PREVENTIVE AGENT OF VITAMIN C AGAINST PB-INDUCED TOXICITY: A REVIEW

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ABSTRACT

Pb poisoning has a wide range of clinical effects on practically all tissues, with the, liver, brain and renals being the main targets because of the abundance of mitochondria in these tissues. One of the most powerful components of water-soluble vitamin C long. The current study has recommended that vitamin C may have an anticancer mechanism in addition to being an anti-inflammatory agent and potent antioxidant in the treatment of neurological disorder, cardiac disease, kidney, and liver disorders. It will also examine the preventive agent of vitamin C combat Pb-induced toxicity in both animals and humans. Pb-induced toxicity in different organ-systems results from increased oxidative stress through the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS).

KEYWORDS

Antioxidant, Pb-induced toxicity Vitamin C, Oxidative stress, (ROS) Anti-inflammatory

1. INTRODUCTION

Pb poisoning is a frequent concern to public health in developing nations because of human activities including mining and farming. Pb is a multi-organ toxin that damages both humans and animals' reproductive systems and causes numerous malignancies, neurological and renal damage, and reproductive abnormalities. It can eventually kill small children [1, 2]. In the treatment of heavy metal poisoning, the use of common medications like chelators has been shown to have a variety of side effects, ranging from mild to severe. These effects can comprise brain damage headache, fever, nausea, and, seizures, vomiting, anaemia, chronic kidney and low blood pressure, liver disease, and severe allergic reactions like anaphylactic shock. [1]

1.1. Ascorbic Acid (AA)

Vitamins are essential vitamins. Since the body cannot generate the majority of vitamins, it is essential to replenish them through diet. Vitamins are separated into two groups based on how efficiently they dissolve: water-soluble vitamins (C and B complexes) (A, D, E, K) fat-soluble vitamins. Howarth and Hirst created ascorbic acid (AA), widely known as vitamin C, for the first time in 1923 following the discovery of the substance by Nobel winner and Hungarian researcher Szent-Gyorgyi [4]. Since then, high dosages of ascorbic acid (AA), have been used to treat and prevent a variety of diseases and conditions, including cancer, atherosclerosis, diabetes, the common cold, macular degeneration, cataracts, glaucoma, stroke, and neurological disease. The antioxidant, spleen, liver kidney disease etc. Anemia, infections, scurvy, poor wound healing, muscle deterioration, bleeding gums, atherosclerotic plaques, and neurotic problems are all frequently linked to this vitamin's lack.

1.2. Dietary Sources of Ascorbic Acid (AA)

Green peppers, red and, tomatoes, strawberries, Citrus fruits, turnips, broccoli, leafy vegetables, and other Indian gooseberry are all sources of ascorbic acid (AA). Animal sources typically contain of vitamin C, which is a very low level. plants contain a large number of ascorbic acid (AA). —they are therefore crucial. [4, 5].

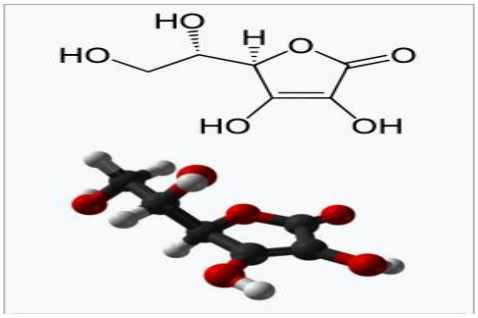

Figure:1 Structure of Vitamin C

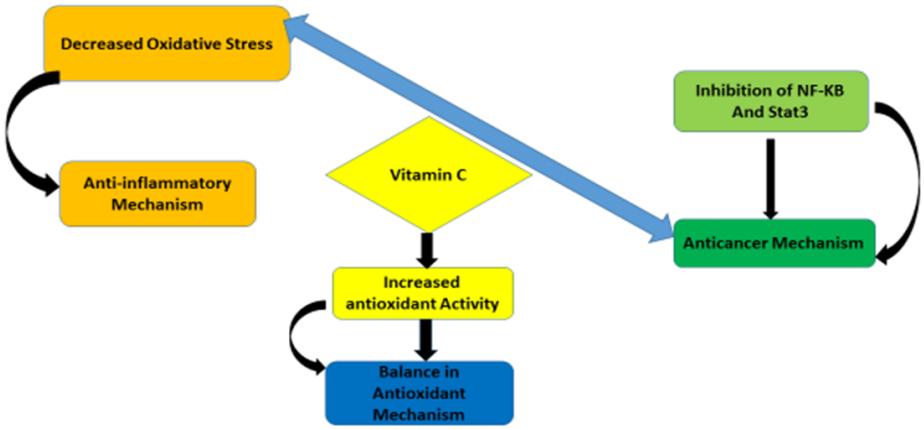

Figure 2. An illustration of the vitamin C's mode of action Vitamin C reduces oxidative stress, inflammation, and cancer by inhibiting NFkB and STAT. It also has anti-cancer properties.

Vitamin C is suitable for reversing the bio-markers and alterations brought on by Pb toxicity in numerous tissues due to induction of (OS) through generation of (ROS) and stimulation of inflammatory response [4,5]. Vitamin C has antioxidant properties and anti-inflammatory and with a wide range of Curative potentials both in vivo and in vitro [3]. The Preventive agent of vitamin C Combat Lead-induced toxicity in both humans and animals will be the main topic of this review.

1.3. Pb Toxicity Epidemiology

According to a WHO report, Pb poisoning is responsible for 600,000 cases of children disability and around 0.6 percent of all diseases that pose a threat to world health [6, 7]. According to the WHO and the US Centers for Disease Control and Prevention, increased blood lead levels are defined as those between 10-15 g/dL [8–11]. Additionally, socioeconomic status has a significant impact on mean blood Pb levels (BLLs) in younger children; nonetheless, non-Hispanic Black people are at a higher risk [10–12]. Pb exposure at work has a number of negative effects on health, including cancer and mortality. Pb can cause a variety of harmful health issues, including

hypertension, reproductive issues, and cognitive deficits in adults even at low concentrations [13,14]. Raised up (BLLs) among adults have significantly decreased, according to data from the Adults Blood Pb Epidemiology and Surveillance programme; however, occupational exposure to Pb, which affects about 94 percent of industrial workers, continues to be a public health concern [2]. Lead is a moldable, gray-blue heavy metal that is naturally occurring and found in conjunction with other elements in our environment. It has a relatively low melting point. Due to its widespread usage in the production of goods including cosmetics, batteries, paints, gasoline, water pipelines, tank connections, poetry glazing, and toys (Figure 1), it is regarded as the main environmental pollutant [7,15]. Additionally, Pb exposure in the environment, which can come from a variety of sources including food, water, air and other consumer products [10], can harm a number of biological systems. Pb particle exposure occurs mostly through ingestion and inhalation, while skin and prenatal exposure have been described in a small number of cases [10,16]. However, there are two (2) separate types of lead: organic Pb and inorganic Pb [16]. In the past, organic lead (tetraethyl and tetra methyl Pb) was made available as a fuel additive to raise the octane rating. This, when compared to inorganic lead, results in extremely high central nervous system toxicity [7]. Pb is found in environmental elements like soil and dust as well as consumer goods like paint and toys. Lead can have severe, irreversible health effects, including disorders of the hepatic, nervous, and renal systems [18, 19]. Additionally, these heavy metals are now much more concentrated in the environment as a result of human activities like farming and mining, the metals are mined manufacturing usage [16,20,21].

Lead Toxicity

Absorption of Pb

Although it is regarded as small and only accounts for 1% of the Pb absorbed in the body system, cutaneous absorption is a type of organic Pb absorption route [22]. According to Papa Nikolaou et al. [23], the sociodemographic profile of the exposed person is connected to the rate at which Pb is absorbed through the gastrointestinal tract. Additionally, because to their pica behaviour, youngsters absorbed almost 50% of Pb compared to adults who only absorbed 15%. (Figure 2). Pb, however, builds up in the blood, soft tissues, and bones when it is absorbed [1,24,25].

Pb distribution

With only 1% of the total Pb concentration in the blood and 99.9% of it in the erythrocytes, Pb concentration in the plasma is the most significant method of distributing Pb to target tissues such the brain, liver, kidney, bones, aorta, teeth and spleen [1,10,23,26]. Additionally, soluble phosphate, which contains more than 95% of the Pb deposited into the bones (Figure 2), and systemic blood flow are both necessary for Pb distribution to the entire body [7,12,27]. However, compared to children, who only account for about 70–73 percent of the total health burden, adults account for about 80–95 percent [12]. Additionally, Pb damages the cytochrome P450 enzymes in the liver, which affects the production of hormones and cholesterol 10. About 94 percent to 70 percent of Pb accumulates in the bones of adults and children, where it is firmly bonded and less toxic [25].

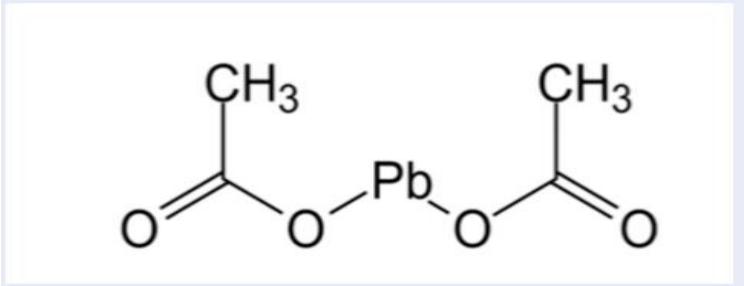

Figure 3. Chemical Structure of Pb Acetate

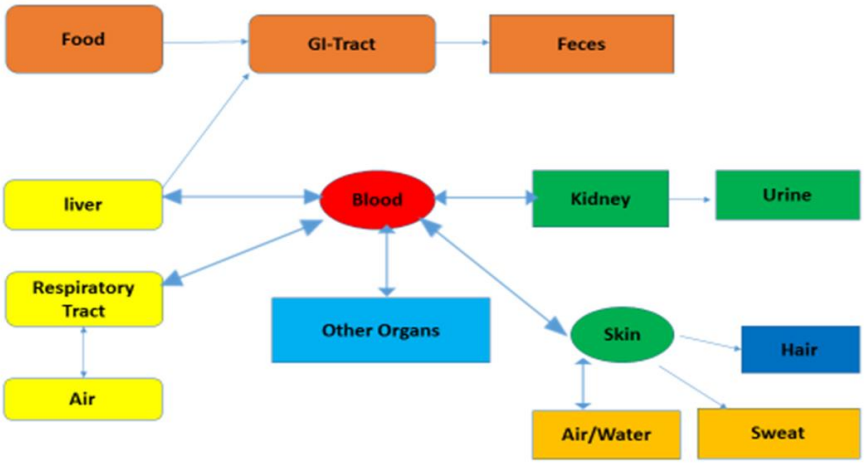

Figure 4. The body's absorption, distribution of lead through the plasma, and excretion of Pb are all factors in the pathophysiology of lead toxicity.

Signs of Pb Toxicity

headache, tiredness, discomfort abdominal, Muscle pain, vomiting, seizure, coma are among the signs of acute poisoning. Constant vomiting, encephalopathy, lethargy, delirium, convulsions, and coma are examples of clinical signs of chronic poisoning [1,7,9,28,29].

Oxidative Stress

The main toxic effects of Pb are elevated levels of (ROS) [1]. (ROS) are by-products of metabolic reactions in aerobic organisms. Under normal circumstances, antioxidant enzymes such, super oxide dismutase, glutathione, glutathione eperoxidase, and catalase (CAT) activity controls reactive oxygen species concentration [12]. However, excessive free radical formation under oxidative stress has detrimental consequences on cells, tissues, inflammatory reactions, and apoptosis [1,12,33,34]. The main effects of increased ROS production in the body system include neurodegenerative disorders like Alzheimer's and Parkinson's [36]. Two notable antioxidant enzymes that are crucial for ensuring lead elimination in the system are superoxide dismutase and catalase. However, the reduced CAT concentration in the serum and decreased SOD concentration lead to a reduction in the removal of superoxide radicals, which causes the impairment in superoxide radicals (O2) scavenging1. Along with specifically targeting sulfhydryl groups, Pb also has the capacity to substitute zinc ions, which are crucial in disabling the antioxidant defense mechanism [1,37]. Lead which destroys (RBCs) by preventing the

breakdown of delta-aminolevulinic acid and raising levels of the substrate alpha-linolenic acid in the blood and urine. [38].

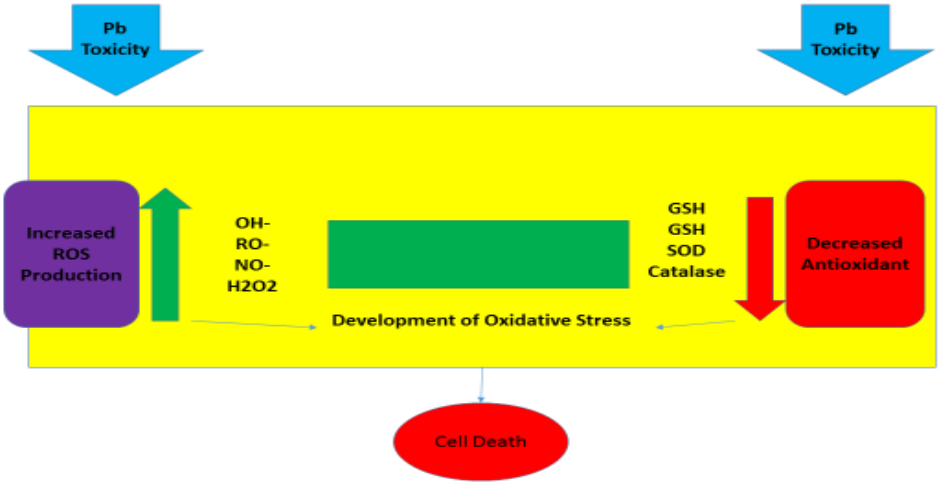

Figure 5. Pb exposure raises the production of ROS and lowers the levels of antioxidants, causing oxidative stress and subsequently apoptosis. This is a schematic representation of Pb-induced toxicity.

Toxic effects of Pb

Nervous System

Lead-induced neurotoxicity is caused by a variety of processes, including, impairment of neurotransmitter transmission, dysregulation of cell signaling altered membrane biophysics, and oxidative stress. Furthermore, the physicochemical composition and unique properties of the materials swallowed affect how quickly lead is absorbed through the digestive tract [12]. During brain development, Pb poisoning interferes with the interaction of glial cells, the trimming and pruning of synapses, and neuronal migration. This failure to properly connect the various brain structures leads to a permanent modification of brain physiology [15,41]. Pb poisoning is multi-systemic, highly toxic to the (CNS), and causes memory loss by inhibiting N-Methyl-D-aspartate receptors, which are necessary for brain development, flexibility, and storage. [30]. When blood Pb levels reach (BLLs)10 g/dL, brain edoema causes a dramatic rise in pressure, which causes irreversible brain damage and alteration that includes diminished visual-motor function, diminished attention, decreased social behaviour, and a deterioration in cognitive ability [30,41].

Kidney System

Ongoing exposure to Pb in the environment or at work may result in acute or chronic nephropathy, which has a number of negative health effects on the kidney, including impairment of the tubular transport mechanism (reabsorption and tubular absorption a), variations to the renal dysfunction, tubular epithelium, hyperuricemia and hypertension, renal failure [42]. In contrast, chelation therapy can reverse the consequences of acute Lead nephropathy in children who have aminoaciduria and proteinuria, while chronic Lead nephropathy develops over time as a result of persistent exposure and is irreversible [43-45].

Bones

After exposure, the human body still stores lead primarily in the bones [46]. By adhering to the cell membrane, altering the architectural makeup of proteins, and interfering with the body's interpretation of genes, it then exerts more harmful effects [18, 47].

Reproductive System

Reduced libido, infertility, abnormal spermatogenesis, variations in serum testosterone, miscarriage, premature delivery pre-eclampsia, abnormal prostatic function and premature membrane eruption in both females and males are just a few of the effects of Pb exposure on the reproductive system in both humans and animals [1].

Lead was found to diminish the number of primordial follicles in female mouse pups, distract preantral follicles, alter luteinizing hormone regulation, lower testosterone synthesis, and promote peritubular testicular fibrosis, according to earlier research [48,49].

Cardiovascular System

Pb exposure is linked to adverse heart clinical burdens such as stroke, peripheral arterial diseases (atherosclerosis and arteriosclerosis), and cardiovascular diseases, which have underlying cardiac dysfunction and abnormalities such as changes in cardiac rhythmicity and left ventricular hypertrophy [49].

Hematological Parameters

Blood Pb makes up just 1–5% of the overall body load, but at lower concentrations, it binds to stored blood cells with an estimated 1% of the blood Pb present in the plasma in an ionized form. At greater quantities, Pb binding sites in the (RBCs) may become saturated, which would increase the amount of lead in the plasma [47]. Additionally, Pb toxicity prevents heme synthesis by hindering the activities of aminolevulinic acid synthatase (AL AS), ferrochelatase, amino levulinic acid and other mitochondrial enzymes, which shorten the lifespan of circulating red blood cells due to persistent membrane instability and contribute to Pb anaemia [1,51].

Spleen

According to the research of Ekanem et al., [18], Pb-induced poisoning in albino rats treated with varying concentrations of Pb acetate resulted in lymphoid follicle hyperplasia inside the white pulp with congested blood vessels and modification in haematological profiles within the spleen. Infiltration of macrophages and lymphocytes, vacuolation of the cytoplasm, erythrocyte stasis, enlarged mitochondria with loss of cristae in lymphoid cells, and spleen cell degeneration were all seen in the studies of Türkay et al., [51].

Literature Review

Previous studies have demonstrated that Bacopa monnieri is utilized to treat a variety of disorders, including diabetes, cancer, neurological diseases, and cardiovascular diseases. [73]

The toxicities of lead are outlined in this review, along with potential advantages of ascorbic acid supplementation in relation to lead poisoning. [74]

Pb exposure in children, followed by evidence from human and animal research demonstrating the effectiveness of ascorbic acid as an additional vitamin to treat Pb poisoning, with a focus on the neurotoxic effects of developing Pb. [75]

exposure to lead, pertinent biomarkers, and the mechanisms behind lead poisoning. Additionally, it informs readers on recent developments in chelation therapy and more recent therapeutic approaches, such as nanoencapsulation, for the treatment of lead-induced toxic symptoms. [76]
The results show that combining VC and VB1 can reduce the harm lead-induced oxidative stress causes to liver cells, although the antioxidant effects rely on their amounts. [77]

The findings indicated that lead-induced metabolic changes may be corrected by co-administering zinc and ascorbic acid. [78]
In this investigation, the potential neuroprotective effects of curcumin and L-ascorbic acid alone or in combination against Pb-induced neurotoxicity will be assessed. Through its antioxidant and antiapoptotic actions, the combo regimen produced outstanding results in preventing lead ac-induced neurotoxicity. [79]

By reducing Pb in the brain and blood circulation and preventing oxidative and inflammatory stress, BVJ has a strong protective effect against brain poisoning. A synergistic impact between the use of BVJ and DMSA in treatment reduced the neurotoxicity brought on by Pb. Additionally, the BVJ's anti-inflammatory and antioxidant properties enhance DMSA therapy. [80]

These results suggest an increased ROS-mediated inactivation and sequestration of NO, which may be associated with hypertension, lipid peroxidation, a decline in antioxidant state, and oxidative DNA damage. the Preventive effects of Vitamin C on these parameters. [81]

Lead (Pb) is a neurotoxic with a variation of well-known effects on the (CNS). Memory has been shown to benefit greatly from vitamin C in prior studies. The goal of the current investigation was to determine how well vitamin C protected against lead-induced amnesia. Administering vitamin C to rats prevents lead from impairing their ability to learn and remember spatial relationships. [82]

RESULT AND DISCUSSION

Antioxidant Mechanism of Ascorbic Acid

As an antioxidant, ascorbic acid prevents oxidative stress-related cellular damage by scavenging reactive oxygen species, neutralizing lipid hydroperoxyl radicals in dependence on vitamin E, and shielding proteins from electrophilic lipid peroxidation products that can cause alkylation. [52]

Vitamin C, is an organic chemical that occurs naturally and has antioxidant characteristics. It may be found in both plants and animals. It serves as a redox buffer that can lower reactive oxygen species and so neutralize them. Future research on the antioxidant effects of vitamin C should ideally focus on certain patient populations. [53]

In addition to acting as a powerful, effective, and affordable antioxidant, vitamin C can also operate as a radical promoter. To further understand the multiple functions of vitamin C, more research is required. [54]

The information presented in this review demonstrates the significance of ascorbic acid as a part of the overall antioxidant defense systems present in cells and tissues. The information is reliable and provides strong support for further research into the role of ascorbic acid antioxidant properties in preserving human health. [55]

Vitamin C and Its Curative Potential Mechanism

Humans with vitamin C deficiencies have poor collagen production, which contributes to the more serious scurvy symptoms. By contributing electrons to numerous enzymatic and non-enzymatic activities, vitamin C serves as an antioxidant (a reducing agent) in addition to its other biochemical functions. By doing this, vitamin C is transformed into an oxidized form, such as dehydroascorbic acid or semi-dehydroascorbic acid. Ascorbate peroxidase uses vitamin C as a substrate in plants. [56, 57]

Nervous System

Vitamin C's ability to bind redox-active metal ions, such as Magnese 2+, Copper 2+, Cadmium 2+, Lead 2+, and Mercury 2+ to produce a tight and active complex of antioxidant with its anti-inflammatory properties, which are reduced swelling in brain cells inside the body what gives it its neuroprotective properties against neurodegenerative disorders of the brain [58].

This review is to update knowledge on the effects of vitamin C on psychiatric disorders like depression, anxiety, and schizophrenia as well as neurodegenerative diseases like, Parkinson's disease, Huntington's disease, Alzheimer's disease and multiple sclerosis, and amyotrophic lateral sclerosis. The ascorbic acid's potential therapeutic effects on the illnesses listed has received considerable interest. [59]

as stated in 2020 [60] by Baty et al. Together, these results may imply that LUT may be helpful for reducing the, neuroinflammation, oxidative damage and cortical cell death brought on by Pb-induced neuronal damage.

According to Singh et al 2017.’s study, treatment of Pb and omega-3 fatty acids dramatically reduced lead's ability to cause histological changes in the brain region and oxidative stress . This might be as a result of its powerful antioxidant capacity and metal-binding ability. [61]

The goal of the study protective effects of mangiferin on neurological damage brought on by lead (Pb) through the activation of Nrf2-governed enzymes, proteins and genes. [62].

Kidney disease

kidney disease is characterized by a steady decline in renal function, which lowers (GFR), abnormalities in urine composition, such as Red blood cells and proteins, and accumulation of uremic toxins as a consequence of the renals diminished capacity to excrete soluble waste [65].

Renal arterial reactivity and kidney function are protected from IRI by Ascorbic acid. In renal ischemia injury, the protective effects of vitamin C are related to levels of Reactive oxygen species, super oxide dismutase, glutathione, and NO.[64]

Further confirmation of these findings was obtained in primary renal mesangial cells. Overall, our research showed that GAS controlled antioxidant systems and the Nrf2 signalling pathway to reduce Pb-induced kidney oxidative stress and inflammation. [63]

It is safe to say that EA offers a considerable amount of defence against lead-induced nephrotoxicity. [66]

Finally, we talked about how vitamin C might help COVID-19 individuals who already have kidney problems by protecting their renal functions. [84]

Anticancer Mechanism

The inhibition of nuclear factor (NF)-kB and signal transducer and activator of transcription3 (STAT3) pathway signals, which are important for cancer development and proliferation by resisting and inhibiting chemotherapy-induced apoptosis in a variety of cancer cells, has been shown in in vitro and in vivo studies to be a key component of vitamin C's anticancer mechanism [67,68,].In this review, we examine the current knowledge regarding vitamin C's impact on cancer cells both in vivo and in vitro. We relate this knowledge to the ability of cancer cells to absorb, metabolize, and compartmentalize this nutrient, with implications for vitamin C's potential therapeutic role in cancer. [69]

According to these findings, intracellular vitamin C can affect inflammatory, malignant, and apoptotic processes by preventing NF-B activation. [70]
Vitamin C treatment of cells resulted in a rapid and sustained activation of p38, and because the specific p38 inhibitor SB203580 reversed the inhibitory effect of vitamin C on IKK activity, I-kappa B alpha phosphorylation, and NF-kappa B activation, it has been determined that TNF-driven IKK activation was inhibited by p38 mitogen-activated protein kinase. The findings show that the intracellular target for high dosage vitamin C is p38. [71]

Cardiovascular System

The significance of Ascorbic acid in cardiovascular problems, such as heart disease, heart failure, cerebrovascular diseases, hypertension, is examined in this review along with clinical and preclinical investigations. Research pitfalls and scepticism surrounding vitamin C with cardiovascular diseases are also covered. [72].

Observational studies and basic research indicate that taking vitamin E or C may lower your chance of developing cardiovascular disease. [85]

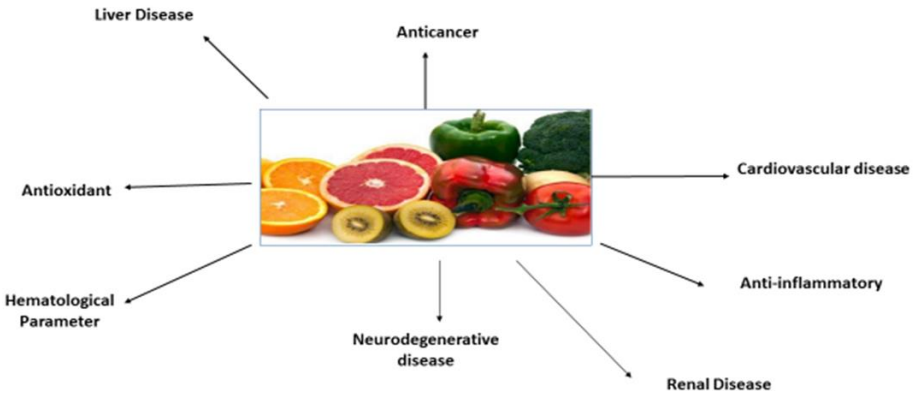

Figure 6. Curative Potential Vitamin C on different organs system

CONCLUSIONS AND FUTURE PERSPECTIVES

Lead toxicity can have catastrophic, irreversible effects on one's health, including damage to the neurological, hematological, cardiovascular, and renal systems. Lead toxicity also causes an increase in oxidative stress and causes molecular, cellular, and intracellular changes in living things. Vitamin C could be employed as a preventative agent against Pb-induced toxicity in light of several documented discoveries on the therapeutic applications and effects of vitamin C on various organ-systems based on its antioxidant, and anti-inflammatory mechanism of actions, anticancer.

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