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5-Fluorouracil-induced cardiotoxicity: An updated brief review

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Abstract
5-Fluorouracil (5-FU) is a widely used chemotherapeutic agent in the treatment of various solid tumors. Several potential pathways have been proposed, including endothelial dysfunction, oxidative stress, mitochondrial damage and disturbances in calcium homeostasis. Additionally, 5-FU may lead to coronary artery spasms, inflammation and direct cardiomyocyte toxicity. These mechanisms often act synergistically, exacerbating the overall cardiotoxic effect. This review article aims to provide a comprehensive overview of the mechanisms underlying 5-FU-induced cardiotoxicity, risk factors associated with its occurrence and the current strategies for prevention and management.

Keywords: 5-Fluouracil, carditoxicity, protein kinase-C

Introduction
Cancer remains a significant global health burden, affecting millions of lives every year (Ricevuto *et al*., 2010) [52]. Among the numerous treatment modalities available, chemotherapy continues to play a pivotal role in cancer management (Jain *et al*., 2019) [24]. One such chemotherapeutic agent, 5-Fluorouracil (5-FU), has been a cornerstone in cancer treatment for several decades (Nair *et al*., 2011) [44]. Charles Heidelberger first synthesized in 1950s and subsequent development as anticancer agent revolutionized cancer treatment along with combining with other drugs to improve therapeutic outcomes (Heidelberger *et al*., 1957) [21]. It is second most commonly used drug and third most associated with toxicities. It is a fluoropyrimidine antimetabolite, heterocyclic aromatic organic chemical, that structure similar with DNA and RNA, interferes with DNA and RNA synthesis in rapidly dividing cancer cells, ultimately leading to their destruction (Lamberti *et al*., 2012) [29]. Its remarkable efficacy has made it a critical component in the treatment of various solid tumors, including colorectal, breast, pancreatic, and stomach cancers (Mallet-Martino *et al*., 2002; Ali, 2012) [34, 2].
However, along with its potent antitumor effects, 5-FU administration can also give rise to a diverse array of adverse effects, encompass a wide range of symptoms affecting multiple organ systems and are a significant concern in cancer therapy (Gelen *et al*., 2021) [17]. The balance between achieving the desired antitumor response and managing the side effects associated with 5-FU treatment is a constant challenge for oncologists and researchers alike (Famurewa *et al*., 2019) [15].
Understanding the complexities of 5-FU-induced toxicity is vital to optimize cancer treatment regimens, enhance patient outcomes and improve the overall quality of life for individuals undergoing chemotherapy. This comprehensive review aims to shed light on the multifaceted aspects of 5-FU-induced toxicity, providing a deep exploration of its mechanisms, clinical manifestations, risk factors and potential mitigation strategies.

Pharmacokinetics of 5-FU
Soon after administration, 5-FU is distributed throughout body including cerebrospinal fluid, blood brain barrier and malignant effusions. Volume of distribution (V_d) ranges from 0.1 to 0.4 L/k and half-life (T1/2) is 10-20 minutes. Approximately 90 per cent of administered drug dose catabolizes by dihydropyrimidine dehydrogenase (DPD) mainly in the liver followed by peripheral blood mononuclear cells (MNC), intestinal mucosa, pancreas, lungs and kidneys and results in the degradation products of carbon dioxide (CO_2), urea, alpha-fluoro-beta-alanine (FBAL) and ammonia which are inactive products (Ali, 2012) [2].

10% of the medicine is excreted in the urine in its unaltered form in 6 hours, while 60% to 90% of given 5-FU is eliminated in the urine as FBAL in 24 hours (Saif *et al*., 2009) [53]. The rate-limiting step of the catabolic process is the conversion of 5-FU to the inactive metabolite dihydrofluorouracil (DHFU) by the DPD in the liver. Renal clearance is less than 20 per cent (Miura *et al*., 2010 and Alvarez *et al*., 2012) [37, 3]. Deficiency of DPD gene is responsible for potentially life-threatening toxicities when fluoropyrimidines are administered (Papanastasopoulos and Stebbing, 2014) [68].

Physical and chemical properties of 5-Flurouracil (https://pubchem.ncbi.nlm.nih.gov/compound/5-Fluorouracil)

Class	Antineoplastic antipyrimidine drug
Proper name	5-FLUROURACIL (5-FU)
IUPAC	2,4-Dihydroxy-5-flouropyrimidine, 5-Flouro 2,4(1H,3H)-pyrimidinedione, 5-Flourouracil, Fluorouracil, 5-Fluoracil
Molecular formula	$C_4H_3FN_2O_2$
Molecular weight	130.08 g/mol
Trade names	Chemoflura, Florac, Fivoflu
Physical state	White to almost white, almost odourless, crystalline powder
P^H	8.6 - 9.4
Solubility	Sparingly soluble in water, slightly soluble in alcohol, almost insoluble in chloroform and ether.
Storage and stability/Shelf life	Store between 15 and 30 °C. Protect from light. Do not freeze.
Composition	Fluorouracil Injection USP (50 mg/mL) is a sterile solution without preservative.
Decomposition	282 ºC.
Melting point	540 ºC.

Mechanism of action of 5-FU

5-FU rapidly enters into the cell through a facilitated transport mechanism as uracil (Diasio and Harris, 1989) [69]. It is metabolized to several active metabolites by DPD: 5-Fluro deoxyuridine monophosphate (5-FdUMP), 5-Flurodeoxyuridine triphosphate (5-FdUTP) and 5-Flurouridine thymidine monophosphate (5-FUTP)-these active metabolites disrupt the action of TS, RNA and DNA synthesis (Longley *et al*., 2003 and Miura *et al*., 2010) [31, 37].

The binding sites are as follows

Thymidylate synthase inhibition 2. Incorporation into RNA and DNA

Thymidylate synthase (TS) inhibition

TP (Tymidine phosphorylase) transforms 5-FU to 5-fluorodeoxyuridine (5-FdUrd) followed by Thymidine kinase (TK) into 5-FdUMP which binds to TS. When 5-FdUMP binds to TS, it forms a stable ternary complex with TS and methylenetetrahydrofolate (CH_2THF) and blocks the normal substrate dUMP and limits dTMP formation which leads to deoxynucleotide pool imbalance which results in disruption of DNA synthesis and repair (Yoshioka *et al*., 1987) [64].

Incorporation of 5-FU into RNA and DNA

5-FU is transformed to fluorouridine by uridine phosphorylase (UP), then to 5-FUMP by uridine kinase (UK). 5-FUMP enter a variety of metabolic pathways, including RNA and DNA synthesis by reducing diphosphate nucleotide to the deoxynucleotide level by ribonucleoside diphosphate reductase resulting in the production of 5-FdUMP. The messenger Ribonucleotide (mRNA) polymerase can also incorporate fluorouridine triphosphate (FUTP) into RNA in place of uridine triphosphate (UTP), producing a false RNA and interfering with RNA processing, leading to blockage of mRNA translation and inhibits RNA and protein synthesis. Direct insertion of FdUMP and FdUTP into DNA and inhibits DNA synthesis and induces single and double strand breaks, leading to DNA fragmentation and cell death (Longley *et al*., 2003; Nagasaki *et al*., 2010 and Miura *et al*., 2010) [31, 37] (Figure.1).

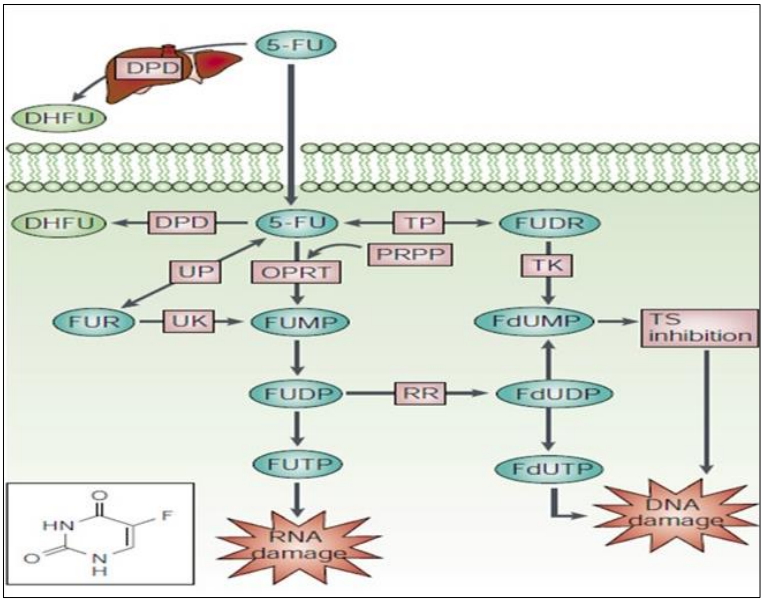

Fig 1: Mechanism of action of 5-FU (Source: Longley *et al*., 2003) [31]

Incidence and risk factors of cardiotoxicity

The incidence of 5-FU-associated cardiotoxicity, which can range up to 35% depending on the dose, dosing schedule, cardiac comorbidity, and patient sensitivity, was initially described by Roth *et al*. (1975) [70]. The incidence of cardiotoxicity in patients receiving anthracyclins ranges from 0.9 to 2.6%, Taxane ranges from 2.3 to 8%, Cyclophasphamide ranges from 7 to 28%, Trastuzumb ranges from 3 to 7% and 5-FU induced cardiotoxicity varies between 0-35% and may depend on cumulative dose, age and schedule of chemotherapy (Polk *et al*., 2013 and Kosmas *et al*., 2008) [47, 5].

Risk factors

Older age, taking other cardiotoxic drugs concurrently, having a history of heart illness, and having cardiovascular risk factors like hypertension, hyperlipidemia, and smoking are all suggested risk factors for fluoropyrimidine cardiotoxicity. (Polk *et al*., 2014 and Lambert *et al*., 2014) [47, 30].

Clinical manifestation

Fluoropyrimidine cardiotoxicity has been described in previous literature with a variety of clinical manifestations, including chest discomfort, MI, ventricilllar fribrillation, QT prolongation, cardiogenic shock and cardiac arrest (Herman *et al*., 2020) [71]. Other reported side effects include hypertension, ventricular and supraventricular tachycardia, hypotension, cardiomyopathy, pericarditis, sinoatrial dysfunction (Polk *et al*., 2014 and Moseri *et al*., 1993) [47, 40].

Effect of 5-FU on organ toxicities

Here are some of the common toxicities associated with 5-FU:

Gastrointestinal Toxicity: Gastrointestinal side effects are common toxicities associated with 5-FU. Patients may experience nausea, vomiting, diarrhea, abdominal pain and mucositis (De forni *et al*., 1992) [13].

Myelosuppression: It results in reduced production of blood cells. 5-FU can cause a neutropenia, anemia, and thrombocytopenia (Kanduri *et al*., 2019) [26].

Hand-Foot Syndrome: Also known as palmar-plantar erythrodysesthesia, this condition causes redness, pain on the palms of the hands, the soles of the feet and blisters. In severe cases it causes peeling of the skin can occur, affecting a patient's ability to perform daily activities.

Neurotoxicity: Some patients may experience neurotoxic effects, such as peripheral neuropathy, which is characterized by numbness, tingling, or weakness in the extremities. Neurotoxicity can impact a patient's quality of life and daily functioning (Kandhuri *et al*., 2019) [72].

Cardiotoxicity: As mentioned in the review, 5-FU can cause diversified side effects on the cardiovascular system, like chest pain, arrhythmias and in rare cases, heart failure (Sara *et al*., 2014) [73].

Dermatological Toxicity: Skin reactions, including rash, itching and increased sensitivity to sunlight (photosensitivity), can occur during 5-FU treatment (Gelen *et al*., 2021) [17].

Hepatotoxicity: 5-FU can affect liver function, leading to elevated liver enzyme levels and liver damage in some cases (Ali, 2012) [2].

Ocular Toxicity: 5-FU can cause eye-related side effects, such as conjunctivitis and tear duct inflammation (Kandhuri *et al*., 2019) [72].

Effects Of 5-FU on Various Biological Systems-Mechanism of Action

5-FU induced oxidative stress-generation of free radicals

Oxidative stress is characterised by an excess of reactive oxygen species (ROS), which are eliminated by the cellular antioxidant defence system, which includes the enzymes catalase (CAT), glutathione peroxidase and superoxide dismutase (SOD). O^{2-} is dismutated to hydrogen peroxide (H_2O_2) by SOD and H_2O_2 is removed by CAT or GPx by transforming into water, thus reduces free radical mediated cell damage (Rashid *et al*., 2013) [50].

The most important antioxidant found in mammalian cells is glutathione (GSH) which is a sign of oxidative stress. GSH is a tripeptide with sulfhydryl groups, a cellular non-enzymatic biomolecule, has antioxidant action directly by reacting with O^{2-}, peroxy radicals, oxygen radicals and forms oxidized Glutathione disulphide (GSSG) by using nicotinamide adenine dinucleotide phosphate (NADPH) and other disulfides (Eskandari *et al*., 2014) [14].

Muhammad *et al*. (2020) [41] studied molecular mechanism of ROS production induced by 5-FU in Wistar rats and observed there is increased release of endothelin-1(ET) through protein kinase-C and binding to NADPH enzyme (NOX-1 and 4) via stimulation of various kinases signaling pathway. Among Rho-kinase and NF-κB signaling pathway play an important role and it stimulate through Mitogen-activated protein kinases/Extra regulated kinases (MAPK/ERK1/2) dependent pathway (Vanhoutte *et al*., 2009) [62]. NF-κB decrease endothelial nitric oxide synthase (eNOS) production and synthesis and cause inactivation of nitric oxide (NO) by reacting with O^{2-} to form potent peroxynitrite ($ONOO^-$) which is very strong responsible for release of free radicals.

Oxidant in 5-FU cardio and pulomonary toxicity. 5-FU also binds to cyclooxygenase enzyme-2 (COX-2) and enhance thromboxane A2 which leads to vasoconstriction. Aforesaid pathway is responsible for 5-FU induced inflammation, oxidative stress and apoptosis (Mohammed *et al*., 2017) [39] (Figure. 2).

Badawoud *et al*. (2017) [6] reported that 5-FU cause an increases inducible NOS (iNOS) levels. Whenever upregulation of iNOS levels leads to down regulation of eNOS to maintain physiological functions and increased iNOS rapidly reacts with O^{2-} to form $ONOO^-$ radical's results in oxidative stress (Schwartz *et al*., 1997 and Famurewa *et al*., 2019) [56, 15].

At the genetic level, oxidative stress can activate nuclear factor erythroid factor (Nrf_2) via conformational modification of its suppressor Kelch-like ECH-associated protein 1(KEAP1) and results in translocation of Nrf_2 from cytosol to nucleus and cause mobilization of MAPK, PKC and phosphatidylinositol 3 kinase (PI3K) to produce ROS production in various organs due to 5-FU induced toxicity (Al-Asmari *et al*., 2016) [1] (Figure. 2).

Lipid peroxidation

In general, ROS production attack polyunsaturated fatty acids

which is present in membranes and forms the peroxyl radicals and causes in change in strucuture of nucleic acids, lipid and protein. Further, these radical attack adjacent fatty acids of membranes, causing LPO as a chain reaction (Priscilla and Prince, 2009) [48] and forms necrosis in heart and various organs (Rajadurai and Prince, 2006) [49].

5-FU also forms $ONOO^-$ which attack lipid membranes results in LPO, DNA damage and increased the release of pro-inflammatory cytokines (Muhammed *et al*., 2017) [74]. It up-regulates the expression of COX-2, which leads to elevated concentrate levels of prostaglandins (PG), platelet aggregation and fibrogenesis in various organs (Arab *et al*., 2018) [4].

Activation of Nuclear factor kappa Beta (NF-κB)

5-FU binds with NOX-subunit enzyme through activation MAPKS and NF-κB signal pathway and catalyze free radicals such as O^{2-} and myeloperoxidase. The primary regulator of inflammation, NF-κB is typically kept in an inactive state by the Kappa B inhibitory protein (Ik-B) in the cytoplasm. Under any stimuli like ROS, elevated FA levels are responsible for phosphorylation of Ik-B and NF-κB signaling pathway activates and results in translocation of NF-κB into the nucleus and subsequent liberation of the active heterodimer (p50 and p65 subunits) and express various target genes including pro-inflammatory cytokines (Chang *et al*., 2012) [10] (Figure. 4).

Apoptosis

Arab *et al*. (2018) [4] stated that an upstream rise in the apoptotic pathways is the MAPKs superfamily which involves ERK, c-Jun N-terminal kinases (JNK) and p38 kinases in 5-FU induced toxicity. Phosphorylation of p38 MAPK and JNK occurs in response to pro-inflammatory cytokines e.g., TNF-α and other cellular stresses such as ROS (Ma *et al*., 2009) [33] and induce pro-apototic Bax expression while inhibiting anti-apoptotic B-cell lymphoma-2 (Bcl-2) expression, thus resulting in activation apoptotic pathway (Muhammad *et al*., 2020) [41] (Figure. 4).

Pathophysiology of cardiotoxicity

Cardio toxicity are the chemicals that are responsible for causing disturbances in function and rhythm of the heart. Several mechanisms have been proposed for 5-FU related cardiotoxicity, some of which are interrelated such as coronary artery vasoconstriction, myocardial toxicity causing necrosis, direct drug or drug metabolite-mediated toxic action on myocytes, direct effect on vascular endothelial dysfunction, hypercoagulable status leading to thrombosis (yuan *et al*., 2019) [66] and accumulation of metabolites (Sorrentino *et al*., 2012) [58], generation of reactive oxygen species (ROS) elevation of serum enzymes lactate dehydrogenase, C-reactive protein, creatine myoglobin protein, decrease in glutathione and elevation of cardiac biomarkers like cardiac troponin (Sara *et al*., 2018) [53], hemorrhagic infarction, myocardial inflammatory reaction with interstitial fibrosis, arterial endothelial injury followed by thrombosis (Bertolini *et al*., 2001) [75].

According to a different idea, the 5-FU formulation contains cardiotoxic impurities called fluoroacetaldehyde and fluoroacetate, which can both be produced when fluorouracil is stored in an alkaline solution (Arellano *et al*., 1998) [76].

Endothelial dysfunction and hypercoagulability

Usually, intact vascular endothelial cells generate and release a wide variety of vasoactive chemicals and that control the coagulation process by expressing various pro and anticoagulant substances (Nimmrich *et al*., 1981) [46]. Many in-vivo studies discussed the effect of 5-FU on vascular endothelial cells in a dose-dependent manner and showed direct endothelial dysfunction. Damage to the endothelium causes tissue factors to be exposed, initiate platelet aggregation, the release of Von Willibrand factor (VWF), an increase in Fibrinopeptide A (FpA) and a reduction in protein C which all make the endothelium more vulnerable to thrombus formation (Jensen and Sorensen, 2012 and Yuan *et al*., 2019) [25, 66] which represents first stage of atherosclerosis formation in 5-FU toxicity (Bonetti *et al*., 2003) [9] (Figure. 3).

The rate of synthesis of the active metabolites that cause 5-FU cytotoxicity is determined by TP which is expressed in both cancer cells and endothelial cells (Schuller *et al*., 2000) [55]. 5-FU produces TP in endothelial cells sustains its own activation, by making endothelial cells more sensitive to 5-FU leading to atherosclerosis and increased vascular damage (Focacceti *et al*., 2015) [16].

Cwikiel *et al*. (1995) [11] evaluated the immediate impact on the vascular endothelium and noted On both a gross and electron microscopic level, fibrin accumulation reveals substantial damage to the intima layer, which is followed by the production of thrombi, and in subsequent investigations analysing the late effects of 5-FU on this structure. The toxic effect of 5-FU on the vascular endothelium was also supported by the results from an *in vitro* study (Cwikiel *et al*., 1996) [12] indicating the special susceptibility of benign endothelial cells to 5-FU. More severe endothelial injury with an increased thrombus formation was found 1, 3, 7, 14 and 30 days after treatment.

According to Cwikiel *et al*.'s (1996) [12] study comparing the side effects of 5-FU and methotrexate on arterial endothelial cells, 5-FU administration was associated with a higher incidence of endothelial damage and subsequent thrombus formation.

Kuzzel *et al*. (1995) [11] also observed increase in fibrinopeptide A and a decrease in protein C activity in the presence of 5-FU, which together responsible for thrombus formation, through release of vasoactive substances. He also noted a connection between elevated FpA and continued thrombus formation and showed that postoperative patients who acquired deep venous thrombi had elevated FpA levels.

According to Altieri *et al*. (2017) [77] effect of 5-FU cause endothelial cell senescence due to some stressors like H_2O_2, high glucose contribute to coronary artery spasm, promote formation and progression of coronary atherosclerotic lesions. The rate of synthesis of the active metabolite actually responsible for the cytotoxicity of 5FU is controlled by thyrosine phosphorylase (TP). TP is prevalent in normal tissues, including the endothelium, despite being preferentially expressed by cancer cells (Schuller *et al*., 2000) [55]. We also propose that 5FU produces TP in endothelial cells and maintains its own activation because TP, also known as platelet-derived endothelial cell growth factor, has been shown to be present in coronary atherosclerotic plaques where it may play a pathogenetic function. By increasing endothelial cells' susceptibility to 5FU and encouraging atherosclerosis, this process may exacerbate the damage caused by 5FU to the vascular system. (Ignatescu *et al*., 1999) [22].

Coronary artery vasospasm

Sara *et al*. (2018) [53] reviewed about cardiotoxicity and

mentioned that 5-FU has direct toxic effects on the vascular eNOS, leading to reduce NO causing coronary spasms. Acetylcholine (ACh) is usually an endothelium-dependent vasodilator via the NO-cyclic-guanosine monophosphate (cGMP) pathway and intact endothelial cells cause vasodilation by a biochemical mechanism of ACh that releases NO which diffuses to the smooth muscles (Hasdai *et al*., 1997). Endothelial cell injury interferes with ACh release lowering NO levels and inducing vasoconstriction which occurs through an endothelium-dependent mechanism (Mosseri *et al*., 1993) [40] (Figure. 2).

According to Tsibiribi *et al*. (2006) [61] direct endothelium-independent vasoconstriction occurs via PK-C which plays a role in 5-FU induced cardiotoxicity. Post treatment with 5-FU, Mosseri *et al*. (1993) [40] found that activation of PK-C, a mediator of vascular smooth muscle, produces direct endothelium-independent vasoconstriction in the white rabbits and pretreatment with Staurosporine, a PK-C inhibitor, decreased 5-FU induced vasoconstriction and concluded that PK-C play important role in vasoconstriction (Figure. 4).

In patients with 5-FU induced cardiotoxicity, Seker *et al*. (2018) [57] reported increased amounts of ET-1, a powerful vasoconstrictor released by injured endothelial cells, cardiomyocytes, cardiac fibroblasts and lung cells in response to hypoxia and ischemia (Figure. 2).

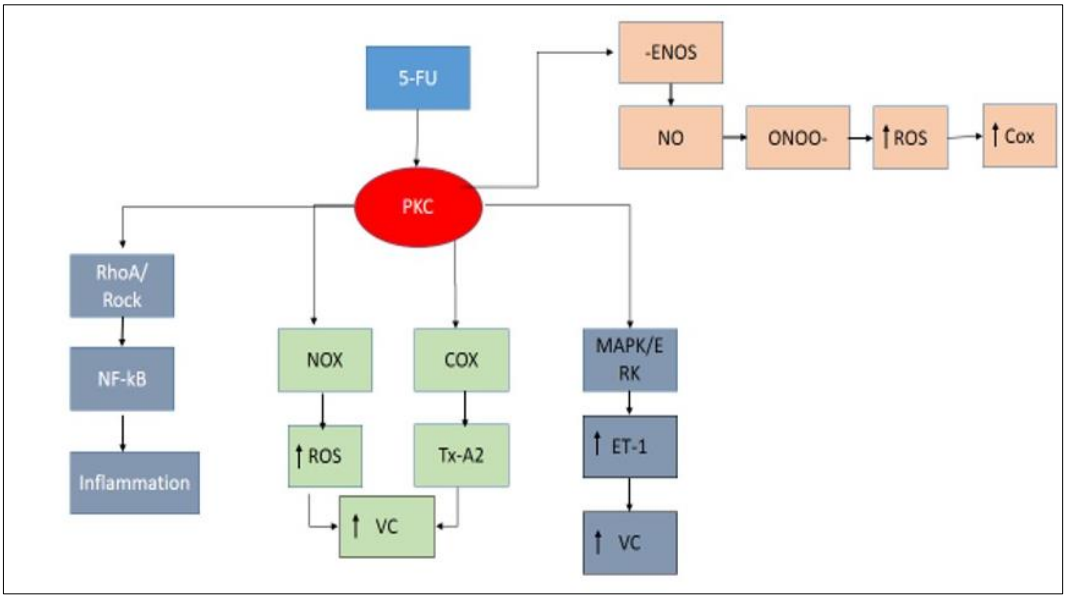

Fig 2: mechanisms contribute to 5-FU induced vasoconstriction and inflammation

Direct myocardial injury

The FBAL, a metabolite of 5-FU is an important mediator inhibits enzyme aconitase and leads to citrate accumulation and disruption of the TCA cycle which impairs adenosine triphosphate synthesis resulting in ischemia and MI within myocyte and hypoxic cell injury in mitochondria (Matsubara *et al*., 1980 and Muneoka *et al*., 2005) [36, 42]. (Figure. 4).

5-FU causes upregulation of Drp1 fission protein resulting in fragmentation of mitochondria and also cause decreased in fusion related proteins-Opa1, Mfn1, Mfn2 leading to disruption of mitochondrial electron transport chain leads to mitochondrial dysfunction (Zhang and Ma, 2018) [11].

Effects of 5-FU on lipid metabolism

A major factor in CVD and the formation of atherosclerosis is hyperlipidemia. (Hassarajani *et al*., 2007) [19]. 5-FU induced toxicity significantly increased serum triglycerides (TG), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-c) and decrease in high density lipoprotein-cholesterol (HDL-c). Increased cholesterol levels cannot be removed from the body due to hepatic dysfunction. One of the risk factors for MI is hypertriglyceridemia. LDL increases platelet aggregation and stimulates the synthesis of numerous cytokines, immune cell chemoattractant proteins and growth factors which aggravates the lesion and cause artery wall thickening. A higher LDL level has a positive association with coronary artery disease, but a lower HDL level has a negative correlation. HDL reduces LDL absorption from artery walls and promotes cholesterol transfer from the periphery of blood vessels to liver (Mohamed and Safat, 2016) [38].

Accumulation of metabolites, cytotoxic effects and interfere with TCA cycle

Generation of metabolites of 5-FU is an important mediator of drug induced cardiotoxicity and the accumulation of a metabolite-FBAL, which is converted to FA and then to fluorocitrate, which inhibit enzyme aconitase, further inhibition of Krebs cycle leading to citrate accumulation, disruption of the tricarboxylic acid (TCA) (Matsubara *et al*., 1980) [36] and severe impairment of energy production, decrease in ATP results in reduced aerobic efficiency resulting in ischemia and myocardial infarction with in myocyte, hypoxic cell injury in mitochondria (Muneoka *et al*., 2005) [42] (Figure. 4). Additionally, FC disrupts the metabolism of nucleosides and integrates into RNA and DNA, causing cytotoxicity and cell death (Arias, 2008) [5].

Effects on erthrocytes and increase in oxygen demand

The effects of 5-FU on the RBC, the major oxygen transporters, cause cardiotoxicity. Spasojevic *et al*. (2009) [59] used a range of biophysical methods to investigate RBC shape in several investigations. He discovered that 5-FU causes a dramatic shift in the metabolism of phosphate compounds due to a fast rise in o^{2-} consumption. Increased synthesis of 2, 3 bisphosphoglycerate (2, 3-BPG) and subsequent deoxygenating of oxy Hemoglobin to deoxy Hemoglobin

were exacerbated by a decrease in PO_2 (Partial Pressure of Oxygen). A severe drop in ATP levels causes several irreversible changes in erythrocyte structure and function, such as echinocytosis, increased membrane fluidity, increased potassium efflux into plasma, non-functioning membrane ion pumps and finally, all of these changes affect normal erythrocyte function, resulting in difficulties in oxygen transport to RBC leading to hypoxia, ischemia and myocardial infarction (Figure. 3).

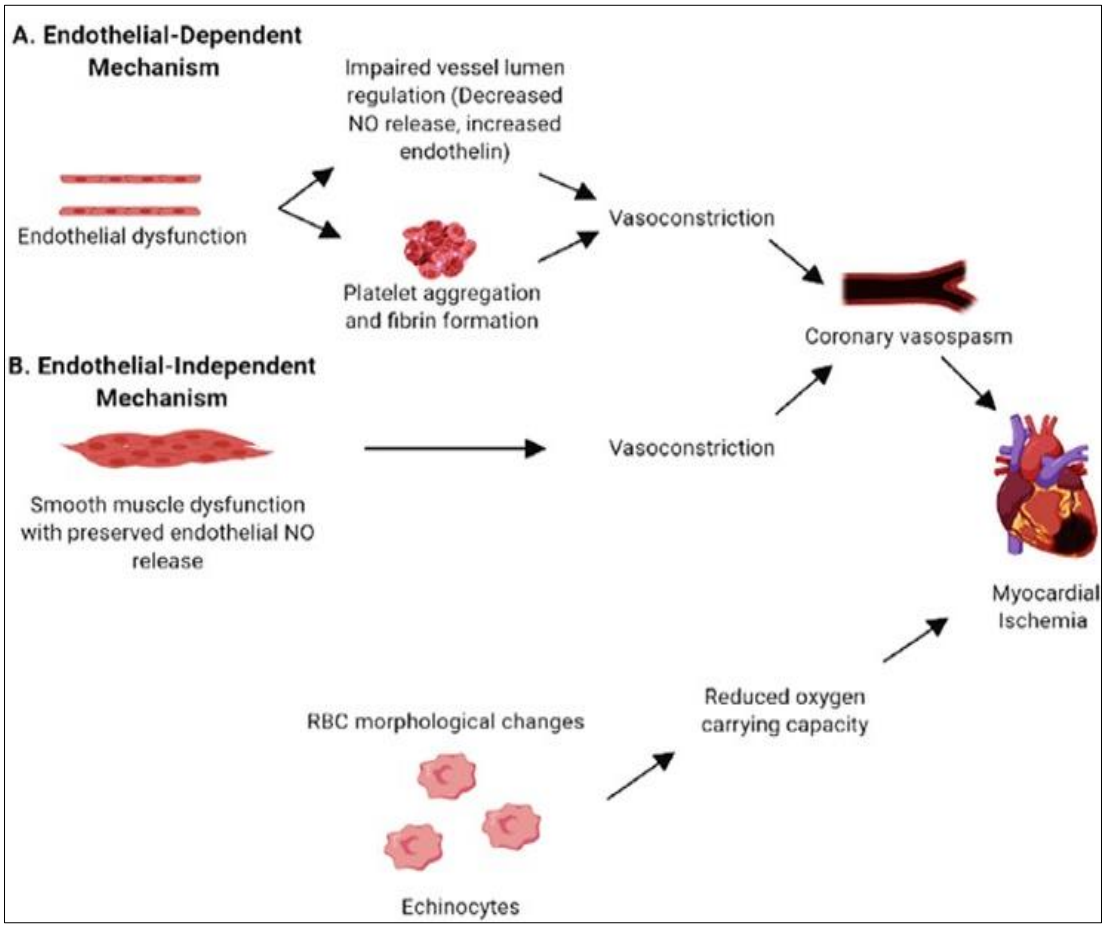

Fig 3: Effects of 5-FU on cardiomyocytes (source: Kandhuri *et al*., 2019) [72].

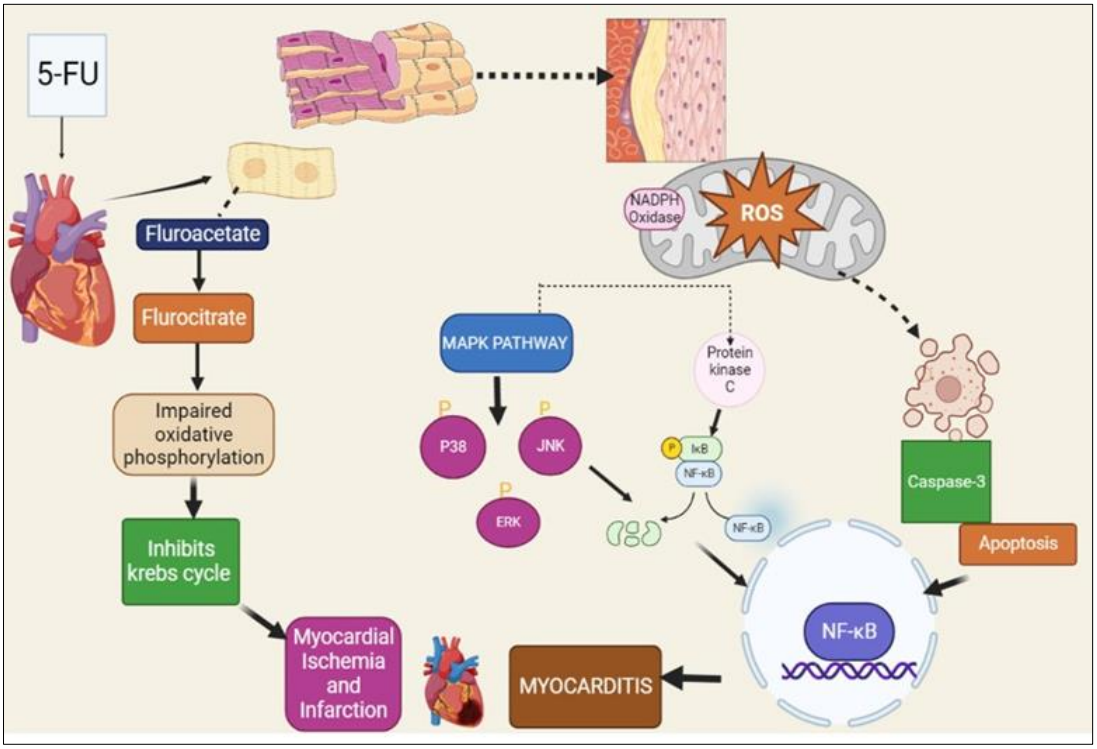

Fig 4: Mechanism of action by 5-FU induced cardiotoxicity

Positive, negative and conflicting findings from the various studies

Prevention and management

Efforts to prevent or manage 5-FU-induced cardiotoxicity have evolved with advances in medical research. This section highlights the latest developments in cardio protective agents, such as dexrazoxane and explores the potential benefits of continuous infusion protocols. Following the diagnosis of acute cardiotoxicity due to drug therapy, then, drug should be ceased immediately along with treating nitrates or calcium channel blockers. Antidote Uridine triacetate is approved for severe, life-threatening cardiac toxicity.

Conclusion

5-Fluorouracil-induced cardiotoxicity remains a significant concern in cancer treatment. By providing a comprehensive overview of its mechanisms, risk factors, detection, management, and future perspectives, this review offers valuable insights for healthcare professionals to enhance patient care, improve outcomes, and drive further research in the field of cardio-oncology. Efforts to minimize cardiotoxicity while maximizing the benefits of 5-FU therapy will play an important role in improving the quality of life for cancer patients.

Conflict of 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.

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