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Toxicology and Applied Pharmacology 456 (2022) 116267

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

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

Synergistic action of organophosphates and COVID-19 on inflammation, oxidative stress, and renin-angiotensin system can amplify the risk of cardiovascular maladies

Prem Rajak [a,*], Sumedha Roy [b], Sayanti Podder [c], Moumita Dutta [d], Saurabh Sarkar [e], Abhratanu Ganguly [a], Moutushi Mandi [f], Anik Dutta [g], Sayantani Nanda [a], Salma Khatun [h]

[a] Department of Animal Science, Kazi Nazrul University, Asansol, West Bengal, India
[b] Cytogenetics Laboratory, Department of Zoology, The University of Burdwan, West Bengal, India
[c] The Orchid School, Pune, Maharashtra, India
[d] Departments of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA
[e] Department of Zoology, Gushkara Mahavidyalaya; Gushkara, Purba Bardhaman, West Bengal, India
[f] Toxicology Research Unit, Department of Zoology, The University of Burdwan, Purba Bardhaman, West Bengal, India
[g] Post Graduate Department of Zoology, Darjeeling Govt. College, West Bengal, India
[h] Department of Zoology, Krishna Chandra College, Hetampur, West Bengal, India

ARTICLE INFO

Editor: Lawrence Lash

Keywords:
Organophosphates
Cardiotoxicity
COVID-19
Renin-Angiotensin System

ABSTRACT

Organophosphates (OPs) are ubiquitous environmental contaminants, widely used as pesticides in agricultural fields. In addition, they serve as flame-retardants, plasticizers, antifoaming or antiwear agents in lacquers, hydraulic fluids, and floor polishing agents. Therefore, world-wide and massive application of these compounds have increased the risk of unintentional exposure to non-targets including the human beings. OPs are neurotoxic agents as they inhibit the activity of acetylcholinesterase at synaptic cleft. Moreover, they can fuel cardiovascular issues in the form of myocardities, cardiac oedema, arrhythmia, systolic malfunction, infarction, and altered electrophysiology. Such pathological outcomes might increase the severity of cardiovascular diseases which are the leading cause of mortality in the developing world. Coronavirus disease-19 (COVID-19) is the ongoing global health emergency caused by SARS-CoV-2 infection. Similar to OPs, SARS-CoV-2 disrupts cytokine homeostasis, redox-balance, and angiotensin-II/AT_1R axis to promote cardiovascular injuries. Therefore, during the current pandemic milieu, unintentional exposure to OPs through several environmental sources could escalate cardiac maladies in patients with COVID-19.

1. Introduction

Scientists and health workers across the world are racing together to halt the recent COVID-19 pandemic triggered by SARS-CoV-2 infection. The disease was first detected in Wuhan province of China in December 2019 and rapidly extended to 213 countries. There have been 611,421,786 confirmed cases with 6,512,438 casualties as of 23rd September 2022 (https://covid19.who.int/). Potent vaccines have been developed by different laboratories and the vaccination program is still continuing in several countries. However, it is to be noted that, vaccines usually does not provide 100% protection from re-infection. Therefore even after vaccination, people have to be serious about COVID-19 and need to follow the proper guidelines released by World Health Organization and local governing bodies to minimize the risk of re-infection. Unfortunately, many European, African, and Asian countries are suffering from subsequent waves of COVID-19 due to emergence of new variants of the virus. The B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.427 (Epsilon), B.1.429 (Epsilon), and B.1.617.2 (Delta) variants detected in many countries are classified as variants of concern. These variants are unusually divergent, each possessing a unique constellation of mutations of potential biological importance and hence can evade the immune barrier developed from a previous SARS-CoV-2 infection.

In majority of cases, virions entering through naso-oral opening first colonize broncho-pulmonary epithelium and fuel necroinflammation-mediated pulmonary ailments (Rajak et al., 2021a). From lungs,

* Corresponding author.
E-mail address: prem.rjk@gmail.com (P. Rajak).

https://doi.org/10.1016/j.taap.2022.116267
Received 9 August 2022; Received in revised form 26 September 2022; Accepted 4 October 2022
Available online 12 October 2022

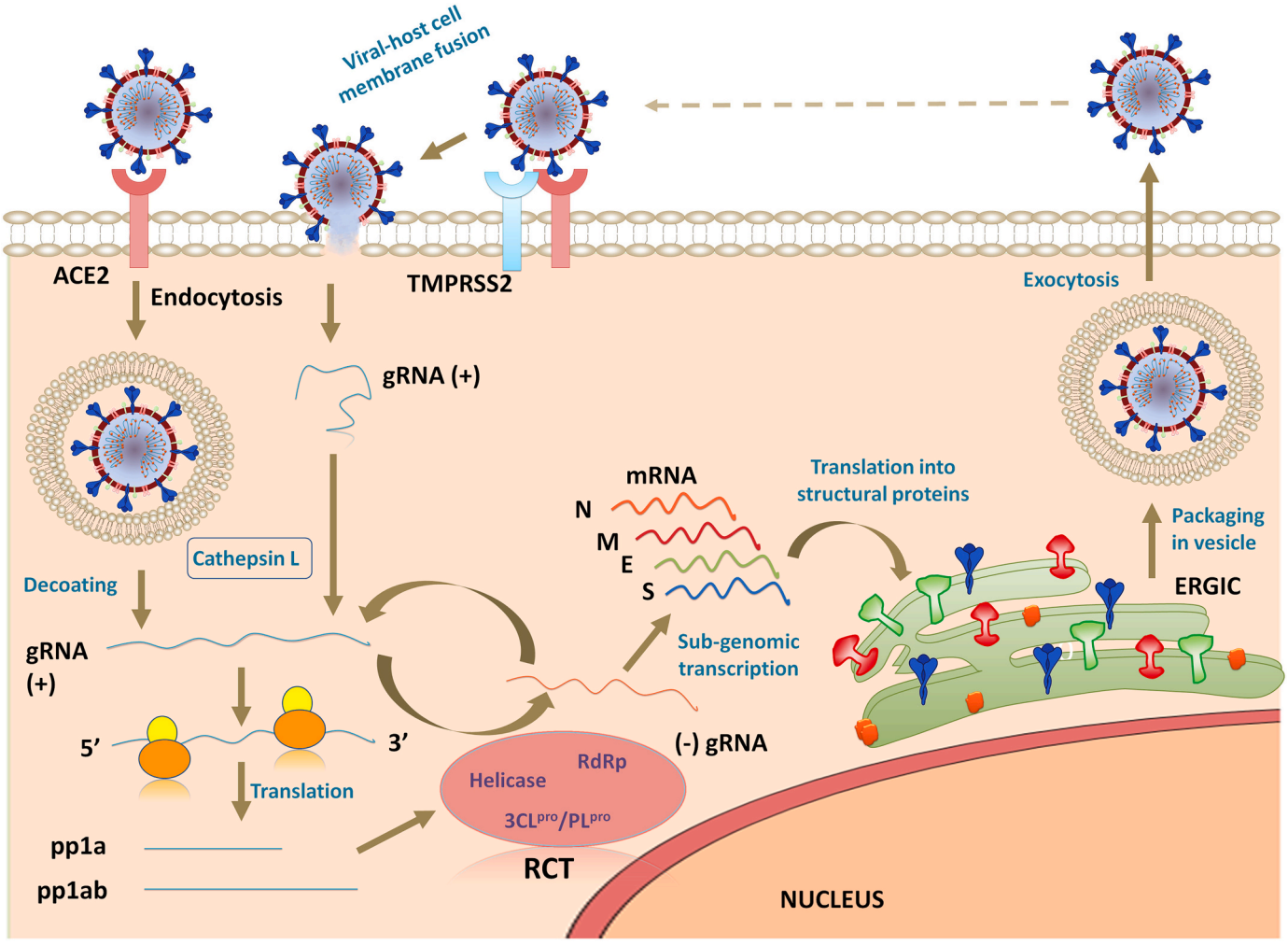

Fig. 1. Life cycle of SARS-CoV-2. Virions of SARS-CoV-2 follow endosomal route using cathepsin or direct viral-host cell membrane fusion using serine protease TMPRSS2 to transfer their genome into the host cytoplasm. Using host cell translational machinery, virus translates (+) ss viral RNA into polyproteins (pp1a and pp1ab) that are processed to generated a nested set of non-structural proteins (NSPs) which serve as proteases ($3CL^{pro}/PL^{pro}$), helicase, and RNA dependent RNA polymerase (RdRP). NSPs utilize (+) ss viral RNA to synthesize (−) ss viral RNA which goes through sub-genomic transcription to produce mRNAs for structural proteins. Structural proteins follow the route of Endoplasmic reticulum-Golgi-intermediate compartment (ERGIC) for their packaging into virions. Mature virions left the existing host cell via exocytosis to infect the new one.

SARS-CoV-2 can spread to other organs via blood by invading the endothelial lining of blood vessels (Rajak et al., 2021b; Varga et al., 2020). Several SARS-CoV-2 entry receptors such as angiotensin converting enzyme-2 (ACE-2), TMPRSS2, cathepsin L, CD26, ezrin, furin, and cyclophilins are expressed in multiple organs in the body including heart. Hence, these organs are under scanner of numerous such pathogenic virions. ACE-2 are the key receptors involved in the priming of spike glycoprotein of virions and are expressed mostly in the pericytes of heart than the lungs (Chen et al., 2020). In addition, expression levels of furin and cathepsin L are similar in heart and lung tissues. However, expression of TMPRSS2 in heart is comparatively low that can be compensated by furin and cathepsin L (Liu et al., 2020). Therefore, cardiovascular system is a potential direct target of infection by SARS-CoV-2 virions. Moreover, different manifestations of infection such as oxidative stress, cytokine storm, and disrupted renin-angiotensin system could further escalate COVID-19 mediated cardiovascular issues in patients.

With the rising population and expanding urbanization in the developing world, demand for food is increasing rapidly to beat the hunger of nearly 7.6 billion people across the globe. Simultaneously, pesticide economy has amplified by several folds worldwide to meet the ever-increasing demand of the crops, fruits, and vegetables in the global market. However, adverse effects of these formulations have been reported on non-targets (Khatun et al., 2017; Dutta et al., 2017; Khatun et al., 2018; Rajak and Roy, 2018; Dutta et al., 2019; Sarkar et al., 2018; Rajak et al., 2021c; Ghanty et al., 2022). Every year ~3.5 billion kilograms of pesticides belonging to organophosphates (OPs), organochlorines, pyrethroids, carbamates, and triazines are used in the agricultural field to enhance crop production. Among them, organophosphate is the leading one with >30% of all pesticide sells in the global market and expected to exhibit a compound annual growth rate of 5.5% during the forecast period 2018–2023 (https://www.mordorintelligence.com/industry-reports/organophosphate-pesticides-market).

OPs are the esters of phosphoric acid. Their generalized molecular architecture is comprised of a central phosphate molecule with alkyl or aromatic substituents. Major OP chemicals include malathion, parathion, acephate, phorate, chlorpyriphos, dichlorvos, and diazinon. Their application has been extended from agricultural sector to residential purpose in the form of flame retardants, plasticizers, antifoaming or anti-wear agents in lacquers, hydraulic fluids, and floor polishing agents. Therefore, massive application and ubiquitous presence of the OP chemicals have contaminated essential food-items such as fruits, crops, meats, vegetables, milk etc., and hence amplified the risk of chronic/acute human exposure to these biocides.

Box 1

Important terminologies at a glance

Myocarditis: It is an inflammation in heart muscles and usually caused by viral infection. It may result in weak cardiac contraction, insufficient pumping of blood as well as irregular heart beat.

Pericarditis: It is an inflammation of the pericardium, the covering of heart. Pericarditis may be caused by microbial pathogens including virus. It is characterized by chest pain, dry cough and anxiety or fatigue.

Arrhythmia: Arrhythmia describes an improper beating of heart in which electrical signals are not working correctly.

***Myocardial infarction* (*MI*)/heart attack**: MI occurs when blood flow decreases or stops to a portion of heart. Most common symptoms includes chest pain that may propagate towards back, shoulder, arm, neck or jaw.

Atrial fibrillation: It is an irregular heart beat that can promote blood clots, strokes and cardiac failure.

Endotheliitis: Endotheliitis is an immune response in which endothelium of blood vessels becomes inflamed and lead to oedema of the surrounding tissue with irritation and pain.

Myocardial hypertrophy: It is an increase in ventricular myocardial mass and associated with heart failure.

Coagulopathy: Coagulopathy is a condition in which blood's ability to coagulate is disrupted. It results in prolonged or excessive bleeding.

***Electrocardiogram* (*ECG*)**: ECG is a simple, painless test that measures electrical activity of heart. It helps to monitor heart rhythm and blood flow.

Troponins (T & I): These are the proteins found in cardiac muscles and participate in muscle contraction. Elevated level of troponins in blood is an indicator of cardiac muscle injury.

NT-proBNP: NT-proBNP (N-terminal prohormone of brain natriuretic peptide) is prohormone which is synthesized in response to left ventricular wall-stretch and assists in vasodilation, dieresis and natriuresis to protect heart from increased blood pressure. It is an important marker of cardiac injury and heart failure.

Fulminant myocarditis (FM): FM is an uncommon ailment caused by sudden and severe inflammation of cardiac tissue often leading to death.

Kawasaki disease: A condition caused by inflamed blood vessels. Symptoms include fever and pilling skin.

The mode of action of OPs is associated with the inhibition of acetylcholinesterase enzyme activity at the synaptic cleft leading to the accumulation of neurotransmitter, acetylcholine (Abou-Donia, 2003; Rajak et al., 2017). These molecular events initiate hyperexcitation, paralysis, and finally death to the exposed organisms. Intriguingly, recent evidences have narrated OPs to a nexus of biological responses producing other toxic-outcomes (Rajak et al., 2014; Mandi et al., 2020; Rajak et al., 2018; Yu et al., 2017; Rajak et al., 2013; Rajak et al., 2015). Among numerous toxic-outcomes, cardiotoxicity has emerged out as a sounding one. Cardiotoxicity is a condition when there is damage to cardiomyocytes and as a result, heart faces difficulties in pumping ample amount of blood throughout the body. In severe cases, cardiotoxicity often leads to cardiomyopathy which is characterized by weakness in heart muscles and alteration in heart-beat rhythm. Other outcome of cardiotoxicity includes inflammation of heart muscles (myocarditis), inflammation of pericardial sac (pericarditis), and damage of blood vessels (acute coronary syndromes). Studies cited in the current literature have validated the toxic impacts of OPs on cardiac tissue of human and model animals therefore pointing towards their undeniable contribution to cardiovascular diseases which are the leading cause of mortality in the developing world (Prabhakaran et al., 2016).

Since, COVID-19 and OPs have similar potential to damage cardiovascular system; therefore, exposure to OPs might escalate cardiac injury in patients with SARS-CoV-2 infection.

Thus, the current literature aims to discuss impacts of SARS-CoV-2 infection on cardiac health of patients and to narrate how exposure to SARS-CoV-2 and OPs could augment the cardiovascular injury.

2. Genetic architecture and lifecycle of SARS-CoV-2

SARS-CoV-2, a member of the Coronaviridae family is a retrovirus which contains positive sense ssRNA as the genetic material. Genome of the virus is 29,903 nucleotides long, flanked by 5′ and 3′ untranslated regions (UTR). Seven stem-loop structures are present at 5′-UTR, while one stem-loop and a pseudoknot have been detected at the 3′-UTR. Genome of the virus contains 14 open reading frames (ORFs) followed by transcriptional regulatory sequences (TRSs). The two main transcriptional units, ORF1a and ORF1ab encode for two major replicase polyproteins such as 1a (PP1a) and 1ab (PP1ab) (Romano et al., 2020). Within the largest polyprotein i.e., pp1ab, non-structural proteins (Nsp1–16) are embedded that constitute the replicase transcriptase complex (RCT). Near the 3'UTR, viral RNA encodes for four structural peptides such as spike (S), envelope (E), membrane (M), and nucleocapsid (N) that are the integral components of a mature virion. The 3′ end of the genome contains nine ORFs interspersed among the structural genes for accessory proteins that are crucial to evade host immune system (Wu et al., 2016).

SARS-CoV-2 invades target cells through interaction between viral spike glycoprotein and the host angiotensin converting enzyme-2 (ACE-2). Other entry factors like Neuropilin-1 (NRP-1), CD147, furin, lysosomal cathepsin L (CTSL), and cathepsin B (CTSB) may also facilitate viral entry into the host cell. After Spike-ACE-2 attachment, protease TMPRSS2 cleaves and activates the spike protein that allows the viral genome to enter either directly into the host cell or via the endocytic pathways (Fig. 1). Once inside the cell, genome of the virus is translated by host ribosome to produce enzymes such as RNA-dependent RNA polymerase (RdRP), helicase, and proteases. Viral enzymes synthesize new viral genomes, mRNAs, and proteins to generate more viral particles which are released from infected cells by the process of exocytosis to infect the fresh one. Similar to other RNA viruses (Cheng et al., 2018), SARS-CoV-2 may also hijack host proteins like DDX5 RNA helicases for more efficient replication.

3. Cardiotoxicity

Cardiotoxicity is the disturbance in electrophysiology of heart and activity of cardiac muscles coupled with inefficient pumping and therefore circulation of blood. Promising symptoms of cardiotoxicity include myocarditis, elevated levels of troponins, abnormal ECG, myocardial infarction, systolic dysfunction, coagulopathy, endotheliitis, necroptosis, endothelial damage, hypertrophy, myocardial edema, and myocardial fibrosis (See Box 1).

Myocarditis is an inflammatory cardiac disorder, induced predominantly by viruses (Dominguez et al., 2016). However fungal, protozoan, and bacterial pathogens can also elicit myocarditis. Various drugs and xenobiotics cause myocarditis which is characterized by inflammatory myocytolysis followed by death of myocytes and replacement by fibrous tissues (Kawai, 1999; Ansari et al., 2003). Viral infections activate antiviral immune response which involves NK cells, macrophages, $CD4^+$, and $CD8^+$ T lymphocytes. These mediators of immune response successfully remove viral particles in major patients. However in some patients, virus induced myocytolysis fuels auto-immune reactions that are primed by release of cellular antigens like myosin or M2 muscarinic receptors and beta1-adrenergic receptors (β1AR) (Jahns et al., 2004). Release of these receptors, trigger the generation of autoantibodies such as anti-β1AR antibodies that bind with β1AR to promote pathological cardiac remodeling and β1AR desensitization as well as downregulation (Patel and Hernandez, 2013). Autoantibodies that act against muscarinic M2-receptor might also play crucial role in pathogenesis of dilated cardiomyopathy (Wallukat et al., 2000). During cardiac remodeling and dilated cardiomyopathy, loss of cardiomyocytes occurs through necrosis, necroptosis, apoptosis, or autophagy, whereas, fibrosis occurs through fibroblast proliferation and extracellular matrix reorganization.

Myocardial infarction is a health emergency defined by reduced or complete cessation of blood flow through coronary artery to a portion of myocardium leading to decreased cardiac functions. It is characterized by myocytolysis, coagulative necrosis, enhanced matrix degradation, and fibrosis. Myocardial infarction may be asymptomatic or, "silent" or, it could be a catastrophic event leading to hemodynamic deterioration and sudden death. Apart from traditional multi-dimensional risk factors like smoking, obesity, hypercholesterolemia, and hypertension, dysregulated immune system and hyper inflammatory responses might be associated with increased risk of myocardial infarction (Widmer and Lerman, 2014). Inflammation has been considered as a crucial factor in both the formation of atherosclerotic plaque and the progression of the plaque to an unstable state, resulting in myocardial infarction. Myocytes subjected to mechanical stress, release Suppression of Tumorigenicity 2 (ST2), a member of the IL-1 receptor family, to regulate the inflammatory response at the site of myocardial infarction. ST2 has been demonstrated to have a high expression level in patients with myocardial infarction and is linked to adverse cardiac remodeling (Schernthaner et al., 2017). Higher levels of circulating Growth Differentiation Factor-15 (GDF15) have been reported in patients with myocardial infarction and its level has been correlated with severity of disease (Wollert et al., 2007). B-type Natriuretic Peptide (BNP) is made by the heart and is secreted in small amount mainly from the ventricles. Plasmatic levels of BNP alter dramatically following the onset of myocardial infarction and are associated with progressive ventricular dilatation, systolic dysfunction, and severity of the disease (de Lemos et al., 2001).

Exposure to toxicants and infectious agents can lead to frequent thrombo-embolic events and coagulopathy (Zbinden and Grimm, 1985). Notably massive intravascular clot formation and coagulopathy are correlated with disease severity and mortality in COVID-19 patients (Iba et al., 2020). It has been indicated that hyper-coagulation state can be triggered by complex inflammatory response, also known as 'thrombo-inflammation', elevated fibrinogen levels, higher D-dimer, and fibrin degradation product levels as well as increased titer of antiphospholipid antibodies (Tang et al., 2020a, 2020b). Elevated levels of pro-inflammatory cytokines are known to induce macrophage activation syndrome/haemophagocytic lymphohistiocytosis leading to pro-thrombotic coagulation state. Moreover, elevated levels of plasminogen activator inhibitor-1 (PAI-1) are associated with excessive venous thrombosis, vascular damage, and increased risk of myocardial infarction (DeLoughery, 1999).

Endothelium is a single layer of squamous cells that line the interior surface of blood vessels. Endothelium does not only act as a selective barrier to toxicants and pathogens but also participates in maintenance of vascular-tone homeostasis by releasing vasoconstrictors such as

Table 1
Cardiovascular issues in COVID-19 patients.

Study site	Type of study	Number of patients participated in study	Symptoms of cardiotoxicity in COVID-19 patients	Reference
USA	Cohort study	70	Detectable cardiac troponin T level in 100% and myocardial injury in 76% of hospitalized patients with viremia.	Siddiqi et al., 2020
China	Cohort study	416	Cardiac injury occurred in 19.7% of patients during hospitalization.	Shi et al., 2020
USA	Trial-based study	45	Patients with modest elevations in high sensitivity troponin T and C-reactive protein coupled with high prevalence of hypertension (80%) and hyperlipidemia (75%).	Sheng et al., 2020
France	Cohort study	237	Patients with acute coronary syndrome (11%). Coronary artery disease (92%) and artery occlusion (69.4%) were prevalent in patients with myocardial infarction.	Koutsoukis et al., 2014
USA	Case report	01	Elevated Troponin-T and N-terminal pro-B natriuretic peptide; cardiomegaly with bibasilar patchy opacities greater in the left lower lobe and right upper lobe atelectasis; ECG showed sinus tachycardia, nonspecific ST-segment depression, T-wave inversions in the anterolateral and inferior leads.	Sharma et al., 2020
China	Single-center, retrospective, observational study	187	27.8% of patients had myocardial injury coupled with elevated Troponin T level, N-terminal pro–brain natriuretic peptide, C-reactive proteins and malignant arrhythmias.	Guo et al., 2015
Italy	Cohort study	113	45% of patients had high sensitive Troponin I and longer hospital stay.	Zaninotto et al., 2020
Brazil	Case report	01	Patient experienced signs of congestive heart failure, tachycardia, creatine kinase myocardial band and elevated levels of troponin.	Dolhnikoff et al., 2020
USA	Cohort study	2736	36% of patients had elevated troponin concentrations with prevalent coronary artery disease, atrial fibrillation, and heart failure.	Lala et al., 2020
Italy	Case report	01	Patient diagnosed with elevated levels of N-terminal pro-brain natriuretic peptide and high-sensitivity troponin T; altered echocardiography and diffuse biventricular myocardial edema.	Inciardi et al., 2020
Italy	Cohort study	614	Elevated troponin values were associated with higher mortality, coronary artery disease and atrial fibrillation.	Lombardi et al., 2020
Turkey	Case report	01	Patient diagnosed with pericardial tamponade, depressed left ventricular contraction and restricted diastolic filling.	Parsova et al., 2020
USA	Case report	01	Patient had acute coronary syndrome, purulent fulminant myopericarditis and cardiac tamponade.	Khatri and Wallach, 2020
Italy	Case report	01	Patient diagnosed with low atrial ectopic rhythm, high-sensitivity troponin T, C-reactive protein and left ventricular systolic dysfunction.	Sala et al., 2020

endothelin-1 and thromboxane A2 as well as vasodilators such as nitric oxide (NO) and prostacyclin (Busse and Fleming, 2006). Exposure to xenobiotics and pathogens like SARS-CoV-2 can promote expression of adhesion molecules, such as ICAM-1, VCAM-1, *E*-selectin, and P-selectin on vascular endothelium by activation of NF-κB and AP-1. These adhesion molecules facilitate leukocyte rolling, adherence, and transmigration through endothelium leading to endothelial damage, necroptosis, and development of vascular endotheliitis by release of pro-inflammatory cytokines and the generation of extracellular ROS (Hattori et al., 2022). Vascular endotheliitis also has adverse effects on other organs like lungs, kidney, and liver.

In case of increased hemodynamic demand, cardiomyocytes increase in volume to alleviate the pressure exerted on cardiac wall. It results in stiffness of myocardium, increase in intercellular muscle fibers, occurrence of myocardial fibrosis, and decrease in cardiac output. Several molecular factors can fuel hypertrophy of cardiomyocytes. For instance, proliferation of fibroblast and production of collagen are stimulated by systemic and myocardial angiotensin II, activated through angotensin (AT)-1 and AT-2 receptors (Yamazaki et al., 1999). Development of macroscopic fibrosis leads to enhanced ventricular stiffness and decreased compliance. Endothelin-1 is another factor which is secreted in response to pressure-overload or mechanical-stretch to induce hypertrophy in cardiac tissues (Yamazaki et al., 1999). G protein coupled receptor (Gq/Glland Gi/Go) mediated hypertrophic response is usually orchestrated by activation of protein kinase C (PKC) which is predominantly implicated in hypertrophic signaling. Small GTP-binding proteins viz. Rho and Ras families contribute to hypertrophic responses through activation of the mitogen-activated protein kinase (MAPK) superfamily-mediated signaling cascades following PKC activation (Denhardt, 1996). Protein phosphatase (calcineurin) is activated by Ca_2^+/calmodulin signaling leading to the dephosphorylation of transcription factor NF-AT3 and onset of gene expression involved in hypertrophic responses as well as myocardial fibrosis (De Windt et al., 2000).

Myocardial oedema is the accumulation of fluid content in myocardium particularly within the extracellular interstitium resulting in systolic and diastolic dysfunction as well as interstitial fibrosis. Extracellular fluid is accumulated due to a dysbalance between the microvascular fluid filtration and the removal of excessive fluid via lymphatics. It can be triggered by myocardial infarction, arterial hypertension as well as by other etiologies such as mechanical, toxic, or ischemic. Membrane blebbing, detachment of actin filaments, mitochondrial condensation, and swelling of the endoplasmic reticulum and the golgi apparatus are apparent in tissues undergone myocardial oedema. Fluid permeability of myocardial microvasculature plays critical role in maintenance of myocardial fluid balance and oedema formation. Luminal surface of myocardial microvasculature is coated with negatively charged glycocalyx composed of proteoglycans, glycosaminoglycans, and absorbed plasma proteins (Pries et al., 2000). Glycocalyx may be adversely affected by circulating inflammatory mediators induced by toxicants and infectious agents leading to alteration in myocardial fluid filtration, development of oedema, and fibrosis (Mehta and Malik, 2006).

3.1. COVID-19 mediated cardiovascular issues

Cardiac injuries are evident in hospitalized patients with COVID-19 (Table 1). There is strong relation between viral infection and myocarditis. Myocardial injury was evident in early cases of COVID-19 in China. In a study involving 138 hospitalized COVID-19 infected patients, elevated concentration of high-sensitivity cardiac troponin I (hs-cTnI) and abnormal electrocardiogram were reported (Wang et al., 2020), which confirmed cardiac injury in these patients. Moreover, National Health Commission of China indicated that, approximately 12% of COVID-19 patients without a history of cardio-vascular disease had elevated troponin level or cardiac arrest during the hospitalization (Zheng et al., 2020). In a large retrospective longitudinal cohort study, patients with COVID-19 were recognized with elevated concentration of high-sensitivity troponin-I and cardiac injury (Raad et al., 2020). Moreover, higher concentration of troponin-I was linked with greater mortality of patients. Clerkin et al., 2020 reported high prevalence of cardiovascular disease in COVID-19 patients. In the same study, >7% of patients experienced myocardial injury from the infection. Shi et al., 2020 have also documented cardiac injury in patients with confirmed COVID-19. Authors reported elevated troponin levels in 20% of patients. Intriguingly, cardiac injury was associated with four-fold increase in mortality risk during SARS-CoV-2 infection. Karbalai Saleh et al., 2020 studied cardiac injury in 386 hospitalized patients with COVID-19. Cardiac ailments were prevalent among 115 individuals (29.8% of total patients) of the study population. Moreover, development of cardiac injury was clearly associated with nearly two-fold higher in-hospital mortality rate compared to those with normal troponin levels. A 37 years old patient with COVID-19 was diagnosed with enlarged heart, myocardial infarction, and a marked decrease in ventricular systolic function. In the same patient, fulminant myocarditis with cardiogenic shock and pulmonary infection were reported (Hu et al., 2020). An otherwise healthy 53 years old woman having COVID-19 showed diffuse ST elevation with higher troponin T and NT-proBNP (N-terminal prohormone of brain natriuretic peptide) levels, with diffuse biventricular hypokinesis, especially in the apical segments of heart and severe left ventricular dysfunction (Inciardi et al., 2020). Infection can promote mild to moderate heart dysfunction with reduced ejection fraction (Wolfler et al., 2020). A hyperinflammatory-state akin to atypical Kawasaki disease coupled with cardiac dysfunction and coronary vessel abnormalities were reported in diseased children (Riphagen et al., 2020). SARS-CoV-2 promotes thrombus formation and acute coronary syndrome by direct vascular or endothelial injury (Varga et al., 2020). Tang et al., 2020a, 2020b reported higher D-dimer levels, fibrinogen degradation products, longer prothrombin time, and activated partial thromboplastin time in COVID-19 patients who did not survive illness thus lending support to coagulopathy. Disseminated intravascular coagulopathy is associated with advanced congestive heart failure (Sarcon et al., 2015). Moreover, SARS-CoV-2 infects the endothelium of blood vessels and facilitates endotheliitis that could be detrimental to blood vascular system (Varga et al., 2020). Thus, above findings unequivocally suggest that, SARS-CoV-2 can fuel cardiovascular maladies in patients.

3.2. OP-mediated cardiovascular issues

3.2.1. Myocardial infarction (MI)

MI, commonly known as heart attack is a medical emergency in which blood clot blocks circulation through the coronary blood vessels to supply the cardiac tissue. MI can be fueled by several factors including exposure to OP chemicals. Several reports are available in support of OP induced MI in human. Chen et al., 2019 retrospectively analyzed clinical data of patients undergone acute OP poisoning. Analysis revealed MI coupled with elevated levels of heart failure markers (N-terminal pro B-type natriuretic peptide) in these subjects. Beside, incidence of abnormal heart beat was prevalent in patients. Intriguingly, a nationwide population-based cohort study conducted by Hung et al., 2015 confirmed that, individuals undergone OP poisoning have greater incidence rates of congestive heart failure than a non-OP poisoning cohort. Notably, out-of-hospital cardiac arrest may also be an outcome of OP intoxication (Kuo et al., 2017). Statistical analyses on a cohort of 7557 individual suggested that, occupational exposure to pesticides including OPs might play a significant role in the development of cardiovascular diseases including coronary heart disease (Berg et al., 2019). A case report of 52 year-old farmer accidentally exposed to parathion in Turkey documented acute inferior MI coupled with hyperglycemia, leucocytosis, mild anemia, and hyponatremia (Karasu-Minareci et al., 2012). However, neither bradycardia nor tachycardia was diagnosed in the patient. Similarly, acute anteroseptal MI followed by demise was

reported in another case where a 57-year-old woman ingested OP compound (Lionte et al., 2007). Mills et al., 2009 analyzed self-reported lifetime use of pesticides and traced significant correlation between lifetime use of 49 pesticides including OPs and fatal or, nonfatal myocardial infarction. There were 476 deaths from MI among 54,069 men enrolled for the study and 839 nonfatal MI among the 32,024 participants. Human serum paraoxonase 1 level are declined by severe OP poisoning (Lincy Juliet et al., 2018) and low paraoxonase activity in serum contribute to the development of MI as well as coronary heart disease (McElveen et al., 1986).

3.2.2. Electrocardiographic abnormalities

Electrocardiogram (ECG) is a graphical representation of voltage versus time of the electrical activity of the heart. The graph is obtained using electrodes placed on the skin and has clinical significance as predictor for cardiac disease prognosis. Adequate studies have reported the detrimental impact of OP exposure on electrical activity of cardiac tissue. In a cross-sectional study involving 107 patients, prolonged Q-Tc interval, elevated ST segment as well as T wave inversion were diagnosed in 62.6%, 33.6%, and 19.6% patients respectively. In the same study, sinus tachycardia and sinus bradycardia were also evident (Paul and Bhattacharyya, 2012). QT interval represents ventricular depolarization and repolarization. It is measured from the start of QRS complex until the T wave termination on ECG. Prolonged Q-Tc interval can potentially cause fast, chaotic heartbeats leading to Torsades de pointes and even casualty. Elevation of ST segment with anterior leads and T-wave inversion indicates acute MI and increased risk of heart failure. Yurumez et al., 2009 conducted a retro-specific study using 85 patients with OP poisoning over a period of 3 years. They found prolongation of the QTc interval (55.5%) as most common ECG abnormality, followed by sinus tachycardia (31.8%). In addition, elevation of the ST segment and low amplitude T waves were seen in 15 cases (17.6%). In a separate study of OP-intoxication, corrected QT interval prolongation, ST–T changes, U waves, and ventricular premature contractions have also been detected in majority of cases (Anand et al., 2009). Nevertheless, sinus tachycardia was the most common electrocardiographic abnormality in these individuals. The U wave is a small (0.5 mm) deflection immediately followed by T wave and its presence in ECG represents cardiac injuries. Electrocardiographic abnormalities such as bradycardia, prolonged PQ interval, prolonged QTc interval (>430 ms), nonspecific ST-T change, supraventricular arrhythmia, and ventricular premature complex with R on T1 have been detected in patients undergone OP exposure by aerial spray (Taira et al., 2006). A case report of a 57 years old woman presented prolonged QTc interval, ST-T changes, right bundle branch block, and ventricular tachycardia (Lionte et al., 2007). Gul et al., 2012 reported a case report of OP poisoning associated with right bundle branch block, QT interval prolongation, and intermittent narrow QRS complexes that were most likely due to automaticity from the region of the left posterior fascicle. It is important to note that, QTc prolongation is associated with higher frequency of ventricular premature contraction (VPC), mortality, and respiratory failure (Chuang et al., 1996; Jang et al., 2015).

3.2.3. Arrhythmia

Arrhythmia is a cardiac complication involving abnormal heartbeat. During this medical condition, the rhythm of heart beat becomes irregular i.e., either too fast or too slow. Disruption of heart's electrical system which is naturally rich with cholinesterases may be the triggering point of irregular auriculo-ventricular contraction. Arrhythmia is generally presented via atrial and ventricular fibrillation. Being a prominent cholinesterase inhibitor, OPs can fuel arrhythmia in human as evidenced in various studies. Using multivariable Cox proportional model Hung et al., 2015 reported that, patients with acute OP-poisoning had higher incidence rates of developing arrhythmia, coronary artery disease (CAD), and congestive heart failure than non-OP poisoning cohort. A 40 years old man who accidently ingested OP-compound had irregular pulse rate paired with atrial fibrillation (Maheshwari and Chaudhary, 2017). In a cross-sectional study involving 107 patients, atrial fibrillation and ventricular tachycardia were evidenced in 5 and 6 cases respectively (Paul and Bhattacharyya, 2012). Notably, ventricular fibrillation was the major cause of death in 5 cases out of a total 17 lethalities. In a separate case of OP-intoxication, idioventricular rhythms and polymorphic ventricular tachycardia have been detected (Brill et al., 1984). A 12 years old child with no past medical or surgical history was complaining of irregular palpitations after accidental exposure to OP compounds in a farm. Further, diagnosis of the patient revealed atrial fibrillation with a rapid ventricular response (Abdelnaby, 2018). Ludomirsky et al., 1982 conducted a clinical study of OP-poisoning in 15 patients and found torsade de pointes- a specific type of abnormal heart rhythm that may lead to sudden cardiac death. Laudari et al., 2014 studied 115 OP-exposed patients and validated cardiac maladies in 57 patients with all having sinus tachycardia and 3 having sinus bradycardia. In the same study, 5 patients were detected with polymorphic ventricular tachycardia and 3 with ventricular fibrillation which ultimately culminated into death. Gul et al., 2012 described a case report of OP poisoning associated with atrial fibrillation and right bundle branch block coupled with abnormal electrocardiography. In an animal model of guinea-pig, injection of OP-nerve agents viz. sarin and soman had fueled marked sinus bradycardia and a subsequent complete atrioventricular block within 1–2 min, followed by idioventricular rhythm (Worek et al., 1995).

3.2.4. Structural remodeling and histopathology

Exposure to OPs can trigger tissue remodeling and spectrum of histopathology in cardiac tissue as advocated by various animal-based studies. For instance, cardiac muscles of female rats exposed to 8, 10, 12, and 20 mg/kg BW of Diazinon had large areas of degenerating muscle fibers with loss of transverse striations and wide interfascicular spaces (Abdou and ElMazoudy, 2010). In another study, male albino rats exposed to chlorpyrifos at a dose of 6.75 mg/kg BW manifested disorganization and degeneration in myocardial fibers with cytoplasmic vacuolization and separation of cardiac myofibrils (El-Wakf et al., 2018). Congested thickened arteries with extravasation of the blood in between the cardiac myofibrils were also noticed. Notably, low level exposure to diazinon, propoxur, and chlorpyrifos triggered fibrosis, hemorrhagic infiltration of myocardial tissues, and degeneration of muscle cells in rabbits (Zafiropoulos et al., 2014). Necrosis or cell death is an important component of fibrosis and cardiac malfunction. Studies have indicated that, exposure to OPs can induce necrosis and/apoptosis in cardiac tissue. For instance, fenthion at a dose of 2 mL/kg BW caused oedema, inflammation, vacuolization, and necrosis in heart of male Sprague-Dawley rats (Yavuz et al., 2008). Subchronic exposure to dichlorvos ensue cardio-histopathological manifestations in the form of lack of striations, myocardial hemorrhage, and necrosis-like features (Imam et al., 2018). Yavuz et al., 2004 analyzed histopathological outcome of methidathion in rodants. They reported diffuse loss of striation and myocytolysis of the cardiomyocytes in rats treated with 5 mg/kg of the OP pesticide. Similarly, Saquib et al., 2012 documented phorate-induced degeneration of cardiac myofibers in male Wistar rats. Soman, a nerve agent has been reported to fuel myocardial degeneration and myocytolysis in heart tissue of rodents and Rhesus macaques (Tryphonas et al., 1996). OPs generate ROS and disturb redox balance in cellular moiety to activate death signals like disruption of mitochondrial permeability transition pore, Ca^{2+} dyshomeostasis as well as ATP or ADP depletion implicated in cell death. In addition, ROS-induced DNA breakdown leads to overactivation of poly(ADP-ribose) polymerase-1(PARP-1), a nuclear enzyme that consumes NAD^{+} culminating into significant ATP consumption, a key feature of necrosis (Los et al., 2002).

Human-based studies demonstrating OP-induced histopathological complications in heart tissue are scarce. Necropsy of patients who died following OP-intoxication revealed cardiac discoloration or blotchiness, myocardial interstitial oedema, vascular congestion, and patchy interstitial inflammation (Anand et al., 2009). Chen et al., 2019 analyzed

Table 2
Organophosphate-induced cardiovascular injuries in non-target animal models.

Organophosphate studied	Model animal	Dose, route and duration of exposure	Signs of cardiotoxicity	Reference
Terbufos-sulfone	Male Wister rats	1/20 of LD_{50}/day, intraperitoneal, 15 days	Damaged mitochondria of cardiomyocytes.	Nurulain et al., 2016
Dichlorvos	Wistar rats	8.8 mg/kg, oral, 21 days	Lack of striations, myocardial hemorrhage and necrosis-like features detected in heart tissues; Cardiac cholesterol, low-density lipoprotein, atherogenic and atherosclerotic indices were elevated.	Imam et al., 2018
Fenthion	Sprague-Dawley rats	0.8 g/kg, subcutaneous, 24 h	Elevated levels of Troponins and myocardial injury, including edema, inflammation, vacuolization and necrosis.	Yavuz et al., 2008
Chlorpyrifos	Male Wistar rats	5.4 mg/kg bw, oral, 4 weeks	Hear tissue with significant increase in Malondialdehyde level, Superoxide dismutase and Catalase activities; reduced Glutathione-S-transferase and Glutathione Peroxidase activity; Histopathology included disorganization and degeneration in myocardial fibers, cytoplasmic vacuolization in cardiac muscle cells and edema in connective tissue and degenerative changes in cardiac muscle cells.	Baş and Kalende, 2011
Dichlorvos	Male rats	Inhalation for 15 mins daily, 28 days	Elevated lactate dehydrogenase, creatinine kinase and troponin levels; development of cardiac oxidative stress; marked fat degeneration and necrosis of the myocardial layer.	Saka et al., 2020
Diazinon	Male Wistar albino rats	20 mg/kg b.w., oral, 4 weeks	Elevated levels of markers of cardiac injury such as lactate dehydrogenase and creatine phosphokinase; increased cardiac lipid peroxidation.	Abdel-Daim et al., 2016
Paraoxon	Male Wistar rats	0.6 LD_{50} + 0.45LD_{50}, Injection, 1 day, 3 day, 1–12 weeks	Cardiac arrhythmia validated by altered ECG (increased P and T wave amplitudes; presence of the deep S wave).	Kuznetsov and Goncharov, 2019
Bis(isopropyl methyl) phosphonate	Male Wistar rats	0.8 mg/kg, intravenous,	Increase in heart rate and blood pressure by stimulation of sympathetic as well as parasympathetic nerves.	Watanabe et al., 2013
Cyclohexylmethyl-phosphonofluoridate	Rhesus monkeys	233 μg/kg, intramuscular, one time administration, monitored for 7 days	Induced cardiomyopathy in the form of degenerative myocytes, cytoplasmic vacuolation and dissolution of fibers.	Koplovitz et al., 1992
Malathion	*Danio rerio*	Treated with 33.3 and 50 μg/mL of malathion for 10 mins. at 52, 76, and 96 hpf	Detected with irregular heart beat (bradycardia).	Simoneschi et al., 2014
Diazinon, propoxur, and chlorpyrifos	Rabbits	Diazinon (2.6 & 5.2 mg/kgday), propoxur (8.8 & 18 mg/kg/day), and chlorpyrifos (8.7 & 18 mg/kg/day) oral administration, 15 months	Triggered fibrosis, hemorrhagic infiltration of myocardial tissues and degeneration of muscle cells.	Zafiropoulos et al., 2014
Diazinon	Female rats	8, 10, 12 and 20 mg/kg bw,	Degenerated cardiac muscle fibers and induced cardiac oxidative stress.	Abdou and ElMazoudy, 2010

Table 3
Organophosphate exposure and symptoms of cardiovascular ailments in human.

Organophosphate compound	Type and location of study	Type of exposure	Number of individuals studied	Signs of cardiotoxicity	References
Phorate	Case report; India	Accidental exposure	01	Abnormal ECG with sinus tachycardia, non-specific ST-T wave changes and a corrected QTc interval of 430–500 msec; elevated levels of Creatine kinase-MB and troponin I.	Muthu et al., 2014
Chlorpyrifos, dichlorvos, Methylparathion, Dimethoate, Profenfos, Chlorpyrifos, Triazos	Hospital-based cross-sectional study; Nepal	Acute exposure	115	Patients diagnosed with sinus tachycardia (49.6%), Hypertension (20%), ECG abnormalities (18.26%), ventricular extrasystole (12.2%) and ventricular fibrillation (0.3%).	Laudari et al., 2014
Mevinphos, Parathion, Phosphamidon, Parathion, Malathion, Tamaron, Diazinon	Clinical study, Israel	Acute exposure	15	Altered ECG (Q-T prolongation) and malignant tachyarrhythmias.	Ludomirsky et al., 1982
Parathion	Case report, India	Acute exposure	01	Patient detected with sinus bradycardia, left ventricular failure and elevated level of troponin I.	Joshi et al., 2013
Dichlorvos, parathion, methamidophos, phoxim etc.	Clinical study, China	Acute exposure	98	52% of patients with acute myocardial injury as evidenced by elevated levels of troponin I, creatine kinase-Mb and N-terminal pro B-type natriuretic peptide.	Chen et al., 2019
Chloropyrifos, dichlorvos, diazinon, parathion, methidathion, phenothoate etc.,	Clinical study, Republic of Korea	Acute exposure	99	11.1% patients experienced abnormal ECG (fluctuation in ST); 34.3% of patients with detectable troponin I levels.	Cha et al., 2014
Not specified	Case report, India	Accidental exposure	01	ECG revealed atrial fibrillation.	Maheshwari and Chaudhary, 2017
Not specified	Cross-sectional study, India	Acute exposure	107	Patients detected with prolonged Q-Tc (62.6%), sinus tachycardia (33.6%), elevated ST segment (25.2%), inverted T wave (19.6%) and first degree heart block (8.4%) as well as atrial fibrillation (4.6%).	Paul and Bhattacharyya, 2012
Not specified	Clinical study, Egypt	Acute exposure	46	Elevated levels of serum creatinine kinase and cardiac trophonin I; abnormal ECG with sinus tachycardia ((34.78%) and sinus bradycardia ((19.56%); prolonged QTc ((32.61%) and PR (8.70%) intervals; elevated ST segment (15.22%).	Kharoub and Elsharkawy, 2008
Not specified	Clinical study, Iran	Occupational (71 patients), suicidal (26 patients) and accidental (3 patients) exposure	100	63% of patients presented abnormal ECG with Sinus tachycardia (31%), non-specific ST-T changes (24%) and atrioventricular arrhythmia.	Taromsari et al., 2013
Not specified	Case report, USA	Acute exposure	01	Patient experienced sinus bradycardia, A-V dissociation, idioventricular rhythms, multiform ventricular extrasystoles, and prolongation of the PR, QRS, and QT intervals. Polymorphic ventricular tachycardia was also detected.	Brill et al., 1984
Parathion	Case report, Turkey	Acute exposure	01	Elevated levels of cardiac injury markers (Troponin I, creatine kinase-Mb); alerted ECG demonstrating ST-segment elevation and AVF derivations accompanied by ST horizontal depression in DI-AVL leads.	Karasu-Minareci et al., 2012
Methyl-parathion; Propoxur; Sichlorvos; Monocrotophos; Malathion; Dichlorovos	Clinical study, Nepal	Acute exposure	37	Patients established electrocardiographical abnormalities (37.8%); sinus tachycardia (40.5%); sinus bradycardia (18.9%); hypertension (13.5%) and hypotension (10.8%)	Karki et al., 2004
Parathion	Case report, India	Acute exposure	01	Myocardial infarction	Kidiyoor et al., 2009

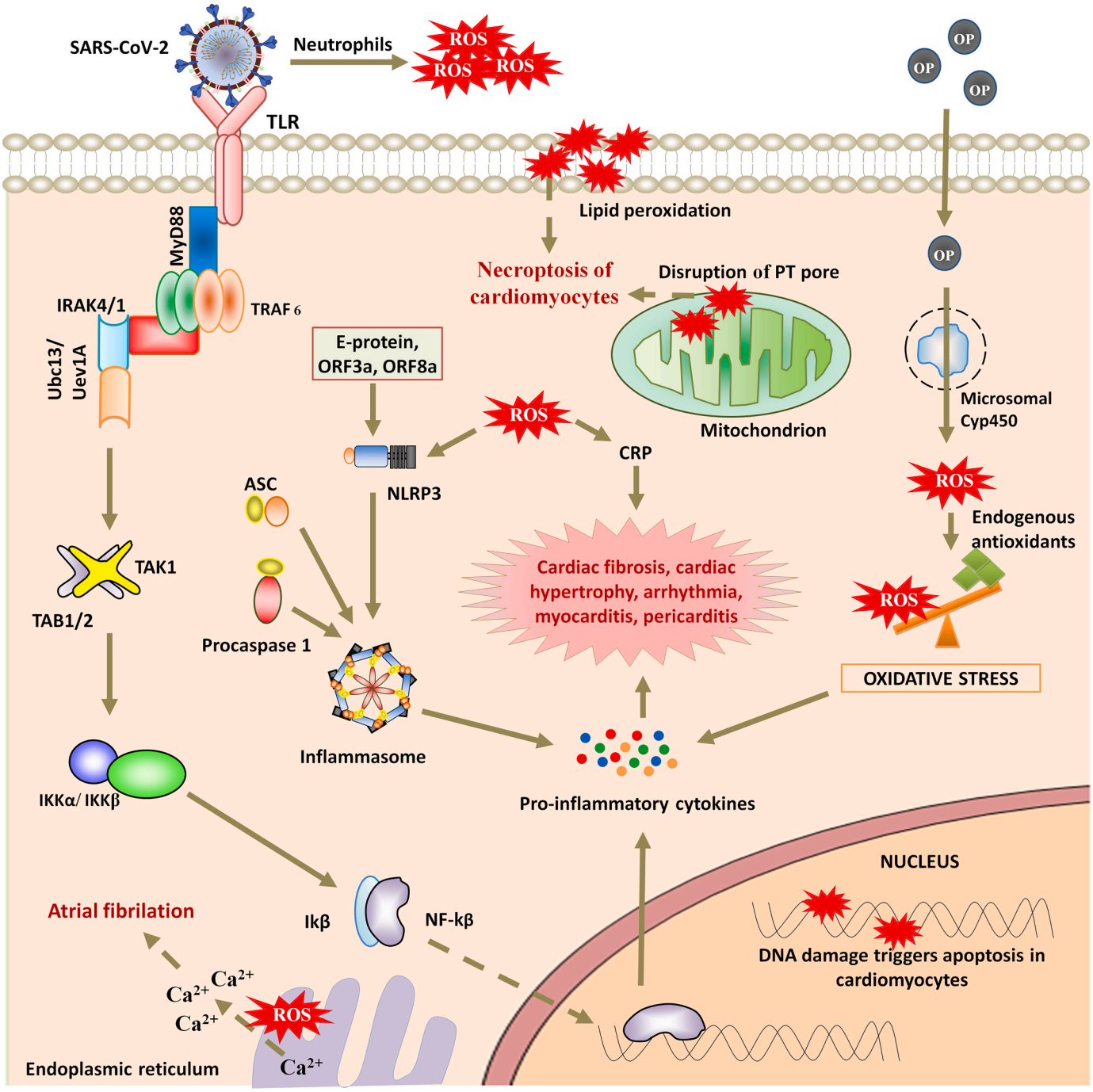

Fig. 2. Induction of proinflammatory cytokines and cardiotoxicity by SARS-CoV-2 and OP. Spike protein of SARS-CoV-2 is immunogenic and recognized by Toll-like receptors (TLRs) to induce signaling cascades associated with production of proinflammatory cytokines. Binding of spike protein with TLR triggers recruitment of adaptor proteins viz. MyD88, IRAK4/1, TRAF-6, and dimeric ubiquitin-conjugating enzyme complex (Ubc13-Uev1A). Recruitment of adaptors activates TAK1/TAB/1/2 which in turn induces IKKα/IKKβ. IKKα/IKKβ phosphorylates Ikβ to promote nuclear translocation of NF-kβ involved in transcription of various proinflammatory cytokines. Viral proteins such as *E*-protein, ORF3a, and ORF8a induce NLRP3-mediated inflammasome formation which activates proinflammatory cytokines. OPs being lipophilic in nature cross the lipid bilayer to enter cytoplasm and produce ROS via microsomal p450. ROS and subsequent oxidative stress overwhelms endogenous antioxidants and amplifies the production of proinflammatory cytokines. In addition, ROS triggers necroptosis via lipid peroxidation and DNA damage. ROS disturbs cytosolic Ca^{2+} homeostasis by inducing the release of Ca^{2+} from cytoplasmic stores viz. endoplasmic reticulum. All these sub-cellular alterations contribute to cardiotoxicity.

clinical data of 98 patients underwent acute OP-poisoning. They detected elevated levels of myocardial injury markers (creatine kinase-Mb and cardiac troponin I) paired with heart failure markers (NT-proBNP) in majority of patients. In a pilot study conducted by Dalvi et al., 1986 post-mortem examination of the heart in fatal cases of OP-intoxication showed focal myocardial damage (micronecrosis) and interstitial cellular infiltrates (myocarditis). Therefore, OP compounds can potentially damage histological architecture of cardiac tissues.

3.2.5. *Carditiis, mural thrombus, ischemia, and cardiomyopathy*

Carditis is an inflammatory condition of heart. This is promoted by immune dysregulation which can be fueled by viral infections and

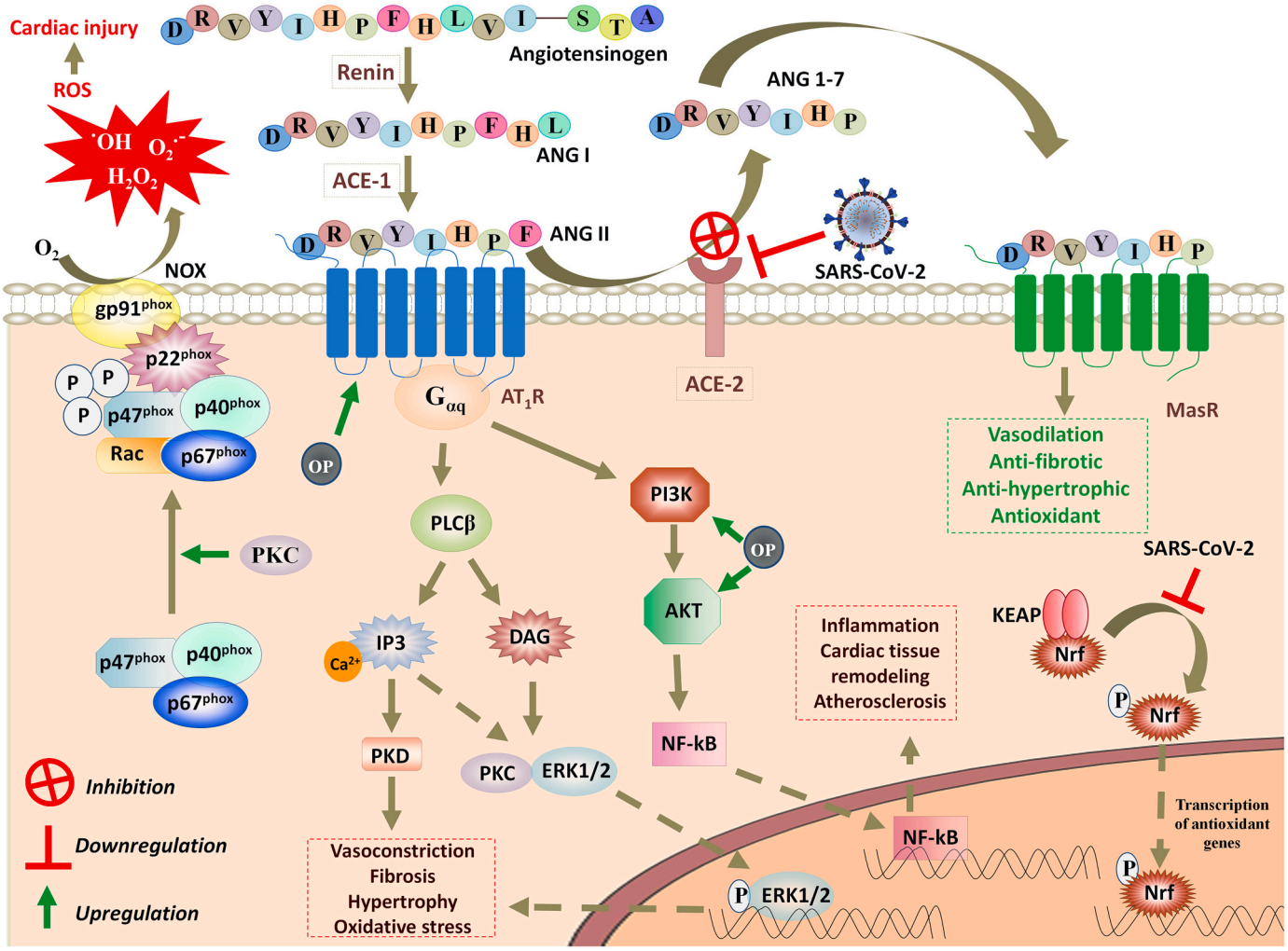

Fig. 3. Cross-talk between renin angiotensin system (RAS), SARS-CoV-2, and OP. Angiotensinogen, angiotensin I (ANG I), ANG II, and ANG 1–7 are the integral components of RAS. Angiotensinogen is cleaved into ANG I by renin. ACE 1 is the carboxypeptidase that cleaves ANG I into ANG II. Further, ANG II is converted into ANG 1–7 by ACE-2. ANG 1–7 acts as a ligand for Mas receptor that counter-regulates ANG II-mediated pathway. ANG II is responsible for vasoconstriction, IR injury, arrhythmia, atherosclerosis, and cardiac tissue fibrosis. Infection by SARS-CoV-2 downregulates ACE-2 on the cell surface and hence fuels aggregation as well as hyperactivation of ANG II. Protein kinase C (PKC) activated by the ANG-II helps to compose NADPH oxidase (NOX) involved in ROS production. OP upregulates ANG II-mediated pathway by activating PI3K or Akt intermediate molecules. SARS-CoV-2 suppresses Nrf-mediated antioxidant gene expression to fuel oxidative stress. All these phenomena are involved in cardiac injury and dysfunction.

exposure to xenobiotics including OP compounds. Carditis affects both cardiomyocytes and pericardial sac. Anand et al., 2009 grossly examined heart in 13 cases of OP-poisoning and identified patchy myocarditis in 2 patients and mural thrombus in 6 patients. In another study of OP-intoxication, post-mortem examination of the heart in five fatal cases revealed micronecrosis and interstitial cellular infiltrates i.e., myocarditis (Dalvi et al., 1986). Increased risk of deep vein thrombosis in patients with OP-intoxication was also evident in a nationwide prospective cohort study conducted by Lim et al., 2015. A case of congestive cardiomyopathy has been reported following long-term OP exposure (Kiss and Fazekas, 1979). Takotsubo cardiomyopathy, also known as stress cardiomyopathy is a sudden, transient cardiac complication that involves dramatic left ventricular apical akinesis and mimics acute coronary syndrome. Jeon et al., 2018 analyzed 147 patients who attempted intentional suicide and reported takotsubo cardiomyopathy as one of the cardiac complications in these patients. Circumferential endocardial ischemia with cardiogenic shock has also been documented with malathion poisoning (Mdaghri et al., 2010). Cardiomyopathy is a condition where it is hard to pump blood to rest of the body. Cardiomyopathy has been detected in rodents treated with soman and sarin (Singer et al., 1987).

Therefore, OP compounds inflict various cardiotoxic effects (Table 2; Table 3) that peril cardiac structure and functions.

4. Mechanistic homology between OP & COVID-19 mediated cardiovascular issues

4.1. Induction of proinflammatory cytokines and inflammation

Cytokines are essential to maintain both structural and functional integrity of several organs. However upon profound secretion, proinflammatory cytokines can modulate cellular microenvironment to impair physiology of various organs including heart and the overall cardiovascular system. Intriguingly, prolonged cytokine hyperexpression is linked to pathogenesis of a variety of cardiac manifestations including heart failure and adverse left ventricular remodeling (Hohensinner et al., 2011). Increased levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β are positively associated with cardiac injuries (Diwan et al., 2003). Indeed, elevated blood serum levels of TNF-α and IL-6 are the potential predictors of mortality due to heart failure (Deswal et al., 2001). Endothelial dysfunction is a key feature of cardiovascular diseases and is linked to elevated levels of TNF-

α, IL-1β, IL-6, and IFN-γ. C-reactive proteins (CRP) are the classic markers of inflammation and myocardial infarction. They can directly interact with atherosclerotic vessels or ischemic myocardium by activation of the complement system, thereby promoting inflammation and thrombosis (Lagrand et al., 1999).

SARS-CoV-2 triggers strong inflammatory response in COVID-19 patients by enhancing the levels of proinflammatory cytokines namely IL-1β, IL-2, IL-6, IL-7, IL-10, GSCF, IP-10, MCP-1, MIP1A, and TNFα inside the body (Blanco-Melo et al., 2020; Huang et al., 2020). Likewise, exposure to OPs increases the synthesis of proinflammatory cytokines and suppresses the level of anti-inflammatory cytokines in human leading to cytokine-dyshomeostasis and massive inflammation (Schäfer et al., 2013; Duramad et al., 2006). Chlorpyrifos-induced up-regulation in mRNA levels of proinflammatory-cytokines namely TNFα, IFN, IL-1β, IL-6, and complement factor-4 was noticed in Zebra-fish larvae (Jin et al., 2015). Interestingly, a relevant increase in IL-22 concentration was reported in 64 green-house workers exposed to OP-pesticides (Fenga et al., 2014). IL-6 fuels myocardial hypertrophy and left ventricular systolic dysfunction. Increased expression of monocyte chemoattractant protein 1 (MCP-1) facilitates infiltration of macrophages in heart leading to cardiac fibrosis and left ventricular systolic dysfunction. NF-kB signaling is central to induction of proinflammatory cytokines and OP can provoke NF-kB signaling via ROS generation (Lee et al., 2014). Similarly, SARS-CoV-2 drives up-regulation of NF-kB signaling to induce proinflammatory cytokines (Neufeldt et al., 2020). Proinflammatory cytokines in positive feedback loop activates NF-kB transcription factor that further provokes inflammatory responses leading to fibrosis and apoptosis of cardiomyocytes. Notably, overexpression of NF-kB contributes to cardiac hypertrophy (Hirotani et al., 2002). Recent evidences have revealed that, OPs like chlorpyrifos activate nucleotide-binding domain (NOD)-like receptor protein 3 inflammasome by an increase in mROS and fuel inflammation-dependent cardiac injury (Zhou et al., 2018). SARS-CoV-2 viroporins such as protein E, ORF3a and ORF8a via mechanisms such as lysosomal disruption and ion-redistribution in the intracellular environment, activate the NLRP3 mediated inflammatory pathogenesis (Shah, 2020). Exposure to OPs and SARS-CoV-2 promotes up-regulation of CRPs (Wu et al., 2016; Wang, 2020) and elevated CRP level is associated with atrial fibrillation and ventricular dysfunction (DuBrock et al., 2018). Therefore, inflammation triggered by SARS-CoV-2 and OP chemicals can aggravate cardiac issues that may amplify the risk of mortality in patients with COVID-19 (Fig. 2).

4.2. Oxidative stress (OS)

OS is an undesirable situation when prooxidants overwhelm antioxidant status at sub-cellular environment. OS is detrimental to various organs including heart. Nrf-2 is a master redox-sensitive signaling molecule that transcribes endogenous antioxidants to counter-regulate oxidative damage. Unfortunately, infection with respiratory viruses including SARS-CoV-2 is known to down-regulate Nrf-2 antioxidant gene expression pathway (Olagnier et al., 2020; Komaravelli and Casola, 2014). Notably, prevalence of OS is evident in COVID-19 patients (Cecchini and Cecchini, 2020). There is a negative correlation between antioxidant enzyme-superoxide dismutase-3 and disease severity in patients (Abouhashem et al., 2020). Moreover, high neutrophil to lymphocyte ratio observed in critically ill COVID-19 patients is associated with excessive levels of reactive oxygen species (ROS) (Laforge et al., 2020). COVID-19 mediated hypoxic conditions imposed by impaired gas exchange may exacerbate OS in patients (Serebrovska et al., 2020; Debevec et al., 2017).

Similarly, exposure to OP chemical triggers OS in heart tissues leading to myocardial damage. For instance, prolonged exposure to monocrotophos induces OS and histological damage in cardiac tissues of rats (Velmurugan et al., 2013). Moreover, exposure to malathion, paraoxon, and chlorpyrifos stimulates ROS, cardiac-lipid peroxidation, and protein damage in heart tissues (Baş and Kalende, 2011).

OS fueled by ROS promotes cardiac remodeling by alteration in gene expression and protein function, both in extracellular matrix and in cardiomyocytes. Superoxide radicals inactivate nitric oxide and promote subsequent endothelial damage by excessive generation of peroxynitrite. At sub-cellular level, ROS acts as intracellular second messenger that contributes to robust release of Ca^{2+} involved in troponin-C mediated vasoconstriction, pathogenesis, and hypertension. Intracellular Ca^{2+} homeostasis is maintained by type-2 ryanodine receptor (RyR2) in atrial myocytes and activity of this cysteine-rich receptor is modulated by OS (Zima and Mazurek, 2016). Dyshomeostasis of Ca^{2+} at sub-cellular moiety is implicated in atrial fibrillation and other cardiac ailments. OS triggers apoptotic pathways in cardiomyocytes. H_2O_2 induces apoptosis in human cardiac progenitor cells by promoting phosphorylation and nuclear translocation of JNK. OS fuels ERK and JNK mediated signaling cascades leading to myocyte injury and heart failure. Moreover, OS triggers Akt-mTOR and NFκB signaling pathway to upregulate cardiac fibrosis and hypertrophy. ROS outburst promotes opening of mitochondrial permeability transition pore that accounts for necroptosis and cardiac dysfunction.

In heart, these OS-mediated signaling events could fuel cardiomyocyte dysfunction, apoptosis, contractile dysfunction, impaired cardiac remodeling, fibrosis, hypertrophy, and heart failure.

4.3. Renin-angiotensin system

Renin Angiotensin System (RAS) is of paramount importance to control fluid-homeostasis, blood pressure, and cardiac physiology within the body. Renin, angiotensin converting enzyme (ACE)-1, ACE-2, angiotensinogen, angiotensin (ANG) I, and ANG II are the major drivers of RAS localized in different portion of heart such as coronary vessels, atria, ventricles, valves, fibroblasts, and myocytes (Paul et al., 2006). Notably, ACE-2 receptors are abundant in thoracic aorta, venous endothelial cells, arterial smooth muscle cells, myofibroblasts, carotid arteries, and veins (Hamming et al., 2004). In an earlier step of RAS, renin, an aspartyl proteinase converts angiotensinogen to ANG I. ACE-1, being a dipeptidyl carboxypeptidase cleaves ANG I to ANG II which in sequel is transformed into ANG 1–7 by monocarboxypeptidase ACE-2 (Donoghue et al., 2000; Tipnis, 2000). ANG II is a biologically active octapeptide that works via ANG II type-I receptor (AT_1R) to promote vasoconstriction, inflammation, and OS (Bader and Ganten, 2008). Profound activation of ANG II/AT_1R is linked to apoptosis, fibrosis, myocardial stunning, and I/R injury. Such detrimental consequences are counter-regulated by ANG1–7 that works through Mas receptor. ANG 1–7/Mas axis is implicated in smooth muscle cell relaxation, antioxidative outcome, and cardioprotection (Ferreira et al., 2012).

SARS-CoV-2 infection can be detrimental to RAS (Fig. 3). Virions upon cellular invasion down-regulate ACE-2 receptors leading to reduced conversion of ANG II into ANG 1–7. It results in excessive accumulation of ANG II and reduced level of ANG 1–7 (Verdecchia et al., 2020). Surplus level of ANG II is linked to cardiac injury. Human Cathepsin A (CatA) is a lysosomal serine carboxypeptidase belonging to RAS. Bouknight et al., 2020 suggested that, OPs like sarin, soman, and cyclosarin may promote RAS impairment and cardiovascular diseases by inhibiting the activity of CatA. Moreover, OPs upregulate aggregation of AT_1R mRNA and protein that lead to hyper-responsiveness of the receptor (Sungkaworn and Chatsudthipong, 2011; Li et al., 2013). It is important to note that, OPs like mevinphos augment the enzymatic

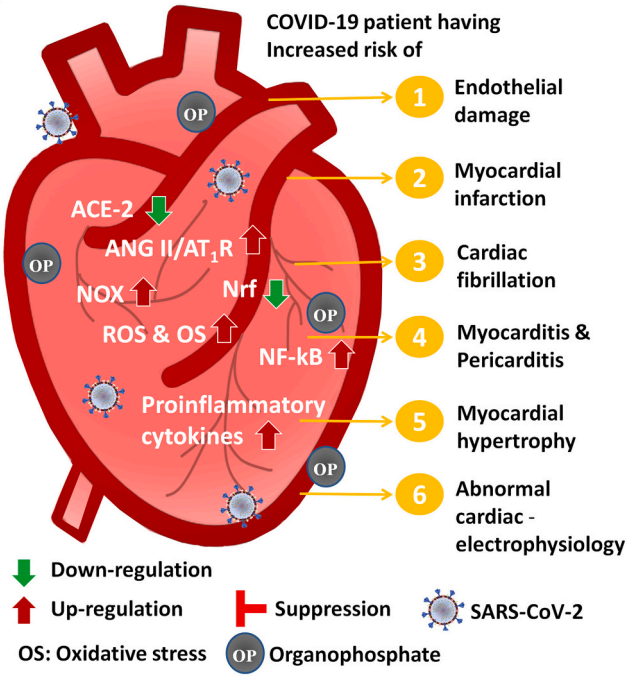

Fig. 4. Brief graphical summary of the literature. SARS-CoV-2 and OP co-exposure disrupts RAS which is characterized by down-regulation of ACE-2, up-regulation of ANG II, and hyperactive ANG/AT_1R signaling pathway. Redox homeostasis is altered by down-regulation of Nrf mediated antioxidant signaling, induction of NOX assembly, and excessive production of ROS. Proinflammatory cytokine levels are amplified by viral and chemical exposure via induction of NF-kB mediated signaling cascade. All these alterations at subcellular moiety lead to cardiovascular issues.

activities of PI3K or Akt which in turn enhances the transcriptional activity of NF-kB (Tsai et al., 2014). Various forms of hypertension are suggestive of disrupted RAS in the cardiovascular environment. Hypertensive responses characterized by sustained elevation in diastolic, mean, and systolic blood pressure are evident in rats following chlorpyrifos exposure (Smith and Gordon, 2005). Li et al., 2020 have unraveled the association between OP esters and hypertension in human. They detected Triethyl phosphate as the most abundant chemical in hypertensive patients with elevated diastolic blood pressure thereby lending support for an imbalanced RAS.

In a human-based study, enhanced levels of ACE, ANG II, AT_1R, matrix metalloproteinases 2/9, monocyte chemoattractant protein-1, and collagen I/III proteins were traced in diffusely thickened intimae of aortic wall. Authors concluded that, these changes can promote development of arterial diseases such as atherosclerosis and hypertension (Wang et al., 2007). AT_1R induced by ANG II triggers spectrum of signaling pathways governing several cardiovascular physiologies. ANG II activates protein lipase C (PLC) and protein lipase D (PLD) with subsequent generation of inositol triphosphate (IP3) and diacylglycerol (DAG). Increased level of IP3 facilitates cytosolic release of Ca^{2+} from intracellular stores that phosphorylates myosin light-chain kinase (MLCK) to fuel vasoconstriction (Shin et al., 2002). Moreover, excessive ANG II activates protein kinase C (PKC) to phosphorylate mitogen-activated protein kinase (MAPK) (Sadoshima and Izumo, 1993). MAPKs like p38 kinases, c-jun-terminal kinases (JNK), and ERK 1/2 are involved in alteration of cardiac myocytes, extracellular matrix, and progression of heart failure (Opie, 2004). Intriguingly, activated AT_1R promotes assembly of NADPH oxidase (NOX) that plays critical role in ROS production. ROS catalyzes oxidative modification of low density lipoprotein and endothelial dysfunction to promote vascular inflammation coupled with atherosclerosis (Landmesser and Drexler, 2003). Akt also plays undeniable role in ANG-II mediated cardiomyocyte hypertrophy (Hingtgen et al., 2006). ANG II induced NOX2/vascular peroxidase 1/hypochlorous acid/ERK1/2 redox signaling pathway exacerbates pathogenesis related to cardiac hypertrophy (Yang et al., 2017).

5. Concluding remarks and future recommendations

Cardiotoxicity is an emerging global concern that can promote cardio-vascular disease and thereafter mortality in human. Several environmental factors are associated with the development of the cardiac disorder. OPs are the potent cardiotoxic agents that facilitate myocardities, systolic dysfunction, arrhythmia, weakening of cardiac muscle, and abnormal electrophysiology of heart. Similar cardiac maladies have also been observed in the patients with COVID-19. As both of these environmental stressors impact cardiac system, the coexposure and synergistic action of both agents may increase the possibility of severe cardiac injuries. Hence, indiscriminate use of these OP pesticides might escalate the severity of cardiac damage in the patients exposed to the SARS-CoV-2 infection. Proper instructions of usage should be followed to minimize human exposure to OP pesticides. Moreover, pesticide residues have been detected in fruits and vegetables, and these food items must be properly washed before consumption to restrain unintentional exposure. It is interesting to note that, certain nutraceuticals have good antiSARS-CoV-2-antioxidant-antiinflammatory properties and hence their intake through regular diet would be beneficial in mitigating cardiotoxicity fueled by OPs and COVID-19 (Fig. 4).

CRediT authorship contribution statement

Prem Rajak: Conceptualization, Writing – original draft, Writing – review & editing, Supervision. **Sumedha Roy:** Conceptualization, Writing – review & editing, Supervision. **Sayanti Podder:** Writing – review & editing. **Moumita Dutta:** Writing – review & editing. **Saurabh Sarkar:** Conceptualization, Writing – review & editing. **Abhratanu Ganguly:** Conceptualization, Writing – original draft. **Moutushi Mandi:** Writing – review & editing. **Anik Dutta:** Writing – review & editing. **Sayantani Nanda:** Writing – review & editing. **Salma Khatun:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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