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*Review*

# Insights into the role of paraoxonase 2 in human pathophysiology

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Paraoxonase 2 (PON2) is a ubiquitously expressed intracellular enzyme that is known to have a protective role from oxidative stress. Clinical studies have also demonstrated the significance of PON2 in the manifestation of cardiovascular and several other diseases, and hence, it is considered an important biomarker. Recent findings of its expression in brain tissue suggest its potential protective effect on oxidative stress and neuroinflammation. Polymorphisms of PON2 in humans are a risk factor in many pathological conditions, suggesting a possible mechanism of its anti-oxidative property probably through lactonase activity. However, exogenous factors may also modulate the expression and activity of PON2. Hence, this review aims to report the mechanism by which PON2 expression is regulated and its role in oxidative stress disorders such as neurodegeneration and tumor formation. The role of PON2 owing to its lactonase activity in bacterial infectious diseases and association of PON2 polymorphism with pathological conditions are also highlighted.

**Keywords.** Anti-oxidative; Lactonase; PON2 expression; PON2 modulators; PON2 polymorphism; Paraoxonase

**Abbreviations:** AD, Alzheimer's disease; Akt, Protein kinase B; AP-1, Activator protein 1; AMPK, AMP-activated protein kinase; ATF4, Activating transcription factor 4; ATF6, Activating transcription factor 6; BiP, Binding immunoglobulin protein; CHOP, C/EBP homologous protein; CVD, Cardiovascular disease; Cyt C, Cytochrome C; eIF2a, Eukaryotic translation initiation factor 2a; FOXO3a, Forkhead transcription factor; GLUT1, Glucose transporter 1; GSK3β, Glycogen synthase kinase 3beta; HS, Homoserine; HSL, Homoserine lactone; IM, Inner membrane; IRE, Iron responsive element; JNK, C-Jun N-terminal kinase; mPTP, Mitochondria permeability transition pore; OM, Outer membrane; PERK, Protein kinase RNA-like endoplasmic reticulum kinase; PI3K, Phosphoionositide 3-kinase; PUMA, P53 upregulated modulator of apoptosis; RISK, Reperfusion injury salvage kinase; STOM, Stomatin; XBP1, X-box binding protein 1.

## 1. Introduction

The paraoxonases PON1, PON2, and PON3 are members of esterase family enzymes and are highly conserved within and between species (figure 1) (Teiber *et al.* 2018). Phylogenetic analysis has revealed that PON2 is the oldest member of the PON family and that PON1 and PON3 have evolved from it (figure 2) (Draganov and La Du 2004). The genes of all the three paraoxonases are located next to each other on the long arm of chromosome 7 in the case of humans, and on chromosome 6 in mice (She *et al.* 2012). PON1 and PON3 are primarily expressed in the liver, and get associated with high density lipoprotein (HDL), whereas PON2 is ubiquitously expressed and is not present in the blood plasma (Ng *et al.* 2001; Kulka 2016). PON2 has been detected in several tissues at mRNA level, protein level, or both, including the brain where the other two PONs are not expressed (Costa et al 2014; Ng *et al.* 2001; Giordano *et al.* 2011). The highest levels of PON2 are expressed in the lungs and small intestine, followed by the heart and liver, whereas lower levels are reported in testis, kidney, and brain (Marsillach *et al.* 2008). Although the name 'PON' suggests


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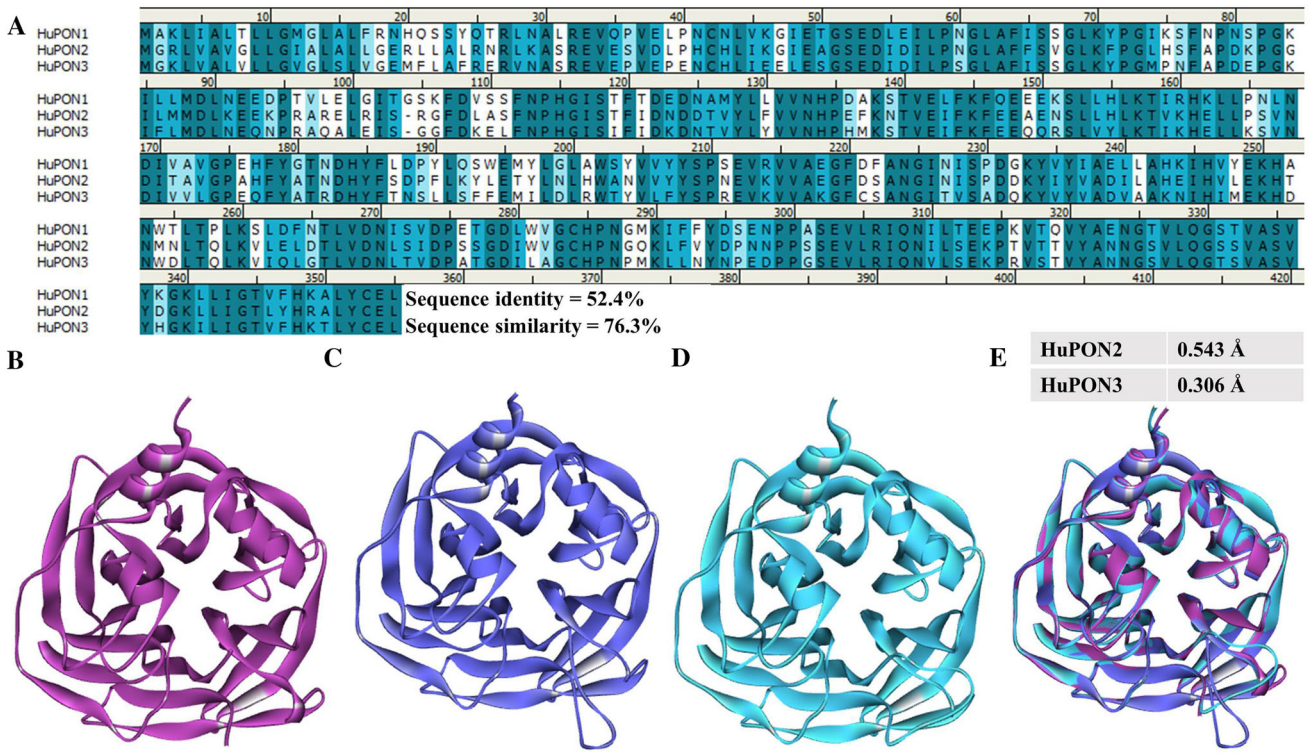


**Figure 1.** Comparative *in silico* analysis of human paraoxonases. (**A**) Sequence alignment of HuPON2 and HuPON3 with Chi-PON1 (PDB:1V04) shows 52.4% sequence identity and 76.3% sequence similarity. (**B**) Crystal structure of HuPON1 (PDB:1V04); magenta color-coded. (**C**) Homology model of HuPON2, prepared from HuPON1 template (PDB:1V04); blue color-coded. (**D**) Homology model of HuPON3, prepared from HuPON1 template (PDB:1V04); cyan color-coded. (**E**) Superimposition of HuPON1 (magenta), HuPON2 (blue), and HuPON3 (cyan), shows the close similarity of all the structures, RMSD values are mentioned in the table. The analysis was performed in Discovery Studio 4.0.

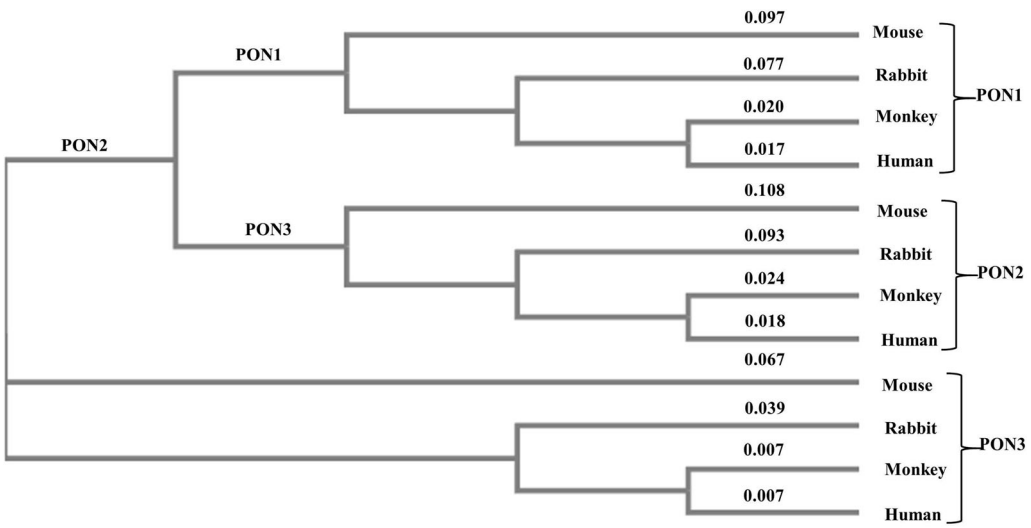


**Figure 2.** Phylogenetic tree showing the evolutionary origin of human paraoxonases. Four mammals were selected randomly, and their sequences were retrieved from NCBI. Sequence alignment and phylogenetic tree construction were done by using Clustal Omega. The scores on the tree correspond to the evolutionary distance between the sequences.

**Table 1.** Comparison of human PON family members

| | PON1 | PON2 | PON3 | References |
|---|---|---|---|---|
| Gene ID | 5444 | 5445 | 5446 | Primo-Parmo *et al.* (1996) |
| Location | 7q21.3 | | | |
| Number of amino acids | 355 | 354 | 354 | Taler-Verčič *et al.* (2020) |
| Subcellular expression | Mainly bound to HDLs in blood plasma | Present on the membrane of mitochondria, on the ER and on the plasma membrane | Mainly bound to HDLs in blood plasma and mitochondria | Horke *et al.* (2008), Devarajan *et al.* (2011), Schweikert *et al.* (2012a), Hagmann *et al.* (2014) |
| *Tissue specific expression* | | | | |
| mRNA level | Mostly enriched in liver with some small amount in thymus and adrenal gland | Enhanced in liver and distributed in almost all other tissues | Enriched in liver and detected in small amount in many other tissues | "Tissue expression of PON1 - Summary - The Human Protein Atlas"; "Tissue expression of PON2 - Summary - The Human Protein Atlas"; "Tissue expression of PON3 - Summary - The Human Protein Atlas") |
| Protein level | Present in plasma | Ubiquitous in occurrence except in blood | Present in hepatocytes mainly | |
| Enzyme classification | EC 3.1.1.2<br>EC 3.1.1.81<br>EC 3.1.8.1 | EC 3.1.1.2<br>EC 3.1.1.81 | EC 3.1.1.2<br>EC 3.1.1.81<br>EC 3.1.8.1 | ("PON1 paraoxonase 1 [Homo sapiens (human)] - Gene - NCBI"; "PON2 paraoxonase 2 [Homo sapiens (human)] - Gene - NCBI"; "PON3 paraoxonase 3 [Homo sapiens (human)] - Gene - NCBI") |
| *Functions/enzyme activity* | | | | |
| Paraoxonase | Significant | Not detected | Not detected | Draganov *et al.* (2005), Costa *et al.* (2014) |
| Arylesterase | Higher than PON2 and PON3 | Present | Present | |
| Lactonase | Present | Higher than PON1 and PON3 | Present | |
| Statinase | Not detected | Not detected | Significant | |
| *Pathophysiological association* | | | | |
| Atherosclerosis | Prevention of HDL and LDL oxidation | PON2 can inhibit HDL and LDL oxidation mainly by reducing ROS production | PON3 can also inhibit HDL and LDL oxidation mainly by reducing ROS produced | Witte *et al.* (2012), Mackness and Mackness (2015) |
| | Reduction of macrophage, oxidative stress and inflammatory response | Associated with mitochondrial ETC helping in sequestering ROS | Associated with mitochondrial ETC helps in sequestering ROS | |
| Inflammatory diseases | Anti-inflammatory properties | Antagonizes inflammatory processes | Anti-inflammatory function | Devarajan *et al.* (2014) |
| Organophosphate toxicity | Organophosphatase activity | No organophosphatase activity | Only against paraoxon | Draganov *et al.* (2005), Gupta *et al.* (2011) |
| Cancer | Lower activity of serum PON1 in cancer patients | Overexpression in cancer cells | Overexpression in cancer cells | Bacchetti *et al.* (2017) |

**Table 1.** (continued)

| | PON1 | PON2 | PON3 | References |
|---|---|---|---|---|
| Quorum quenching (infectious disease) | Lactonase activity helps in quorum quenching | Highest lactonase activity | Inactivate acyl-homoserine lactones | Camps *et al.* (2011) |
| Ageing | Antioxidant, lower level of expression in elderly | Antioxidant, lower level of expression in elderly | Antioxidant, lower level of expression in elderly | Levy *et al.* (2019) |

paraoxonase but PON2 and PON3 have almost no paraoxonase activity (Draganov *et al.* 2005). Only PON1 has a weak paraoxonase activity, but all the three PONs exhibit anti-oxidant and anti-inflammatory activities. Their physiological function(s) and native substrates, however, remain ambiguous (Richter *et al.* 2009; Grdic Rajkovic *et al.* 2011). The native enzyme activity of paraoxonases was found to be lactonase, suggesting that despite its promiscuous nature the endogenous substrates of paraoxonases are lactones (Draganov *et al.* 2005).

Subcellular localization studies of PON2 show that it is particularly present at the perinuclear region, endoplasmic reticulum (ER), and mitochondria (Horke *et al.* 2007). At the plasma membrane level, PON2 is a transmembrane protein with its enzymatic domain facing the extracellular compartment, and thus plays an important role in rescuing peroxidation of membrane components (Hagmann *et al.* 2014). Mitochondria are cytoplasmic organelles whose integrity is essential for maintaining specific physiological, biochemical, and morphological features of cells. They, therefore, play an essential role in the life and death of the cells (Rasheed *et al.* 2017). The fact that PON2 is located in mitochondria suggests its anti-oxidative nature, and thus its cytoprotective role. Therefore, PON2 deficiency causes mitochondrial dysfunction in these cells (Devarajan *et al.* 2011). In addition to its antioxidant activity, PON2 has a remarkably high lactonase activity as compared to PON1 and PON3 (Teiber *et al.* 2008). The lactonase activity of PON2 may be responsible for its anti-inflammatory role. It was reported in the intestinal epithelial cells that PON2 silencing exacerbated inflammatory processes thereby disturbing the mucosal integrity (Précourt *et al.* 2012). However, a mutant PON2 (PON2-Asn254Ala/Asn323Ala) lacking lactonase activity does not affect the anti-inflammatory functions (Stoltz *et al.* 2009). *In vivo* studies also suggest that PON2 knocked out mice has exacerbated macrophage inflammatory response (Ng *et al.* 2006). The mechanism by which PON2 accomplishes anti-inflammatory function is poorly understood mainly due to the lack of its targets or substrates in physiological conditions.

Association of PON2 with coenzyme Q and preventing reactive oxygen species (ROS) generation in mitochondria is irrespective of its lactonase activity (Altenhöfer *et al.* 2010; Devarajan *et al.* 2014). These observations suggest that the antioxidative nature of PON2 might be independent of its lactonase activity. PON1 has been well studied as compared to PON2 and PON3, and recently evolved for the stereospecific hydrolysis of G-type of nerve agents (Gupta *et al.* 2011). However, PON2 is emerging as an important defense system owing to its location, expression, and significant lactonase activity. The protective role of PON2 has been well documented in vascular, neuronal, macrophage, and other cells against oxidative stress as the downregulation of PON2 was found to be antagonizing its protective effect (Schweikert *et al.* 2012b). Reportedly, PON2 overexpression prevents ER and/or oxidative stress (Horke *et al.* 2007). Several chronic diseases develop due to elevated levels of ROS. Therefore, understanding the role of PON2 in scavenging cellular ROS can be an important finding. Although, the cytoprotective role of PON2 is well established, the mechanism by which it reduces ROS and thereby apoptosis, is not well understood (Witte *et al.* 2012). Therefore, efforts are being made to understand the associated signaling pathways and their pathophysiological relevance (Devarajan *et al.* 2018).

It would be of many benefits to studying PON2 overexpression and its contribution to cancer as it confers apoptosis resistance (Horke *et al.* 2008; Witte *et al.* 2011). Moreover, PON2 is attracting significant interest due to its expression in the nervous system and its role in preventing neurodegeneration (Giordano *et al.* 2011). Here, we have described the enigmatic role of PON2 in molecular physiology and redox

homeostasis, and how the modulation of its expression could be a therapy for several diseases.

## 2. Regulation of PON2 expression

Owing to the pathophysiological role of PON2 in several diseases, strategies attempting to modulate its level of expression could have important health implications. In this regard, several bioactive molecules are known to regulate PON2 expression and activity, which are discussed below in details.

### 2.1 *Transcription factors*

PON2 gene transcription is regulated in an integrated multistep pathway. PON2 expression is under genetic control and regulated by cellular oxidative stress as well as by cholesterol content (Rosenblat *et al.* 2004; Shiner *et al.* 2006). Low transcriptional activity of PON2 has been recognized as one of the major culprits in recurrent abortion due to its inadequate antioxidative defense (Dikbas *et al.* 2018). Several transcription factors such as peroxisome proliferator-activated receptor γ (PPARγ), sterol regulatory element-binding protein 2(SREBP-2), and activator protein-1 (AP-1) activation are known to upregulate PON2 expression. Reportedly, stimulating macrophages with urokinase activates phosphoinositide 3-kinase (PI3K) through platelet-derived growth factor ß which further activates NADPH oxidase resulting in the production of ROS, which is ultimately involved in the regulation of PON2 expression (Shiner *et al.* 2007a, b; Fuhrman *et al.* 2009). More recently, two new transcription factors, Wilms tumor 1 associated protein (WTAP) and the baculoviral IAP repeat-containing 3 (BIRC3) are shown to modulate PON2 expression and activity (Carusone *et al.* 2020). Furthermore, it was demonstrated that the glucocorticoid-glucocorticoid receptor complexes are directly involved in the transactivation of AP-1 which is responsible for transcriptional activation of the PON2 gene (Shiner *et al.* 2004, 2007a). Contradictorily, some findings suggest the role of the glucocorticoid receptor in directly regulating PON2 expression irrespective of AP-1 (Lim and Kim 2009). These findings indicate that cellular PON2 expression has a direct or indirect role in signaling pathways associated with ROS production and cholesterol biosynthesis (Fuhrman *et al.* 2009).

Epigenetic regulation of PON1 has also been established (Huen *et al.* 2015; Mahrooz *et al.* 2019); however, the epigenetic regulation of PON2 and PON3 are not studied well (Holland *et al.* 2015; Mahrooz and Mackness 2020). Xiao *et al.* showed that PON2 had very little methylation as compared to PON1 and PON3 in case of patients with cerebral infarction and control (Xiao *et al.* 2019).

### 2.2 *Hormones*

Hormonal regulation of PON2 has been very-well investigated, where sex steroids have gained much attention (Giordano *et al.* 2011; Siddiqui *et al.* 2016). This could be useful to understand the etiology of various neurodegenerative disorders as PON2 levels are higher in central nervous system tissues that is the brain and peripheral region of female mice than male mice (Costa *et al.* 2014). The lower expression of PON2 in males as compared to females may have wider consequences for the predisposition to oxidative stress diseases. This includes neurodegenerative diseases such as Alzheimer's, Parkinson's, cardiovascular diseases as well as Covid-19, where males are more susceptible to the disease than females (Liguori *et al.* 2018; Levy *et al.* 2019; Jin *et al.* 2020). For example, the incidence of Parkinson's disease is 90% higher in males as compared to female (Wirdefeldt *et al.* 2011; Costa *et al.* 2014), suggesting that the higher PON2 levels in dopaminergic neurons of females may provide better protection against oxidative stress (Giordano *et al.* 2011, 2013). The gender difference in PON2 expression levels may be attributed to the positive modulatory effect of estrogens in female mice (Leranth *et al.* 2000; Kitamura *et al.* 2009; Bwire 2020). Estradiol-induced increase in PON2 mRNA, as well as protein levels, in a time- and concentration-dependent manner, in both male and female striatal astrocytes, is probably due to the activation of estrogen receptor-alpha. Similarly, in ovariectomized female mice, it was observed that PON2 mRNA and protein levels decreased as compared to that in a male in brain regions and liver (Cheng and Klaassen 2012; Giordano *et al.* 2013).

Interestingly, some plant hormones also have a modulatory effect on PON2 expression. Glabridin, the licorice phytoestrogen, has been found to increase PON2 expression, and protects its activity. Glabridin interacts with PON2, and prevents its oxidation, thus

preserving its activity, in hyperglycemic patients (Yehuda *et al.* 2011). Furthermore, as PON2 is expressed ubiquitously in all tissues, and the levels of expression is more or less higher in females in each tissues examined, the reported higher sensitivity of males to oxidative stress in the brain, the heart, the kidney, or the liver may be related to the similar mechanism (Klein 2000; Valle *et al.* 2007).

### 2.3 *Post-translational modifications (PTMs)*

PTMs take place either on the amino acid side chains or at the C- or N- termini of PON2 protein, thereby regulating its catalytic activity. There are contradictory studies on the dependence of PON2 enzyme activity on N-glycosylation. Ser311Cys polymorphism or ubiquitination at Lys168 have been found to modulate PON2 activity (Mandrich *et al.* 2015). Amino acid substitution at position 311 from serine to cysteine in recombinant PON2 altered glycosylation, and decreased lactonase activity but protein production and localization are normal (Stoltz *et al.* 2009). Likewise, studies are pointing to side-chain modification of amino acid residues regulating the catalytic activity of PON2. Carusone *et. al.* found that N-(3-oxododecanoyl)-L-homoserine lactone (3OC12-HSL) induced post-translational modification at multiple positions in PON2. For instance, post-translational modification at position 144, nearby two SNPs (A148G and S311C) has been shown to affect PON2 activity (Carusone *et al.* 2020).

### 2.4 *Non-steroidal anti-inflammatory drugs (NSAIDs)*

Commonly used NSAIDs are reported to affect PON2 specific lactonase and arylesterase activity. NSAIDs, like diclofenac sodium and tenoxicam, have been tested *in vitro*, causing a significant decline in lactonase activity (Solmaz Avcıkurt and Korkut 2018). On the other hand, antenatal steroid therapy did not affect PON2 mRNA expression in placentae of unexplained intrauterine growth restricted pregnancies as compared to the non-treated group (Dikbas *et al.* 2017). It is also hypothesized that increased cholesterol content may be the cause of decreased PON2 expression (Rosenblat *et al.* 2004). Therefore, hypocholesterolemic drugs may prove to be positive modulators of PON2. One such drug, atorvastatin, has been reported to upregulate PON2 expression in various cell types (Shiner *et al.* 2007b).

### 2.5 *Nutraceuticals*

Dietary factors including flavonoids and polyphenols have long been known to possess antioxidant properties, and modulate intracellular antioxidant enzymes. The underlying molecular mechanisms by which flavonoids may induce PON2 gene expression have not been fully elucidated (Pandey and Rizvi 2009; Costa *et al.* 2016). Flavonoids from pomegranate are reported to affect the DNA binding activity of the transcription factor AP-1, which is present in the promoter region of the PON2 gene (Shiner *et al.* 2007a). It is also proposed that increasing concentrations of plant polyphenol, quercetin, in murine macrophages resulted in upregulated PON2 at mRNA as well as protein levels (Boesch-Saadatmandi *et al.* 2009). PON2 gene is partly regulated by NADPH oxidase, which is a molecular target of quercetin (Shiner *et al.* 2004).

Chlorogenic acid, a major phenolic compound of Yerba mate, a plant species consumed as traditional tea, could increase the relative expression of PON2 mRNA as well as enzyme activity *in vitro* in macrophages. On the other hand caffeic acid, a metabolite of chlorogenic acid in the plasma, did not affect PON2 gene expression, but increased its enzyme activity at an appropriate concentration (Monteiro *et al.* 2007; Fernandes *et al.* 2012).

Eicosapentaenoic acid (EPA) is a long-chain omega-3 polyunsaturated fatty acid that was investigated for its cardioprotective property. EPA administration increased HDL cholesterol, decreased fasting blood sugar, and upregulated PON2 gene expression in patients with type 2 diabetes mellitus (Endo and Arita 2016; Golzari *et al.* 2019). More recently, higher glucose concentration as compared to physiological levels was found to downregulate PON2. The formation of advanced glycation end products is induced by elevated glucose levels. In human umbilical vein endothelial cells (HUVECs), overexpression of PON2 reduced both the early and the late glycation end products, induced ROS, ER stress, and inflammation (Morresi *et al.* 2019; Ravi *et al.* 2020).

Negative modulation of PONs, especially PON1, is also reported for several metals, and vice-versa susceptibility to toxicity and neurotoxicity of metals is affected by different levels of PONs (Costa *et al.* 2017). Therefore, pharmacological, dietary, lifestyle,

and environmental factors modulating PON2 could be considered as important factors for the prevention and cure of several diseases. Certain modulators of PON2 are broadly classified and summarized in table 2.

## 3. Role of PON2 in cancer

Several studies in the recent years have confirmed the overexpression of PON2 in cancerous cells. Reportedly, PON2 could be involved in tumor survival and stress resistance. An elaborate clinical study, conducted on tumor samples taken from more than 10,000 patients with different types of cancer, showed a high expression of PON2 in multiple types of solid tumors, suggesting that overexpression of PON2 in cancer cells causes resistant to chemotherapy and other unfavorable conditions causing malignancy (Shakhparonov *et al.* 2018). Similarly, overexpression of PON2 in bladder cancer cell lines led to a significant increase in cell proliferation and resistance to oxidative stress (Bacchetti *et al.* 2017). More recently, a study reported PON2 as an oncogene in gastric cancer, overexpression of which was correlated to tumor diffusion and invasion (Wang *et al.* 2019). Therefore, it is suggested that PON2 can be used as molecular biomarker for the prognosis of multiple types of cancer (Bacchetti *et al.* 2021; Campagna *et al.* 2020).

The fact that PON2 helps in apoptotic escape represents a major clinical complication in cancer biology. However, the distinct regulatory pathways are poorly understood. Both PON2 and PON3 are involved in modulating mitochondrial superoxide anion production and ER stress-induced apoptosis (Bacchetti *et al.*

**Table 2.** Summary of some recently studied modulators of PON2

| Modulators | Regulation | Mode of action | References |
|---|---|---|---|
| *Synthetic drugs* | | | |
| Atorvastatin | Upregulates PON2 mRNA and activity in human monocyte derived macrophages | Anti-atherogenic role | Rosenblat *et al.* (2004), Ninic *et al.* (2018) |
| Pioglitazone | Upregulates PON2 protein expression in brain striatum of mice | Stimulating effect on PPARγ | Blackburn *et al.* (2020) |
| NSAID-Tenoxicam | Downregulates lactonase as well as arylesterase activity in-vitro in human monocytic cell line | Inhibitory effect on PON | Solmaz Avcıkurt and Korkut (2018) |
| NSAID-Diclofenac sodium | Downregulates lactonase activity in-vitro in human monocytic cell line | – | Solmaz Avcıkurt and Korkut (2018) |
| *Nutraceuticals* | | | |
| Quercetin | Upregulates PON2 mRNA, protein and lactonase activity in mouse striatal astrocytes | Activates JNK/AP-1 pathway | Boesch-Saadatmandi *et al.* (2009), Costa *et al.* (2016) |
| Yerba mate extracts | Upregulates PON2 mRNA and activity in macrophage and monocyte | – | Fernandes *et al.* (2012) |
| *Hormones* | | | |
| Estrogen | Upregulates PON2 mRNA and protein in mice astrocytes | Estrogen receptor -α | Giordano *et al.* (2013) |
| Human chorionic gonadotropin | Upregulates PON2 mRNA and protein in human lung carcinoma cell line | Pro-tumorigenic role | Sahoo *et al.* (2015) |
| Phytohormone (Glabridin) | Upregulates PON2 mRNA, protein and activity in-vitro in monocytes and in-vivo in hyperglycemic mouse liver and heart | Anti-atherogenic effect | Yehuda *et al.* (2011) |
| *Dietary compounds* | | | |
| Pomegranate juice | Upregulates PON2 mRNA, protein and activity in mouse macrophage cell line | Activation of TFs $PPAR_{\gamma}$ and AP-1 | Shiner *et al.* (2007a) |
| Eicosapentaenoic acid (EPA)[fish oil] | Upregulates PON2 mRNA | – | Golzari *et al.* (2019) |
| Glycation end products | Downregulates PON2 mRNA, protein expression and activity in HUVECs | – | Ravi *et al.* (2020) |

2019). Unfolded protein response (UPR) pathway is a pathway that is activated in response to ER stress, and aims at limiting misfolded proteins accumulation (Walczak *et al.* 2019). It is hypothesized that ER stress causes protein misfolding leading to the expression of molecular chaperon HSP70 (Bip) in the ER lumen. Bip helps in the dimerization of Protein kinase RNA like Endoplasmic Reticulum Kinase (PERK) leading to C/EBP Homologous Protein (CHOP)-mediated apoptosis (figure 3) (Sato *et al.* 2000). The antioxidant nature of PON2, and its involvement in the UPR pathway, suggests an endogenous defense mechanism that PON2 may contribute towards the prevention of various diseases (Horke *et al.* 2008). Overexpression of antioxidant enzymes is not always beneficial. Witte *et. al.* suggested that PON2 overexpression reduced CHOP expression, and thus apoptosis via the c-Jun N-terminal Kinase (JNK) pathway (Witte *et al.* 2011).

Another theory put forward for the anti-apoptotic role of PON2 is that p53 transcriptionally represses PON2, and in case of any mutation in p53, there is overexpression of PON2 (figure 3). PON2 was shown to be overexpressed in pancreatic cancer tissues i.e. pancreatic ductal adenocarcinoma where mutations in TP53 are present which facilitate the metastatic progression (Nagarajan *et al.* 2017). Along with PON2, other factors like Hypoxia-Inducible Factor-1 (HIF 1) may also come into play, and support tumor progression through multiple pathways (Amelio *et al.* 2018). It is also reported that PON2 positively modulates the expression of Glucose Transporter 1 (GLUT 1), and thus inhibits the AMP-activated protein kinase (AMPK) pathway (Nagarajan *et al.* 2017; Pan *et al.* 2019). AMPK pathway of apoptosis functions in response to cellular starvation in normal cells, and serves as a possible metabolic tumor suppressor (Li *et al.* 2015). As PON2 overexpression causes an increase in GLUT 1 expression, there is more and more glucose intake, which shuts down the AMPK pathway. Therefore, by inhibiting the AMPK pathway PON2

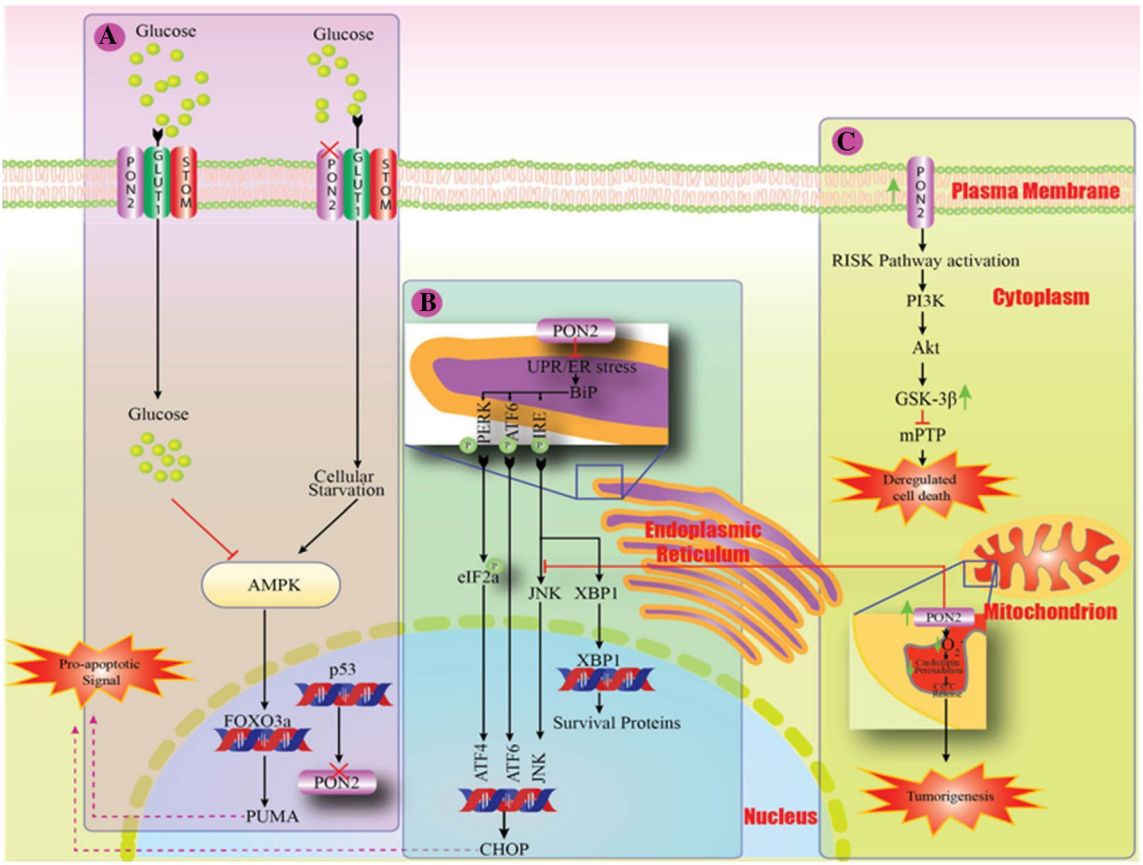


**Figure 3.** Overview of PON2 and its regulation of different key cell signaling pathways involved in cancer. (**A**) PON2 expression is transcriptionally regulated by p53. This in turn regulates glucose uptake by GLUT1 and thus inhibit the AMPK pathway of cell death. (**B**) Similarly, PON2 inhibits ER stress induced CHOP expression as well as cardiolipin peroxidation and cytochrome C release in mitochondria, thereby preventing apoptosis. (**C**) PON2 activates RISK pathway and helps in reducing mitochondrial dysfunction.

stabilizes the tumor. This is very similar to Warburg's phenomenon suggesting aerobic glycolysis where glucose is used for various biosynthetic pathways that promote cell proliferation (Faubert *et al.* 2013; Hu *et al.* 2019). Moreover, PON2 counteracts lipid peroxidation, which may add to stabilizing tumor cells. For example, PON2 attenuates cardiolipin peroxidation in the mitochondrial membrane to prevent intrinsic apoptosis (Witte *et al.* 2011). In yet another study, regulation of PON2 protein expression through the Wnt/GSK3β/β-catenin pathway in leukemia and oral squamous cell cancer (OSCC) was demonstrated (Krüger *et al.* 2016). In OSCC, the anti-apoptotic nature of PON2 was correlated with resistance to radiotherapy (Krüger *et al.* 2015). PON2 overexpression in bladder cancer cells is also shown to resist chemotherapy by counteracting the induced ROS due to its antioxidative property (Fumarola *et al.* 2020). In the case of ovarian cancer, it was noticed that PON2 expression was enhanced in the early stages of cancer but at later stages, there was no change in the expression. This might be because PON2 regulates tumorigenesis in a Spatio-temporal manner (Devarajan *et al.* 2018).

On the other hand, PON2 may also be indirectly involved in tumorigenesis via Reperfusion Injury Salvage Kinase (RISK) pathway. PON2 reduces cardiolipin peroxidation, cytochrome C release, and activation of caspase (figure 3) (Sulaiman *et al.* 2019a, b). Downregulation of PON2 may be important in targeting cancer. According to a report, valproic acid stimulation led to a decrease in PON2 expression in glioblastoma multiforme cells. This in turn inhibited cancer progression by increasing ROS production which ultimately promoted apoptosis via the Bim cascade (Tseng *et al.* 2017).

## 4. Role of PON2 in cardiovascular diseases

Unlike PON1 and PON3 that remain associated with HDL, and perform an anti-oxidative function, PON2 appears to be present in endothelial cells, smooth muscle cells, and macrophages where it remains associated with membranes of ER and nucleus (Shih and Lusis 2009; She *et al.* 2012). The cardioprotective role of PON2 is shown in both experimental and human heart failure. This may be attributed to significantly increased PON2 activity, its ability to improve mitochondrial function, and diminish ROS generation (Li *et al.* 2018). Recent studies have shown that in endothelial cells, PON2 prevents

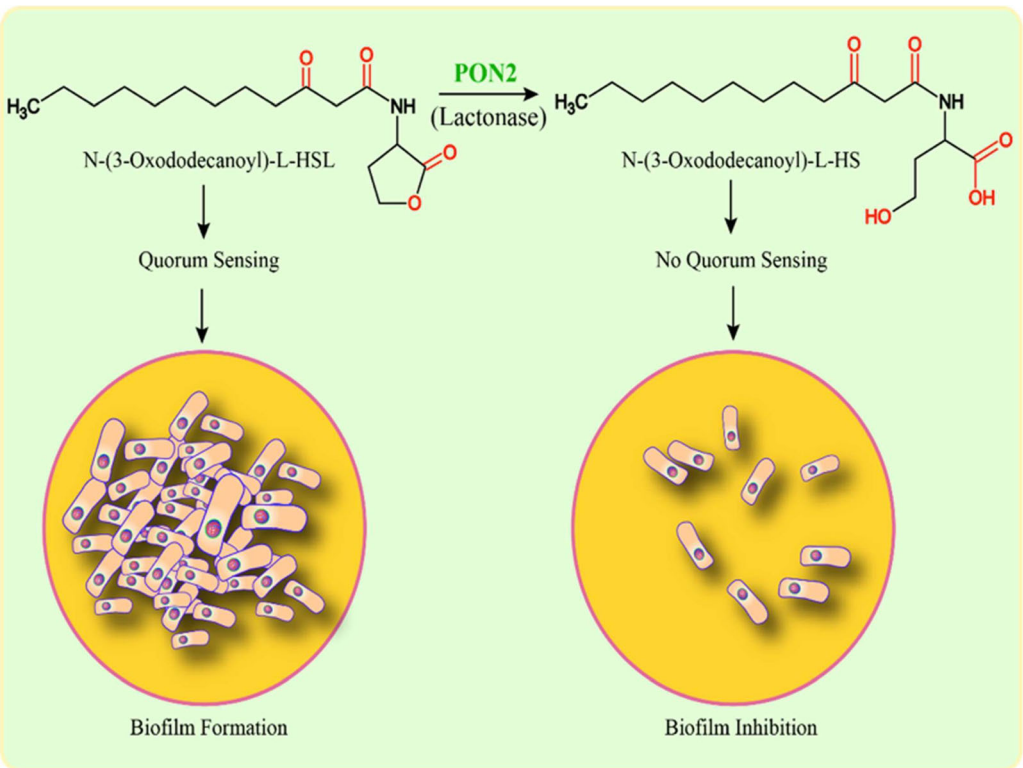


**Figure 4.** Schematic diagram showing 3OC12-HSL as quorum sensing (QS) molecule which when hydrolyzed by PON2 inhibits biofilm formation.

systemic coagulation and inflammation by regulating the activity of tissue factors by a redox-dependent mechanism (Ebert *et al.* 2018). In rats with hemorrhagic shock, it was found that under hypoxic and ischaemic conditions, PON2 regulates the expression of endothelial tissue-related genes such as plasma thrombomodulin transcription factors and endothelial tissue factor activating the mechanism of coagulation (Xu *et al.* 2020).

Oxidative stress is one of the main causes of atherosclerosis. Hydrolysis of peroxidized lipid is one of the important functions that may contribute to the cardio-protective nature of PON2 (Hagmann *et al.* 2014). An *in vivo* study demonstrated that PON2 prevents the oxidation of lipoprotein, thus enhancing the protective capacity of HDL and reducing the intracellular oxidative stress levels of macrophages (Chen *et al.* 2016). The RISK pathway, PI3K/Akt/GSK-3β (figure 3C), is cardioprotective against Ischemia-Reperfusion Injury (IRI), PON2 reportedly activates the pathway and therefore prevents mitochondrial dysfunction, and hence oxidative stress in cardiomyocytes (Sulaiman *et al.* 2019a, b). Apart from cholesterol, triglycerides are also independent risk factors for atherosclerosis, and diacylglycerol acyltransferase 1 (DGAT1) is a rate-limiting enzyme in the triglyceride biosynthetic pathway (Lundberg 1985; Farese *et al.* 2000). Rosenblat *et. al.* found that PON2 increases DGAT1 activity, and thus the rate of triglyceride formation. Therefore, one of the mechanisms of the protective role of PON2 in atherosclerosis may be attributed to its regulatory effect on DGAT1 activity which is sensitive to oxidative stress (Rosenblat *et al.* 2009). But in the case of pro-atherogenic infection, the anti-atherogenic activity of PON2 was attributed to its ability to destroy quorum sensing molecule which is due to the lactonase activity of the enzyme (Kim *et al.* 2011). The pro-atherogenic infection is contributed by quorum sensing molecules, such as N-(3-oxododecanoyl)-L-homoserine lactone (3OC12-HSL) of *Pseudomonas aeruginosa* (Turkay *et al.* 2004).

The role of PON2 was also pointed out in obesity. It was found that PON2 deficient mice had altered mitochondrial function in white adipose tissue which further prevented its conversion to brown adipose tissue, and hence contributed to diet-induced obesity (Shih *et al.* 2019). A comparative *in vivo* and *in vitro* study in type 2 diabetes patients showed a significant decrease in PON2 enzyme activity in monocyte/macrophage cells (Lixandru *et al.* 2017). It was correlated to abdominal obesity and insulin resistance (Qujeq *et al.* 2018). However, the underlying molecular mechanisms remain unrecognized.

## 5. PON2 and infectious diseases

Owing to the hydrolytic activity of PON2, it has a crucial role in infectious diseases and associated anomalies such as oxidative stress, inflammation, and changes in the serum proteins (Camps *et al.* 2017). Studies show that PON2-deficient mice are more prone to bacterial infections than wild-type mice (Stoltz *et al.* 2007). The role of PON2 in cutaneous defense against bacterial infections due to its high level of expression and activity in human keratinocytes is also reported (Simanski *et al.* 2012). Most gram-negative bacteria use lactones as quorum sensing (QS) molecules (Rutherford and Bassler 2012). Hydrolytic activity, mainly lactonase activity of PON2, is responsible for the control of QS in gram-negative bacteria such as *P. aeruginosa,* therefore offering an important defense mechanism against bacterial infections (figure 4) (Farid and Horii 2012). PON2 hydrolyzes and inactivates certain homoserine lactones (HSL), and therefore attenuates HSL mediated immune responses (Teiber *et al.* 2008; Devarajan *et al.* 2013). Thus, PON2 plays a pivotal role in regulating host cell responses to QS molecules by decreasing their availability for receptor-mediated effects such as calcium release and stress signaling (Horke *et al.* 2015). The quorum quenching ability of PON2 is also associated with lung pathophysiology of cystic fibrosis (CF) patients. $PPAR_{\gamma}$ is a mammalian anti-inflammatory transcription factor that is inhibited by 3OC12-HSL (Jahoor *et al.* 2008). Studies suggest that *P. aeruginosa* infected CF patients have reduced expression of $PPAR_{\gamma}$ and PON2 genes (Griffin *et al.* 2012). Therefore, PON2 has been found to play a crucial role in defense against infectious diseases.

Moreover, the role of PON2 in the case of innate immune response to viral infection is also elucidated. *In vitro* and *in vivo* studies have shown an increase in PON2 gene expression, protein levels, and activity in response to HIV-1 infection which may be attributed to dephosphorylation of Signal transducer and activator of transcription 5 (STAT5) (Yuan *et al.*, 2010).

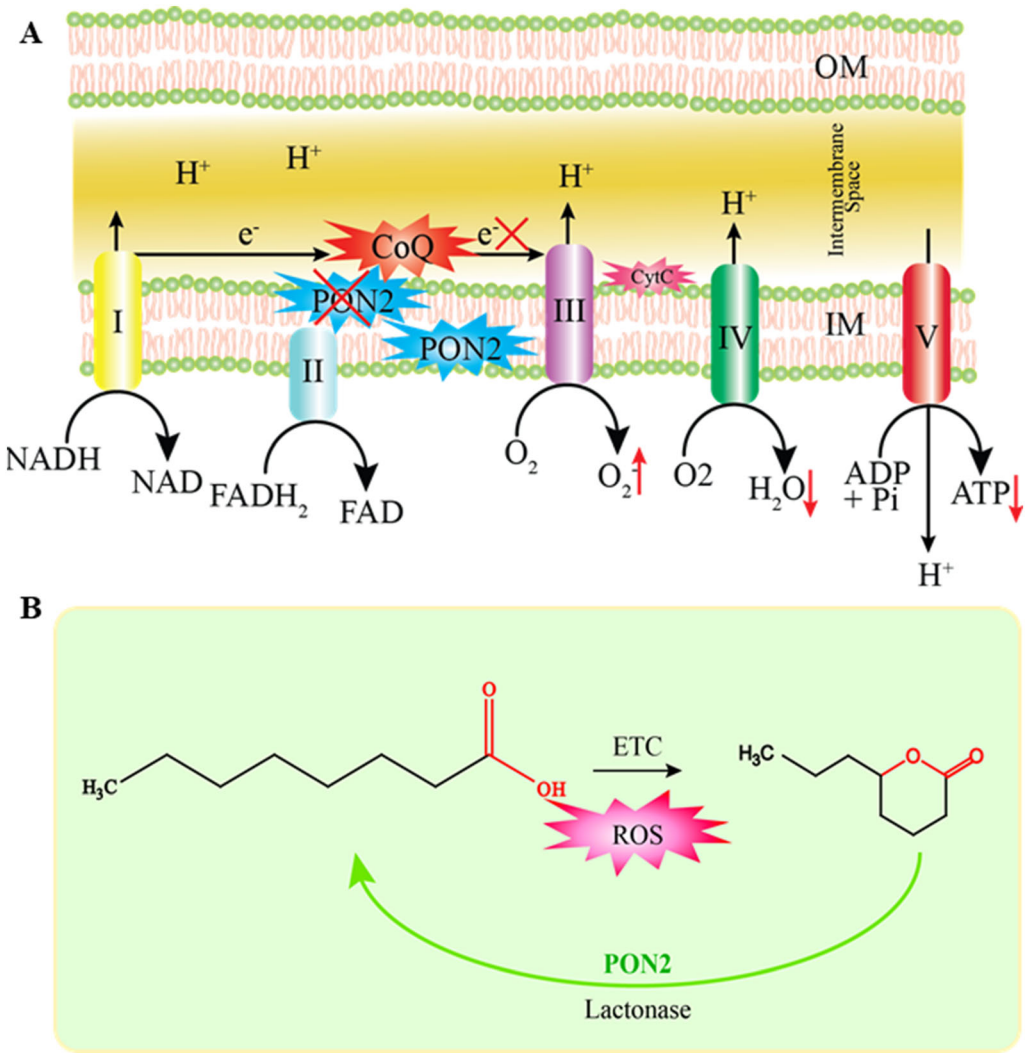


**Figure 5.** Function of PON2 in mitochondria. (**A**) Model diagram shows the presence of PON2 protein in the inner mitochondrial membrane. It's association with complex III and coenzyme Q suggests its major role in anti-oxidative function. (**B**) Flowchart showing the formation of lactone by ROS in the fatty acid chain of plasma membrane and its reversal back to normal by the lactonase activity of PON2.

## 6. Role of PON2 in neurodegenerative diseases

PON2 has been identified as a novel and major intracellular factor with an antagonizing role in oxidative stress in the central nervous system (Costa *et al.* 2014). It is an intracellular protein, localized on the inner mitochondrial membrane and bound to Coenzyme $Q_{10}$, a major site for the generation of ROS. PON2 sequesters unstable coenzyme Q during the Q cycle and prevents it from passing electrons to oxygen molecules instead of cytochrome C. Its absence or deficiency causes redox imbalance and reduced electron transport activity. It may thus contribute to mitochondrial dysfunction and various oxidative stress disorders (figure 5A) (Devarajan *et al.* 2011; Enriquez and Lenaz 2014).

Dopaminergic regions of the brain have the highest levels of PON2. There is also evidence that suggests the expression of PON2 is higher in astrocytes than in neurons (Giordano *et al.* 2011). In an experiment on the study of PON2 levels in the brain during development, the highest expression levels were detected in premature mice with a gradual decline in aged mice. The authors attributed significantly high levels of PON2 in early brain development to its role in protecting brain cells from oxidative stress during the developmental stages (Giordano *et al.* 2011; Hayashi *et al.* 2012). Garrick *et.al.* suggested that lower expression levels of PON2 during the developmental stages, in the brain of neonatal and young adult animals, make them more susceptible to neurological insult by oxidants (Garrick *et al.* 2016).

As higher PON2 levels are associated with increased resistance to oxidative stress-induced toxicity and neuroinflammation in brain cells, the possibility of modulating PON2 levels in neuronal cells may represent a much beneficial neuroprotective strategy (Costa *et al.* 2013). Reportedly, quercetin, a plant flavonoid, helps in mitigating ROS in $PON2^{+/+}$ mice better than in $PON2^{-/-}$ mice and thus has an ameliorating effect on Alzheimer's disease (AD) (Khan *et al.* 2020). Though, several hypotheses for the neuroprotective mechanism of quercetin have been put forward yet the exact mechanism is elusive. Either the quercetin induces a low level of oxidative stress and induces PON2 expression through JNK/AP-1 pathway or due to its phytoestrogen activity, PON2 expression is induced (Ruotolo *et al.* 2014; Costa *et al.* 2016).

The role of PON2 in Parkinson's disease (PD) was speculated recently. A study reports that DJ 1, a gene responsible for PD, interacts with PON2 and is neuroprotective in the PD model (Parsanejad *et al.* 2014). However, in the case of $MPP^+$ (1-methyl-4-phenylpyridinium) induced PD model, lovastatin has a neuroprotective function irrespective of PON2 (Aguirre-Vidal *et al.* 2015). Apparently, the overexpression of PON2 is cytoprotective, however, its implications can be different depending on the type of cells, for instance, PON2 overexpression is neuroprotective, however, in case of tumor cells the cytoprotective nature of PON2 may inhibit apoptosis and help in cancer progression.

## 7. PON2 polymorphism and its association with human pathophysiology

Two common polymorphisms of PON2 are found, Ala/Gly at position 148 and Ser/Cys at position 311 (Mochizuki *et al.* 1998). A few studies are present which demonstrate the relationships of these two PON2 polymorphisms with different pathophysiological conditions (table 3) (Shin 2009; Elnoamany *et al.* 2014). PON2 Ser311Cys polymorphism has been associated with cardiovascular disease (CVD) but there are still controversies regarding it. Some findings claim that Ser at 311 is more at risk of developing CVD, whereas Cys at 311 prevents premature development of CVD (Martinelli *et al.* 2004; Chen *et al.* 2016). On the other hand, few studies report that there is not much significant change between these two polymorphic forms (Sanghera *et al.* 1998). Therefore, more functional studies need to be carried out for PON2 Ser311Cys polymorphism and its relationship with CVD. More recently, it has been reported that polymorphism at Ser311Cys is responsible for interaction with another gene $PPAR_{\Upsilon}$, and polymorphic forms of both the gene can serve as biomarkers of risk for coronary heart disease (González-Castro *et al.* 2018).

**Table 3.** PON2 polymorphism and association with human pathophysiology

| PON2 Polymorphism | Pathophysiology | References |
|---|---|---|
| *Ala/Gly polymorphism at position 148* | | |
| Gly at position 148 | Diabetic nephropathy in type II diabetes | Calle *et al.* (2006) |
| | Risk of preterm delivery | Chen *et al.* (2004) |
| | Cataract | Baig *et al.* (2019) |
| *Ser/Cys polymorphism at position 311* | | |
| Cys at position 311 | Coronary heart disease | Robertson *et al.* (2003) |
| | Diabetic nephropathy in type II diabetes | Wang *et al.* (2013) |
| | Noise induced hearing loss | Fortunato *et al.* (2004) |
| | Risk of preterm delivery | Chen *et al.* (2004) |
| Ser at position 311 | Alzheimer's disease | Janka *et al.* (2002) |
| | Sporadic Amyotrophic Lateral Sclerosis | Slowik *et al.* (2006), Valdmanis *et al.* (2008) |
| | Coronary heart disease | Sanghera *et al.* (1998) |
| Gly 148 and Ser 311 | Cataract | Baig *et al.* (2019) |

PON2 Cys311Ser polymorphism is also linked with AD. PON2 311Ser along with another gene apoE4 allele helps in the development of AD and vascular dementia (Janka *et al.* 2002; Nie *et al.* 2017). The Cys allele of Cys311Ser polymorphism is associated with sporadic Amyotrophic Lateral Sclerosis (ALS) (Saeed *et al.* 2006; Slowik *et al.* 2006). Valdmanis *et. al.* conducted a study on French, Canadian and Swedish population, and found that Cys311Ser polymorphism in PON2 was relevant risk factor for the development of ALS irrespective of patients' nationality (Valdmanis *et al.* 2008). On the other hand Cys311Ser PON2 polymorphism was not associated with ALS in Italian population (Ricci *et al.* 2011).

Although PON1/3 are not expressed in the brain, polymorphisms in these are associated with

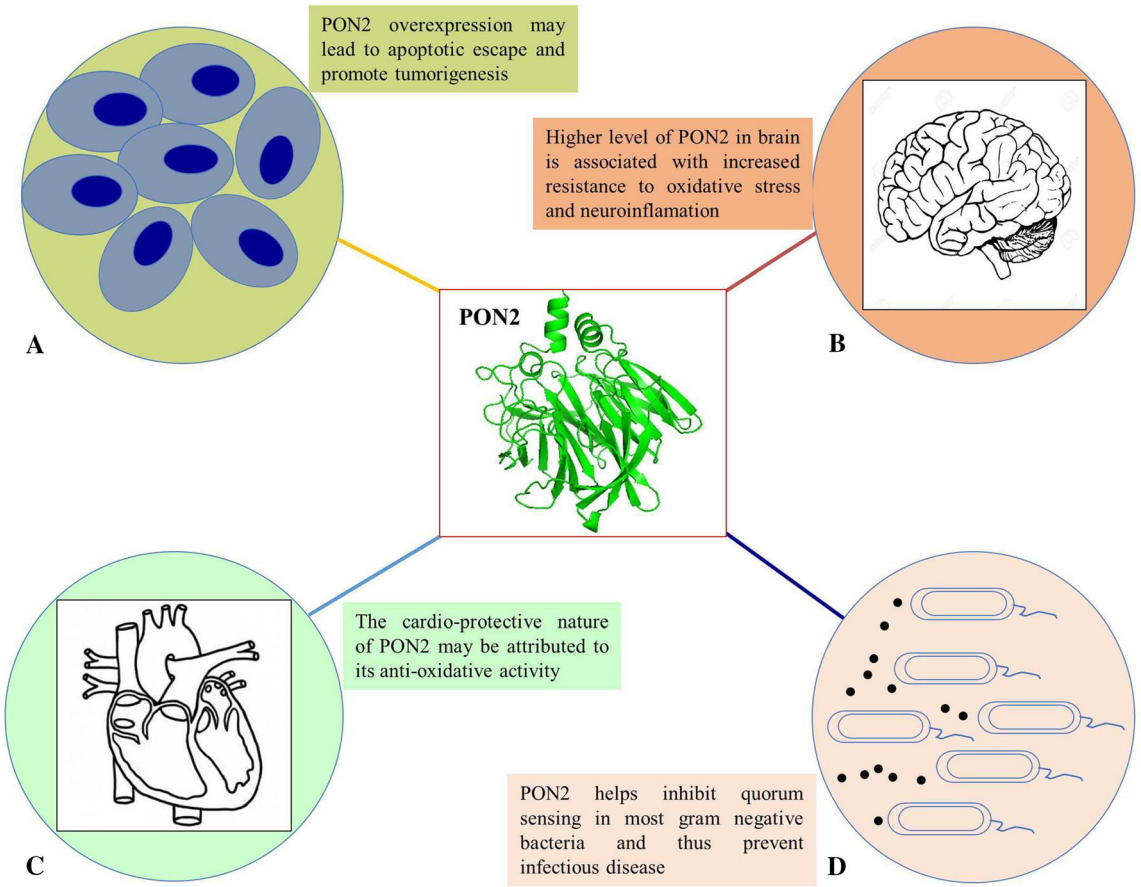


**Figure 6.** Multifaceted role of PON2. (**A**) PON2 overexpression is linked to cancer and cell survival, (**B**) positive modulation of PON2 in brain causing neuroprotection, (**C**) PON2 deficiency leads to mitochondrial dysfunction, leading to increase in mitochondrial oxidative stress, and (**D**) highly efficient lactonase activity of PON2 helps in quenching quorum sensing and thus controlling a vast majority of infectious diseases.

neurodegenerative conditions, possibly via regulatory aspects of lipid metabolism (apolipoproteins) (Reichert *et al.* 2021). Activity and expression level may be associated with PON polymorphism and neurodegeneration. All the PONs can hydrolyze oxidized form of lipids whereas PON1 has in addition organophosphatase activity (Levy *et al.* 2019). Gene to gene interaction with other polymorphisms across the PON gene family may also be responsible for their neuroprotective nature (Dardiotis *et al.* 2018). Moreover, ROS may cause the formation of lactone in the fatty acid chain of the plasma membrane. The lactonase activity of PON2 may help in mitigating this change (figure 5b) (Draganov *et al.* 2005; Hong *et al.* 2012).

Recently, the association of PON2 polymorphism has been demonstrated in the metabolism of acetylcholinesterase inhibiting drugs (AChEI) such as donepezil hydrochloride and pyridostigmine bromide. The polymorphic forms of PON2, Ala/Gly at position 148 and Ser/Cys at position 311, showed different arylesterase activity, and thus responded differently to these drugs. PON2 with Gly148 and Cys311 allele had increased arylesterase activity, and also the enzyme became more efficient in inhibiting the drug in these cases. The arylesterase activity of PON2 could be responsible for the hydrolysis of AChEI used against AD and thus attenuating the efficacy of these drugs (Parween *et al.* 2021).

## 8. Conclusions and future perspectives

PON2 has emerged as an important cellular antioxidant against oxidative stress, mainly due to its expression in several tissues and additionally mitochondrial localization. This lactonase enzyme has shown the potential of being an important biomarker as it plays a relevant role in determining susceptibility to oxidative stress and neuroinflammation. Its overexpression may provide a novel

strategy for neuroprotection, whereas in tumor cells a useful therapeutic strategy would be helpful in lowering the expression of PON2. A lower rate of occurrence of a wide variety of diseases such as Alzheimer's, Parkinson's, and CVD in females as compared to males suggests that attempts aimed at increasing the PON2 level of expression in males might be useful.

Deciphering the mechanism of PON2 upregulation will also provide useful insights into the pathophysiology of several diseases and thus a therapeutic lead due to its multifaceted role (figure 6). In general, the increase of PON2 activity was associated with gene transcription. The upregulation of PON2 might therefore occur through the stabilization of the PON2 protein or due to its overexpression through an increased translation rate. The kind of cellular signaling pathways that distinct phenolic compounds activate, and the structure and concentration of phenolic compounds themselves also determine the regulation of PON2 activity. Further, understanding the associations of PON2 polymorphism with pathophysiological conditions and drug metabolism would be advantageous for the development of future precision medicines. However, additional studies need to be performed to explain the mechanisms of action of these modulators in the regulation of gene expression and activity.

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