *Cell Stress Chaperones.* 2020.
164. Marinella MA. Indomethacin and resveratrol as potential treatment adjuncts for SARS-CoV-2/COVID-19. *Int J Clin Pract.* 2020:e13535.
165. McLachlan CS. The angiotensin-converting enzyme 2 (ACE2) receptor in the prevention and treatment of COVID-19 are distinctly different paradigms. *Clin Hypertens.* 2020;26:14.
166. Wahedi HM, Ahmad S, Abbasi SW. Stilbene-based natural compounds as promising drug candidates against COVID-19. *J Biomol Struct Dyn.* 2020:1-10.
167. Lin CY, Yao CA. Potential Role of Nrf2 Activators with Dual Antiviral and Anti-Inflammatory Properties in the Management of Viral Pneumonia. *Infect Drug Resist.* 2020;13:1735-41.
168. Olgarnier D, Brandt AM, Gundersen C, Villadsen NL, Krapp C, Thielke AL, et al. Nrf2 negatively regulates STING indicating a link between antiviral sensing and metabolic reprogramming. *Nat Commun.* 2018;9(1):3506.
169. Divya CS, Pillai MR. Antitumor action of curcumin in human papillomavirus associated cells involves downregulation of viral oncogenes, prevention of NFkB and AP-1 translocation, and modulation of apoptosis. *Mol Carcinog.* 2006;45(5):320-32.
170. Hesari A, Ghasemi F, Salarinia R, Biglari H, Tabar Molla Hassan A, Abdoli V, et al. Effects of curcumin on NF-kappaB, AP-1, and Wnt/beta-catenin

- signaling pathway in hepatitis B virus infection. *J Cell Biochem.* 2018;119(10):7898-904.
171. Shih LJ, Chen TF, Lin CK, Liu HS, Kao YH. Green tea (-)-epigallocatechin gallate inhibits the growth of human villous trophoblasts via the ERK, p38, AMP-activated protein kinase, and protein kinase B pathways. *Am J Physiol Cell Physiol.* 2016;311(2):C308-21.
  172. Kesic MJ, Simmons SO, Bauer R, Jaspers I. Nrf2 expression modifies influenza A entry and replication in nasal epithelial cells. *Free Radic Biol Med.* 2011;51(2):444-53.
  173. Furuya AK, Sharifi HJ, Jellinger RM, Cristofano P, Shi B, de Noronha CM. Sulforaphane Inhibits HIV Infection of Macrophages through Nrf2. *PLoS Pathog.* 2016;12(4):e1005581.
  174. Cho HY, Imani F, Miller-DeGraff L, Walters D, Melendi GA, Yamamoto M, et al. Antiviral activity of Nrf2 in a murine model of respiratory syncytial virus disease. *Am J Respir Crit Care Med.* 2009;179(2):138-50.
  175. Yu JS, Chen WC, Tseng CK, Lin CK, Hsu YC, Chen YH, et al. Sulforaphane Suppresses Hepatitis C Virus Replication by Up-Regulating Heme Oxygenase-1 Expression through PI3K/Nrf2 Pathway. *PLoS One.* 2016;11(3):e0152236.
  176. Shen J, Wang G, Zuo J. Caffeic acid inhibits HCV replication via induction of IFN $\alpha$  antiviral response through p62-mediated Keap1/Nrf2 signaling pathway. *Antiviral Res.* 2018;154:166-73.
  177. Nio Y, Sasai M, Akahori Y, Okamura H, Hasegawa H, Oshima M, et al. Bardoxolone methyl as a novel potent antiviral agent against hepatitis B and C viruses in human hepatocyte cell culture systems. *Antiviral Res.* 2019;169:104537.
  178. Teijaro JR. Pleiotropic Roles of Type 1 Interferons in Antiviral Immune Responses. *Adv Immunol.* 2016;132:135-58.
  179. Motwani M, Pesiridis S, Fitzgerald KA. DNA sensing by the cGAS-STING pathway in health and disease. *Nat Rev Genet.* 2019;20(11):657-74.
  180. Gunderstofte C, Iversen MB, Peri S, Thielke A, Balachandran S, Holm CK, et al. Nrf2 Negatively Regulates Type I Interferon Responses and Increases Susceptibility to Herpes Genital Infection in Mice. *Front Immunol.* 2019;10:2101.
  181. Mills EL, Ryan DG, Prag HA, Dikovskaya D, Menon D, Zaslonka Z, et al. Itaconate is an anti-inflammatory metabolite that activates Nrf2 via alkylation of KEAP1. *Nature.* 2018;556(7699):113-7.
  182. Md Nesran ZN, Shafie NH, Ishak AH, Mohd Esa N, Ismail A, Md Tohid SF. Induction of Endoplasmic Reticulum Stress Pathway by Green Tea Epigallocatechin-3-Gallate (EGCG) in Colorectal Cancer Cells: Activation of PERK/p-eIF2 $\alpha$ /ATF4 and IRE1 $\alpha$ . *Biomed Res Int.* 2019;2019:3480569.
  183. Palomera-Avalos V, Grinan-Ferre C, Izquierdo V, Camins A, Sanfeliu C, Canudas AM, et al. Resveratrol modulates response against acute inflammatory stimuli in aged mouse brain. *Exp Gerontol.* 2018;102:3-11.
  184. Zhang C, Zhou Y, Zhou Y, Lu Y, Wang D. Regulation of eIF2 $\alpha$  expression and renal interstitial fibrosis by resveratrol in rat renal tissue after unilateral ureteral obstruction. *Ren Fail.* 2016;38(4):622-8.
  185. Liu J, Fan C, Yu L, Yang Y, Jiang S, Ma Z, et al. Pterostilbene exerts an anti-inflammatory effect via regulating endoplasmic reticulum stress in endothelial cells. *Cytokine.* 2016;77:88-97.
  186. Zhou Q, Chen B, Wang X, Wu L, Yang Y, Cheng X, et al. Sulforaphane protects against rotenone-induced neurotoxicity in vivo: Involvement of the mTOR, Nrf2, and autophagy pathways. *Sci Rep.* 2016;6:32206.
  187. Woo M, Kim M, Noh JS, Park CH, Song YO. Kimchi attenuates fatty streak formation in the aorta of low-density lipoprotein receptor knockout mice via inhibition of endoplasmic reticulum stress and apoptosis. *Nutr Res Pract.* 2017;11(6):445-51.
  188. Woo M, Kim MJ, Song YO. Bioactive Compounds in Kimchi Improve the Cognitive and Memory Functions Impaired by Amyloid Beta. *Nutrients.* 2018;10(10).
  189. Woo M, Noh JS, Cho EJ, Song YO. Bioactive Compounds of Kimchi Inhibit Apoptosis by Attenuating Endoplasmic Reticulum Stress in the Brain of Amyloid beta-Injected Mice. *J Agric Food Chem.* 2018;66(19):4883-90.
  190. Kim HJ, Noh JS, Song YO. Beneficial Effects of Kimchi, a Korean Fermented Vegetable Food, on Pathophysiological Factors Related to Atherosclerosis. *J Med Food.* 2018;21(2):127-35.
  191. Joo HK, Choi S, Lee YR, Lee EO, Park MS, Park KB, et al. Anthocyanin-Rich Extract from Red Chinese Cabbage Alleviates Vascular Inflammation in Endothelial Cells and Apo E(-/-) Mice. *Int J Mol Sci.* 2018;19(3).
  192. Shin JS, Noh YS, Lee YS, Cho YW, Baek NI, Choi MS, et al. Arvelexin from Brassica rapa suppresses NF-kappaB-regulated pro-inflammatory gene expression by inhibiting activation of IkappaB kinase. *Br J Pharmacol.* 2011;164(1):145-58.
  193. Yousefian M, Shakour N, Hosseinzadeh H, Hayes AW, Hadizadeh F, Karimi G. The natural phenolic compounds as modulators of NADPH oxidases in hypertension. *Phytomedicine.* 2019;55:200-13.
  194. Karimian MS, Pirro M, Johnston TP, Majeed M, Sahebkar A. Curcumin and Endothelial Function: Evidence and Mechanisms of Protective Effects. *Curr Pharm Des.* 2017;23(17):2462-73.
  195. Zhang M, Xu Y, Qiu Z, Jiang L. Sulforaphane Attenuates Angiotensin II-Induced Vascular Smooth Muscle Cell Migration via Suppression of NOX4/ROS/Nrf2 Signaling. *Int J Biol Sci.* 2019;15(1):148-57.
  196. Tan SM, de Haan JB. Combating oxidative stress in diabetic complications with Nrf2 activators: how much is too much? *Redox Rep.* 2014;19(3):107-17.
  197. Silva-Islas CA, Maldonado PD. Canonical and non-canonical mechanisms of Nrf2 activation. *Pharmacol Res.* 2018;134:92-9.
  198. Nair S, Doh ST, Chan JY, Kong AN, Cai L. Regulatory potential for concerted modulation of Nrf2- and Nfkb1-mediated gene expression in inflammation and carcinogenesis. *Br J Cancer.* 2008;99(12):2070-82.
  199. Chen KK, Minakuchi M, Wuputra K, Ku CC, Pan JB, Kuo KK, et al. Redox control in the pathophysiology of influenza virus infection. *BMC Microbiol.* 2020;20(1):214.

200. Pedruzzi LM, Stockler-Pinto MB, Leite M, Jr., Mafra D. Nrf2-keap1 system versus NF-kappaB: the good and the evil in chronic kidney disease? *Biochimie*. 2012;94(12):2461-6.
201. Cecchini R, Cecchini AL. SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression. *Med Hypotheses*. 2020;143:110102.
202. Hawiger J, Zienkiewicz J. Decoding inflammation, its causes, genomic responses, and emerging countermeasures. *Scand J Immunol*. 2019;90(6):e12812.
203. Morena M, Cristol JP, Senecal L, Leray-Moragues H, Krieter D, Canaud B. Oxidative stress in hemodialysis patients: is NADPH oxidase complex the culprit? *Kidney Int Suppl*. 2002(80):109-14.
204. Kurutas EB. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. *Nutr J*. 2016;15(1):71.
205. Delgado-Roche L, Riera-Romo M, Mesta F, Hernandez-Matos Y, Barrios JM, Martinez-Sanchez G, et al. Medical ozone promotes Nrf2 phosphorylation reducing oxidative stress and pro-inflammatory cytokines in multiple sclerosis patients. *Eur J Pharmacol*. 2017;811:148-54.
206. Song MG, Ryoo IG, Choi HY, Choi BH, Kim ST, Heo TH, et al. NRF2 Signaling Negatively Regulates Phorbol-12-Myristate-13-Acetate (PMA)-Induced Differentiation of Human Monocytic U937 Cells into Pro-Inflammatory Macrophages. *PLoS One*. 2015;10(7):e0134235.
207. Herpers B, Wink S, Fredriksson L, Di Z, Hendriks G, Vrieling H, et al. Activation of the Nrf2 response by intrinsic hepatotoxic drugs correlates with suppression of NF-kappaB activation and sensitizes toward TNFalpha-induced cytotoxicity. *Arch Toxicol*. 2016;90(5):1163-79.
208. Li W, Khor TO, Xu C, Shen G, Jeong WS, Yu S, et al. Activation of Nrf2-antioxidant signaling attenuates NF-kappaB-inflammatory response and elicits apoptosis. *Biochem Pharmacol*. 2008;76(11):1485-9.
209. Mohan S, Gupta D. Crosstalk of toll-like receptors signaling and Nrf2 pathway for regulation of inflammation. *Biomed Pharmacother*. 2018;108:1866-78.
210. Wardyn JD, Ponsford AH, Sanderson CM. Dissecting molecular cross-talk between Nrf2 and NF-kappaB response pathways. *Biochem Soc Trans*. 2015;43(4):621-6.
211. Clavo B, Rodriguez-Esparragon F, Rodriguez-Abreu D, Martinez-Sanchez G, Llontop P, Aguiar-Bujanda D, et al. Modulation of Oxidative Stress by Ozone Therapy in the Prevention and Treatment of Chemotherapy-Induced Toxicity: Review and Prospects. *Antioxidants (Basel)*. 2019;8(12).
212. Leon OS, Menendez S, Merino N, Castillo R, Sam S, Perez L, et al. Ozone oxidative preconditioning: a protection against cellular damage by free radicals. *Mediators Inflamm*. 1998;7(4):289-94.
213. Khatlani T, Algudiri D, Alenzi R, Al Subayyil AM, Abomaray FM, Bahattab E, et al. Preconditioning by Hydrogen Peroxide Enhances Multiple Properties of Human Decidua Basalis Mesenchymal Stem/Multipotent Stromal Cells. *Stem Cells Int*. 2018;2018:6480793.
214. Vide J, Virsolvy A, Romain C, Ramos J, Jouy N, Richard S, et al. Dietary silicon-enriched spirulina improves early atherosclerosis markers in hamsters on a high-fat diet. *Nutrition*. 2015;31(9):1148-54.
215. Al-Awwadi NA, Araiz C, Bornet A, Delbosc S, Cristol JP, Linck N, et al. Extracts enriched in different polyphenolic families normalize increased cardiac NADPH oxidase expression while having differential effects on insulin resistance, hypertension, and cardiac hypertrophy in high-fructose-fed rats. *J Agric Food Chem*. 2005;53(1):151-7.
216. Sinha N, Dabla PK. Oxidative stress and antioxidants in hypertension-a current review. *Curr Hypertens Rev*. 2015;11(2):132-42.
217. Martinez-Sanchez G, Schwartz A, Donna VD. Potential Cytoprotective Activity of Ozone Therapy in SARS-CoV-2/COVID-19. *Antioxidants (Basel)*. 2020;9(5).
218. Hybertson BM, Gao B, Bose SK, McCord JM. Oxidative stress in health and disease: the therapeutic potential of Nrf2 activation. *Mol Aspects Med*. 2011;32(4-6):234-46.
219. Dodson M, de la Vega MR, Cholanians AB, Schmidlin CJ, Chapman E, Zhang DD. Modulating NRF2 in Disease: Timing Is Everything. *Annu Rev Pharmacol Toxicol*. 2019;59:555-75.
220. Hayashi G, Jasoliya M, Sahdeo S, Sacca F, Pane C, Filla A, et al. Dimethyl fumarate mediates Nrf2-dependent mitochondrial biogenesis in mice and humans. *Hum Mol Genet*. 2017;26(15):2864-73.
221. Satoh T, Lipton S. Recent advances in understanding NRF2 as a druggable target: development of pro-electrophilic and non-covalent NRF2 activators to overcome systemic side effects of electrophilic drugs like dimethyl fumarate. *F1000Res*. 2017;6:2138.
222. Saidu NEB, Kavian N, Leroy K, Jacob C, Nicco C, Batteux F, et al. Dimethyl fumarate, a two-edged drug: Current status and future directions. *Med Res Rev*. 2019;39(5):1923-52.
223. Moreno JA, Gomez-Guerrero C, Mas S, Sanz AB, Lorenzo O, Ruiz-Ortega M, et al. Targeting inflammation in diabetic nephropathy: a tale of hope. *Expert Opin Investig Drugs*. 2018;27(11):917-30.
224. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet*. 2016;387(10026):1377-96.
225. Addo J, Agyemang C, de-Graft Aikins A, Beune E, Schulze MB, Danquah I, et al. Association between socioeconomic position and the prevalence of type 2 diabetes in Ghanaians in different geographic locations: the RODAM study. *J Epidemiol Community Health*. 2017;71(7):633-9.
226. Agyemang C, Beune E, Meeks K, Addo J, Aikins AD, Bahendeka S, et al. Innovative ways of studying the effect of migration on obesity and diabetes beyond the common designs: lessons from the RODAM study. *Ann N Y Acad Sci*. 2017;1391(1):54-70.
227. Agyemang C, Meeks K, Beune E, Owusu-Dabo E, Mockenhaupt FP, Addo J, et al. Obesity and type 2 diabetes in sub-Saharan Africans - Is the burden in today's Africa similar to African migrants in

- Europe? The RODAM study. *BMC Med*. 2016;14(1):166.
228. Boateng D, Agyemang C, Beune E, Meeks K, Smeeth L, Schulze M, et al. Migration and Cardiovascular Disease Risk Among Ghanaian Populations in Europe: The RODAM Study (Research on Obesity and Diabetes Among African Migrants). *Circ Cardiovasc Qual Outcomes*. 2017;10(11).
  229. Chilunga FP, Henneman P, Meeks KA, Beune E, Requena-Mendez A, Smeeth L, et al. Prevalence and determinants of type 2 diabetes among lean African migrants and non-migrants: the RODAM study. *J Glob Health*. 2019;9(2):020426.
  230. Galbete C, Nicolaou M, Meeks K, Klipstein-Grobusch K, de-Graft Aikins A, Addo J, et al. Dietary patterns and type 2 diabetes among Ghanaian migrants in Europe and their compatriots in Ghana: the RODAM study. *Nutr Diabetes*. 2018;8(1):25.
  231. Boateng D, Galbete C, Nicolaou M, Meeks K, Beune E, Smeeth L, et al. Dietary Patterns Are Associated with Predicted 10-Year Risk of Cardiovascular Disease Among Ghanaian Populations: the Research on Obesity and Diabetes in African Migrants (RODAM) Study. *J Nutr*. 2019;149(5):755-69.
  232. Danquah I, Galbete C, Meeks K, Nicolaou M, Klipstein-Grobusch K, Addo J, et al. Food variety, dietary diversity, and type 2 diabetes in a multi-center cross-sectional study among Ghanaian migrants in Europe and their compatriots in Ghana: the RODAM study. *Eur J Nutr*. 2018;57(8):2723-33.
  233. Nam GE, Kim YH, Han K, Jung JH, Park YG, Lee KW, et al. Obesity Fact Sheet in Korea, 2018: Data Focusing on Waist Circumference and Obesity-Related Comorbidities. *J Obes Metab Syndr*. 2019;28(4):236-45.
  234. Finer N, Garnett SP, Bruun JM. COVID-19 and obesity. *Clin Obes*. 2020;10(3):e12365.
  235. Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, et al. Obesity and Mortality Among Patients Diagnosed With COVID-19: Results From an Integrated Health Care Organization. *Ann Intern Med*. 2020.
  236. Kass DA. COVID-19 and Severe Obesity: A Big Problem? *Ann Intern Med*. 2020.
  237. Klang E, Kassim G, Soffer S, Freeman R, Levin MA, Reich DL. Severe Obesity as an Independent Risk Factor for COVID-19 Mortality in Hospitalized Patients Younger than 50. *Obesity (Silver Spring)*. 2020.
  238. Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol*. 2020.
  239. Negi CK, Jena G. Nrf2, a novel molecular target to reduce type 1 diabetes associated secondary complications: The basic considerations. *Eur J Pharmacol*. 2019;843:12-26.
  240. Xu L, Nagata N, Ota T. Glucoraphanin: a broccoli sprout extract that ameliorates obesity-induced inflammation and insulin resistance. *Adipocyte*. 2018;7(3):218-25.
  241. Kunnumakkara AB, Bordoloi D, Padmavathi G, Monisha J, Roy NK, Prasad S, et al. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. *Br J Pharmacol*. 2017;174(11):1325-48.
  242. Zhang Z, Zhou S, Jiang X, Wang YH, Li F, Wang YG, et al. The role of the Nrf2/Keap1 pathway in obesity and metabolic syndrome. *Rev Endocr Metab Disord*. 2015;16(1):35-45.
  243. Bayliak MM, Abrat OB, Storey JM, Storey KB, Lushchak VI. Interplay between diet-induced obesity and oxidative stress: Comparison between *Drosophila* and mammals. *Comp Biochem Physiol A Mol Integr Physiol*. 2019;228:18-28.

