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Exploring the effects of oxidative stress caused by opioid drugs: A systematic review

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ABSTRACT

Drug abuse poses serious challenges in various countries worldwide. It causes the amount of oxidative stress to elevate and lead to the abnormality of physiological changes in the body. Concerning the varied of effects in this situation, this systematic review aimed to scrutinize the relation between drug addiction and the oxidative stress in animal models. A systematic literature search using PubMed via National Library of Medicine (NIH) with the keywords as follow: “Oxidative stress” or “oxidant” or “free radical” and “opioid” or “opioid drug addiction” or “animal opioid addiction”. A total of seven relevant articles underwent further analysis for data extraction. Tramadol was shown has an effect on testicular tissue abnormalities due to the presence of oxidative stress that change the gene expression, besides, it can lead to altered neurotransmitter in cerebral cortex. Morphine appear has different reaction of withdrawal symptoms in male and female. It also has greater elevation of symptoms when induced with naloxone. The combination of morphine and remifentanil reveal the changes in myocardium due to the oxidative stress changes, however, in combination with anakinra it happened to reduce the morphine tolerance which has the antinociceptive properties. Evidence indicate that chronic codeine administration can cause changes in liver function and DNA damage. Current research confirms that oxidative stress and drug addiction have an association leading to the disturbance of the body's normal physiology.

Keywords: *Oxidative stress; oxidant; free radicals; opioid addiction and animal studies*

INTRODUCTION

Oxidative stress (OS) is described as an imbalance between excessive oxidant free radicals and insufficient antioxidant system destruction among those radicals as an internal defensive mechanism (Pizzino et al., 2017). Under physiological circumstances, oxidant chemicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) are created, and various antioxidant defense systems eliminate them (Checa & Aran, 2020).

ROS are molecules composed of a minimum of one oxygen atom and one or more unpaired electrons and they are created as natural byproducts of the normal oxygen metabolism (Jakubczyk et al., 2020). This compound play critical roles in cell signalling, homeostasis, and defence systems, also consist of superoxide anion radical (O_2^-), hydroxyl radical (• OH), and singlet oxygen, these species can react with many biological components, such as lipids, proteins, and DNA, causing oxidative stress and possible damage (Griendling et al., 2016). Meanwhile, the term "reactive nitrogen species" (RNS) refers to nitrogen-containing reactive species such as nitric oxide (NO ▪), peroxynitrite, and nitrogen dioxide radical (NO_2 ▪), which resemble ROS (Li et al., 2016).

OS is produced when the antioxidant balance is disrupted, resulting in metabolic dysregulation, oxidation of DNA, proteins, and lipids, or oxidative damage in organs, tissues, or cells. Thus, inactivation of biological molecules will lead to pathological changes and one's body will develop many harmful diseases (Manzoor et al., 2022). Drug addiction is one of the brain disease that caused by the imbalance of free radical. Previous studies found that drug can cause oxidative stress in two ways, first is by reducing the antioxidant system's function and the other is by increasing the production of free radicals (Heilig et al., 2021). To simplify, ROS and RNS triggered the production of oxidative stress by alteration of mitochondrial respiration, cellular metabolism, immunological response, tyrosine nitration and cysteine oxidation, or in other word the formation of ROS and RNS are exceeding the antioxidant capabilities (Lennicke & Cochemé, 2021). The combination of these conditions causes oxidative stress, which contributes to a variety of diseases, including cardiovascular disease, neurological disorders, and cancers (Brillo et al., 2021).

Opioid medications such as, morphine, heroin, and codeine have been extensively documented in their ability to induce oxidative stress (Dinis-Oliveira, 2019). Previous studies found that drugs can cause oxidative stress by reducing antioxidant levels in the body, it affects endogenous antioxidant defenses including catalase (CAT), glutathione peroxidase (GSH), and superoxidase dismutase (SOD) (Samarghandian et al., 2014) (Hristov, 2022). In contrast of this event, when a free radical steals an electron from lipids, the process is known as lipid peroxidation, because it is impossible to measure lipid peroxidation in living subjects, the quantity of malondialdehyde (MDA) reactive species in biological samples might be a suitable technique for determining lipid peroxidation levels (Ayala et al., 2014). In addition, these biological markers are considered as the major markers to measure the oxidative stress in one's body. They are critical for maintaining redox equilibrium and protecting cells from oxidative damage and their levels of activities are directly related to general health and disease processes (Camkurt et al., 2019).

OBJECTIVES OF STUDY

The objectives of this review is to provide an overview of existing studies on the effect of oxidative stress caused by opioid dependence in animal models, since this is a very common topic to be discussed among the researchers. Other than that, it is also to narrow down the gap between the oxidative stress and its complications on internal organs and organelles.

MATERIALS & METHODS

Literature review

A comprehensive evaluation of the literature was carried out in order to uncover relevant research on the claimed association of oxidative stress and opioid drug addiction in rats. A database, PubMed via National Library of Medicine (NIH) (published between 2011 and 2021) was utilized to conduct a comprehensive search of biomedical research publications. The search strategy included a mix of the two sets of keywords listed. Oxidative stress or oxidant or free radical and opioid or opioid drug addiction or animal opioid addiction.

Selection of research articles

The findings were varied to original studies published in English with abstracts. The review omitted review papers, news, case reports, and other original materials that were not related to oxidative stress or opioid addiction. Only studies that reported a connection between oxidative stress and opioid addiction were included in this review.

Inclusion and exclusion criteria

Only studies that indicated a clear correlation between oxidative stress and opioid addiction were included in this review. The following were the inclusion criteria: (i) animal studies OR (ii) studies that has direct association between oxidative stress and opioid drugs OR (iii) studies that examine the potential treatment for oxidative stress and opioid addiction.

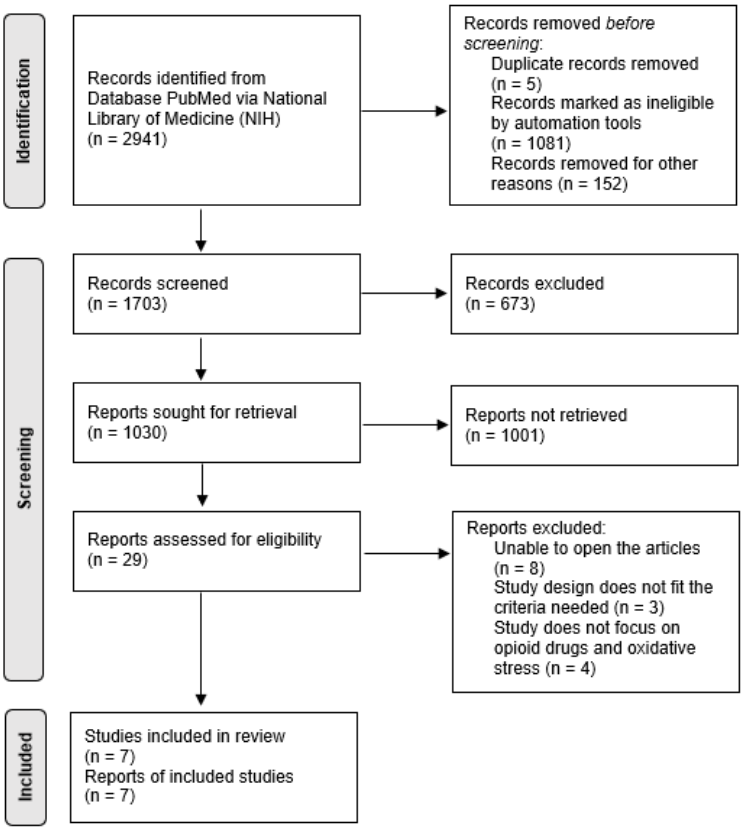
The exclusions listed below were also considered: (i) studies that use other types of drugs OR (ii) studies that has no effect on oxidative stress OR (iii) combination of opioid and other types of drugs.

Selection of research articles

Before being included in the review, papers were assessed in three phases. Studies that did not meet the inclusion criteria purely based on the title were omitted in the first phase. The remaining studies' abstracts were analyzed in the second phase, and lastly the studies that did not match the inclusion criteria were eliminated (Figure 1). To standardize the data collection, all data extraction was done separately using a data extraction form. The following information was collected from the studies: Type of opioid drugs, treatment groups, parameter and method of analysis, findings, and conclusion as shown in Table 1.

Figure 1

Flow chart of the articles selected from PubMed via NIH



Notes: Final 7 related articles to opioid drugs and its causes in animals are included in this studies.

RESULTS

Based on the reviews of the association between OS and opioid addiction, most of the results (Table 1), show that there are various key factors that usually correlates in one another and how they are lead in production of ROS followed by the changes that appear in both biological and physical in one's body.

DISCUSSION

Effects of oxidative stress caused by opioid drugs on internal organs

Liver

Despite the fact that tramadol, a commonly abused opiate, has been demonstrated to induce hepatic harm, no research has been conducted to investigate the effect of long-term codeine usage on liver structure and function (Shah et al., 2020). Based on the review, following 6 weeks of codeine administration, histological analysis of the liver tissues indicated significant fatty degeneration of the hepatic parenchyma, inflammatory cell infiltration of the portal system, and substantial collagen fiber deposition. After 6 weeks of codeine treatment, blood total protein, albumin, and globulin levels decreased. Interestingly, following codeine administration, hepatic function indicators (serum ALT y-GT, and AST) and hepatic marker enzyme activity (ALT, LDH, ALP, and AST) rose, indicating that codeine caused liver damage (Akhigbe et al., 2020). The impairment in liver function and increased

Table 1

Intervention of drug addiction in animals and its association with oxidative stress

Types of opioid drug	Treatment groups	Parameter and method of analysis	Findings	Conclusion	References
Tramadol	Group I: control (21 days) Group II: tramadol (21 days) Group III: tramadol (21 days + 4 weeks	Blood collection and biochemical estimations in serum LPO and antioxidant enzymes activities in testicular tissue Epididymal sperm count and mortality Isolation of tRNA from testicular tissue Reverse transcription – PCR analysis	MDA concentration ↑, CAT, GSH, SOD concentration ↓ in blood serum and testis After tramadol, epididymal sperm count and mortality ↓ Reference genes: Caspase-3, BCl-2, Bax Housekeeping gene; β-actin GII & GIII: ↓ BCl-2 GII: Bax and caspase-3 ↑ GIII: Bax ↑	Tramadol administration causes biological anomalies in testicular tissue associated with oxidative stress due to an increase in LPO and alterations in gene expression.	(Ibrahim & Salah-Eldin, 2019)
Morphine	Group I: male, vehicle Group II: male, morphine Group III: female, vehicle Group IV: female, morphine	Somatic withdrawal Tail flick (TF) and acoustic startle assays Oxycodone self-administration (SA) studies; (i) intravenous catherer implantation (ii) oxycodone self-administration (SA)	GII and GIV: Produce acute and protracted withdrawal sign Male ↑ somatic withdrawal sign compared to female. Withdrawal associated with greater initial oxycodone SA. GII: ↑ wet dog shake and ptosis, ↓ tail withdrawal latency GIV: ↓ response in progressive ratio (PR)	Prior opioid exposure increases male's sensitivity to initiate misuse and lowers the reinforcement effectiveness of oxycodone in females.	(Mavrikaki et al., 2021)
Codeine	Group I: control Group II: codeine 4 mg/kg Group III: codeine 10 mg/kg	Biochemical assay; DNA fragmentation assay, detection of oxidative DNA damage, oxidative marker, antioxidant activities, and markers of inflammation in hepatic tissue Apoptosis assay Na+- K+ -ATPase and Ca2+-ATPase assay Determination of liver function Histology	GII & GIII: body, liver, organo-somatic weight ↓ Liver function: ALT, LDH, AST ↑ in GII and GIII compared to GI Hepatic enzyme, AST and ACT ↑ in GIII compared to GII Oxidative markers: GII and GIII MDA, MPO, H2O2, AGE ↑ SOD, CAT, GPx, GST, GSH ↓ NO and TNF-α ↑ Proton pumps: Na+- K+ -ATPase and Ca2+-ATPase ↑ in GII and GIII Apoptosis: DNA damage, hepatic caspase-3 GIII > GII > GI GII: Moderate severity in hepatic parenchymal fatty degeneration GIII: inflammatory cells with thick collagen fibre infiltrate the portal tract	Chronic codeine treatment caused liver damage via a caspase3-mediated route by increasing free radical and TNF-α production while decreasing antioxidant buffering capacity.	(Akhigbe et al., 2020)

Notes: All opioid drugs, effect varies on animals.

Table 1 (continued)

Intervention of drug addiction in animals and its association with oxidative stress

Morphine	Group I: control (S) Group II: 100 mg/kg anakinra (A) Group III: 5 mg/kg morphine (M) Group IV: M + A Group V: morphine tolerance (MT) Group VI: MT + A	Antinociception test; (i) tail flick (TF) test (ii) hot-plate (HP) test Total antioxidant status (TAS) measurement Total oxidant status (TOS) measurement Measurement of elF-2α, ATF-4, CHOP, caspase-3	Antinociception test: GI: both TF and HP presence % MPE value GIII > GV in TF and HP GIV: ↓ morphine tolerance in TF and HP TAS and TOS levels in dorsal root ganglions (DRG): GII: ↓ TOS GIII and GV: ↓ TAS GIII: ↑ TOS GIV: ↓ TOS GV: ↑ TOS GVI: ↓ TOS elF-2α, ATF-4, CHOP, caspase-3: GIII: ↑ elF-2α, ↑ CHOP, no changes in caspase-3 GIV: ↓ ATF-4 GV: ↑ ATF-4, ↑ caspase-3	Anakinra possesses antinociceptive characteristics, boosts morphine analgesic efficacy, and reduces tolerance development after continuous morphine administration.	(Avci & Taşkiran, 2020)
Tramadol	Group I: control Group II: 30 mg/kg tramadol Group III: 60 mg/kg tramadol	Determination of lipid peroxidation, nitric oxide (NO) and antioxidant defences Oxidative DNA damage, tumor necrosis factor alpha (TNF- α), interleukin (IL)-6 and monoamines Gene expression study Western blot	GII and GIII: MDA and NO ↑ GSH, GPx, SOD, and mRNA activity ↓ ↑ NF-κB p65 in GII compared to GI ↑ oxidative DNA damage (8-Oxo-dG) in GII ↑ apoptosis (p53) in GII ↑ altered monoamines in GII and GIII	Chronic tramadol use causes oxidative stress, inflammation, apoptosis, and changes in neurotransmitters in the cerebral cortex. Tramadol enhanced lipid peroxidation, NO, monoamine neurotransmitters, and lowered antioxidant defence enzyme activity and expression in the cerebrum. Chronic tramadol treatment expressed inflammation and apoptosis markers and reduced anti-apoptotic proteins in rat cerebrum.	(Mohamed & Mahmoud, 2019)

Notes: All opioid drugs, effect varies on animals.

Table 1 (continued)

Intervention of drug addiction in animals and its association with oxidative stress

Morphine & Remifentanil	Group I: SHAM Group II: control Group III: IPC Group IV: RPC Group V: RE *R1, R5, R10, R20 for T15, T60, T120	Tissue superoxide anion by dihydroethidium fluorescence Determination of myocardium malondialdehyde (MDA) level Determination of nitrotyrosine in myocardium Immunofluorescence assay for myocardial nitrotyrosine Determination of myocardial superoxide dismutase (SOD) activity Determination of myocardial 8-hydroxy-2-deoxyguanosine level Determination of infarct size	Haemodynamics; no differences between groups except R1:T15 (heart rate, mean arterial blood pressure, rate pressure product all ↓) Superoxide anion production; ↑ remifentanil, ↑ DHE MDA concentration; ↑ in GV Nitrotyrosine concentration; ↑ dose of remifentanil, ↑ nitrotyrosine concentration Immunofluorescence assay for myocardial nitrotyrosine; ↑ dose remifentanil, ↑ nitrotyrosine concentration for 2 hours No significant changes in myocardial SOD concentration when the different doses of remifentanil were administered for 2 hours Myocardial 8-OHdG level; for 2 h of infusion, ↑ dose of remifentanil, ↑ myocardial 8-OHdG concentration Infarct sizes; ↑ dose of remifentanil, ↑ infarct sparing effect in GIV	After acute, high dosage exposure, high concentrations of remifentanil can cause oxidative alterations in the rat's myocardium. The dose and duration of administration of remifentanil had an influence on its infarct sparing effect.	(Mei et al., 2013)
Morphine & Naloxone	Group I: control 1 Group II: morphine 10 mg/kg Group III: morphine 80 mg/kg Group IV: control 2 Group V: addicted morphine Group VI: withdrawal morphine + naloxone Group VII: abstinent	Assessment of morphine dependence and withdrawal symptoms Real-time PCR Western blotting	GVI: ↑ wet dog shakes, stereotyped head bobbing, sweeping tail movement, yawning, irritability, teeth chattering, swallowing, diarrhea CART mRNA and protein: ↑ in NAc, ↓ in hippocampus GII: no changes in mRNA and CART GIII and GVI: ↑ CART mRNA GV: ↓CART GVII: CART same as GI and GIV	The modulatory role of CART peptide in the rewarding and reinforcing effects of opioids lessens with time and is enhanced when animals are subjected to acute stress, such as naloxone-induced withdrawal syndrome or abrupt high dosage injection of morphine.	(Bakhtazad et al., 2016)

Notes: All opioid drugs, effect varies on animals.

hepatic enzyme activities reported after codeine therapy are attributed, at least in part, suggests increased free radical generation and decreased hepatic tissue enzymatic antioxidant activity (Kalas et al., 2021).

Lipid peroxidation (LPO) of the hepatic cell membrane increased free radical production and decreased antioxidant activity may have resulted in membrane fluidity loss and increased membrane permeability (Ayala et al., 2014). This eventually resulted in hepatic enzymes (ALT, y-GT and AST) seeping into the circulation from hepatocytes. The increased activity of the liver's enzymatic in codeine-treated individuals could have been due to higher peroxidation of lipids in the liver, resulting in more enzyme permeability into the bloodstream (Kalas et al., 2021). Aside from LPO, it also produced hepatic protein breakdown and oxidative DNA damage, as demonstrated by raised 8-0H-dG and AGE levels in the liver. This suggests that codeine eliminated the liver's massive macromolecule buildup. Increased hepatic DNA fragmentation in codeine-treated mice may have been caused by increased oxidative DNA damage in liver cells (Poetsch, 2020).

The continuous activity of such macromolecules enables the development and ongoing operation of the gradient of electricity over the cellular membrane, which is essential for a number of metabolic functions such as cell volume maintenance (Lang, 2007). Codeine considerably lowered the activity of hepatic Na^+-K^+-ATPase and Ca^{2+}-ATPase in the current study. Because necrosis is defined by the triggering of proteolytic enzymes that cause cell lysis, changes in the activity of Na^+-K^+-ATPase and Ca^{2+}-ATPase increase necrosis development via calcium development. As a result of the findings, it is possible to conclude that codeine can cause hepatic atrophy and is associated with hepatic cachexia (Akhigbe et al., 2020). It is not unreasonable to assume that Codeine-induced oxidative injury is coupled with an increase in nitric oxide (NO) production. The results of this investigation demonstrated that codeine administration increased the levels of NO and the non-infectious inflammatory marker TNF- in the liver. NO is known to regulate a wide range of biological activities. The concentration, cellular redox state, metal abundance, protein thiols, low-molecular-weight thiols (glutathione), and other nucleophile targets all have an impact on its effects (Vaja & Rana, 2023). Though NO can work as a detoxifying agent and remove superoxide, causing cell toxicity, its interaction with superoxide may also result in the production of peroxynitrite, a strong oxidant that decomposes to produce hydroxyl radicals under certain conditions (Vaja & Rana, 2023).

Kidneys

The kidneys' role in tramadol breakdown and elimination renders them vulnerable to toxic injury. The kidneys discharge drug metabolites, and some of these can cause cellular damage, leading to renal illness. The amounts of creatinine and urea in the blood are two typical biochemical indicators used to assess renal function (Treacy et al., 2019). Plasma creatinine levels are used to quantify glomerular filtration rate, whereas urea levels are utilized to assess xenobiotic nephrotoxicity (Besseling et al., 2021). Tramadol-treated rats' renal functions were shown to be impaired in this study by a considerable rise in urea and creatinine concentrations in the plasma (Sheweita et al., 2018). This finding supports earlier research and is a sign of renal toxicity, which causes a reduction in glomerular filtration rate, resulting in a buildup of creatinine and urea in the blood.

Polyunsaturated fatty acids, which are ubiquitous in all cellular membranes, are susceptible to oxidative peroxidative assaults, culminating in lipid peroxidation. As a consequence, lipid peroxidation was used to assess oxidant-induced damage to cells (Harayama & Shimizu, 2020). Tramadol-treated patients had significantly higher hepatic and renal malonaldehyde (MDA) levels. It has been found that higher MDA levels indicate an increase in free radical formation and are regarded as a helpful indicator of oxidative stress state (Owoade et al., 2019). However, in the opposite circumstance, tramadol treatment causes a large quantity of insatiable free radicals to form, leading to oxidative stress (Owoade et al., 2019). This study found indications of antioxidant enzyme suppression in the liver and kidneys of rats, including catalase (CAT), reduced glutathione (GSH), and superoxide dismutase (SOD) (Ranjith et al., 2023). CAT, GSH, and SOD are antioxidant enzymes that help to scavenge oxidative free radicals. The decrease in antioxidant enzymes identified in this study might be attributed to their depletion as an outcome of tramadol-induced oxidative stress (Gusti et al., 2021).

Brain

Tramadol is a painkiller that is prescribed for the relief of moderate to severe pain; nevertheless, long-term use has been related to a variety of negative consequences including oxidative DNA damage, oxidative stress, inflammation apoptosis, and monoamine neurotransmitters (Mohamed & Mahmoud, 2019). The results demonstrated that continuous tramadol treatment has a prooxidant impact, as evidenced by dramatically raised levels of MDA and NO in rats' cerebrum. Brain tissue is especially sensitive to ROS degradation due to its high quantities of polyunsaturated fatty acids and low levels of antioxidant defenses (Xia et al., 2020).

Along with greater peroxidation of lipids and NO, the rat cerebrum's GSH content and activity, as well as the messenger RNA (mRNA) quantity of antioxidant enzymes SOD and GPx were all drastically lowered (Petrovic et al., 2020). The findings of this analysis supported previous research that demonstrated increased oxidative stress after tramadol use. The outcomes from (Zhao et al., 2019), who reported a substantial reduction in the activity of mitochondrial electron transport chain (ETC) complexes I, III, and IV in rats exposed to tramadol misuse, in contrast to complex II, may explain the mechanism behind the increased formation of ROS from tramadol usage. These findings suggest that tramadol-induced oxidative stress causes damage to the mitochondria. Furthermore, inhibiting the D_2 receptors for dopaminergic alleviated drug-induced cellular damage and mitochondrial

dysfunction, but activating them resulted in decreased GSH content, indicating that the system of dopamine receptors plays a role in regulating tramadol effects in mice (Bameri et al., 2018).

Excessive ROS levels may cause cell membrane lipid peroxidation as well as DNA and protein damage, resulting in cell death (Su et al., 2019). ROS can irritate by stimulating the redox-sensitive regulatory factor (NF-B), which leads to the production of a number of inflammatory mediators. In this study, NF-B activation was demonstrated to be implicated in tramadol-induced inflammation in the rat cerebrum (Mittal et al., 2014). Tramadol therapy caused an important and influenced by dose rise in NF-B p65 subunit, TNF-, and IL-6 mRNA abundance in the brain. When NF-B is activated, a variety of cytokines, chemokines, and other inflammatory agents are released. Tramadol-induced stimulation of cerebral NF-B has also been linked to considerably higher blood levels of TNF- and IL-6. According to these observations, tramadol can promote both systemic and cerebral inflammation (Nakhaee et al., 2021).

Tramadol increased iNOS, the gene and protein transcription in the rat cerebrum is dose-dependent, as well as NF-B and pro-inflammatory cytokines. The significant increase in NO levels in tramadol-induced rats' cerebrum is explained by enhanced iNOS expression (Mohamed & Mahmoud, 2019). NO can be cytotoxic, depending on the redox condition of the cells. When exposed to oxidative stress, NO may mix with superoxide radicals to form peroxynitrite, a potent oxidant that attacks and damages proteins and DNA (Le Gal et al., 2021). Both oxidative damage and inflammation can trigger cell death through apoptosis. Tramadol-induced oxidative stress and inflammation were associated with broad and dose-dependent elevations in pro-apoptotic biomarkers p53, Bax gene, and protein expression (Gambini & Stromsnes, 2022). Tramadol can reduce the production of both tramadol-induced rats' cerebrum contains the gene and protein of the anti-apoptotic biomarker Bcl-2, indicating that tramadol has the capacity to cause cell death by apoptosis in rats. The Bcl-2 protein family, which includes p53, Bax, and Bcl-2, controls apoptosis. Bcl-2, on the other hand, exerts an anti-apoptotic effect by suppressing mitochondrial cytochrome c release (Mohamed & Mahmoud, 2019). As a consequence, in tramadol-induced rats, increased ROS and RNS production caused a discrepancy in the Bcl-2 protein group and death in the cerebrum.

Tramadol is an anesthetic that is hypothesized to alleviate moderate to chronic pain is caused by reacting to opioid receptors and thereby changing the noradrenergic, GABAergic, and serotonergic systems (Gong et al., 2014). Ex vivo tramadol therapy has been shown to boost DA and DA metabolite release in certain brain regions. Tramadol can impede NE absorption while increasing 5-HT release, which explains the much higher NE and 5-HT levels found in the current study. It was discovered that continuous tramadol treatment enhanced the levels of monoamine neurotransmitters in rats' cerebrum (Xia et al., 2020). Neurotransmitter alterations, as well as inflammatory state, are linked to mental and emotional wellness. Recent research suggests that dysfunctional serotonergic and dopaminergic neurotransmission causes central nervous system dysfunction (Teleanu et al., 2022).

Heart

This review evaluated oxidative indicators in cardiac tissue following various amounts of opioid exposure. The levels of stress indicators were higher than those produced by ischemia or preconditioning remifentanil. This high oxidative stress milieu, which existed prior to the creation of ischemia reperfusion damage, lowered the myocardium's susceptibility to opioid protection. It also caused DNA damage, as seen by increased cardiac 8-OHdG levels (Xiang et al., 2021). Oxidative stress arises when the generation of damaging free radicals surpasses the antioxidant defense's ability to combat and eliminate them (Sharifi-Rad et al., 2020). Because the level of SOD remained stable, this oxidative stress is most likely the result of elevated reactive species production rather than a decline in counter-regulation (Islam et al., 2022). Elevated oxidative stress in cells is regularly established with high-dose opioid exposure, which is generally found over time, but the findings of this study suggest that comparable increases can also be detected with short-term high-dose exposure (Dossena & Marino, 2021). It is likely that continuous or high-dose opioid medication will overload the cell's antioxidant capability. Indeed, the current investigation found that short-term high-dose remifentanil dramatically enhances myocardial superoxide generation while also increasing oxidative stress (Dossena & Marino, 2021).

Excessive cellular oxidative stress in a cell can cause it to malfunction, pro-apoptotic, and even cytotoxic. It was established in these studies that a high level of oxidative stress can also interfere with cellular activity (Forman & Zhang, 2021). The absence of cardio-protection from high-dose remifentanil may be related to a disturbance in protective signalling caused by elevated levels of free radicals and lipid peroxidation (Mei et al., 2013). It's also probable that the increased oxidative stress produces secondary cell damage, as seen by elevated levels of myocardial 8-OHdG, which suggests DNA damage. In these animals, administering antioxidants or medicines containing antioxidants may substantially recover the myocardium's ability to be protected by preconditioning and post-conditioning (Martins et al., 2021). It would be interesting to see if remifentanil's cardio-protective qualities are affected by targeted antagonism of reactive oxygen or reactive nitrogen species at high doses.

Reproductive organs

Tramadol was classified as a narcotic, along with codeine and dextropropoxyphene, but it is now available with a standard prescription (Edinoff et al., 2021). Tramadol is a synthetic derivative of codeine, a centrally acting

analgesic medicine, and its toxicity and abuse were revealed as an atypical opioid, since it produces analgesia by combining two opioids (Trescot et al., 2008). Physical and psychological dependence were the result of tramadol addiction. It has been discovered that rising tramadol dose effects behavioral changes, namely restlessness, hyperactivity, or increased excitability and convulsions (Fuseini et al., 2019). These findings might be linked to tramadol biotransformation into an active metabolite, which is essential for substantial m-agonist effects; also, the metabolite accumulation has a high affinity for the m-receptor, which may result in nervous system alterations (Gong et al., 2014).

This medication is a synthetic opioid that causes cellular damage by increasing LPO, which may be used as a marker of ROS-induced cell damage. By triggering an inflammatory response, tramadol produces oxidative stress in various organs, which is significantly reduced during the withdrawal phase (Pathan & Williams, 2012). This inflammatory response has previously been demonstrated to generate oxidative stress in animals by causing changes in cell membrane fatty acid content after tramadol therapy, resulting in a decrease in fluidity (Chen et al., 2018). This impact was accompanied with a considerable decrease in antioxidant enzymatic activity, such as SOD, GSH, and CAT as well as an increase in MDA levels (Edinoff et al., 2021). According to a recent study, tramadol administration resulted in an increase in apoptotic spermatogenic cells as well as a decrease in testosterone and total cholesterol (Ibrahim & Salah-Eldin, 2019). These may enhance spermatogenic cell damage by increasing ROS. Previous research indicated that because the plasma membrane of testicular cells and the sperm is rich in polyunsaturated fatty acids, they are susceptible to oxidative damage induced by free radicals. Cellular membrane LPO may eventually lead to cell dysfunction and structural damage. As a result, the alterations found in testicular structures, such as germ and Leydig cells, may be related to tramadol-induced peroxidation of polyunsaturated fatty acids in their plasma membranes (Mannucci et al., 2022).

Tramadol abuse and withdrawal, like at the cellular level, contribute to a reducing in the mRNA transcription of the anti-apoptotic Bcl-2 followed by a rise in the pro-apoptotic index Bax and Caspase-3 production in testicular organs (Ibrahim & Salah-Eldin, 2019). High levels of Bax protein expression, despite low levels from the expression of Bcl-2, result in a high Bax/Bcl-2 ratio, which promotes apoptosis in numerous tissues and cancer cells. The researchers discovered a substantial increase in the Bax/Bcl-2 gene expression ratio following tramadol therapy and withdrawal, which might have resulted in testicular degeneration due to apoptosis. The increased production of pro-apoptotic genes Bax and caspase-3 was coupled by a reduction in the expression of anti-apoptotic Bcl-2, indicating that tramadol is hazardous at levels within cells and can cause apoptosis in the testis (Cahyadi et al., 2022). These can have an impact on spermatogenesis and sperm motility. However, to avoid tramadol toxicity, more suitable limitations and reevaluations of this prescription must be implemented.

Effects of oxidative stress caused by opioid drugs on organelles

Mitochondria

Mitochondria are well-known essential organelle which is the power-house of the cells, also an important source of the ROS formation (Singh, 2021). One of the factor influencing ROS is from the mitochondrial electron transport chain (ETC), which is the key element of oxidative phosphorylation. During ETC, electrons pass through a sequence of protein complexes (Complexes I–IV) in the inner mitochondrial membrane. As electrons flow down the chain, certain seep out and integrate with molecules of oxygen (O_2), forming superoxide radicals (O_2^-) (Murphy, 2009). Next is Complex I (NADH dehydrogenase), the primary mechanism for ROS generation. When electrons from NADH enter Complex I, some leave and react with O_2 to produce O_2^-. This mechanism happens mostly when mitochondria are not actively making Adenosinetriphosphate (ATP) or energy (Okoye et al., 2023). Lastly, ubiquinone (CoQ) and cytochrome C are additionally capable of creating ROS. CoQ, which transports electrons between Complexes I and III, may release electrons and generate O_2^-, whereas, cytochrome C produced during apoptosis (Zhao et al., 2019).

A study done by Picca et al (2020) stated that, improper balance of mitochondrial fission and fusion, which leads to dysfunction of the mitochondria, is one of the primary pathogenic events in the course of MI/R damage. As a result, increased mitochondrial fusion may be essential for balancing the dynamics of mitochondria and maintaining the function of the mitochondria. Optic atrophy 1 (OPA1), which is predominantly located in mitochondrial inner membranes, affects not only mitochondrial fusion but also mitochondrial respiration (Ding et al., 2020). Reduced OPA1 expression in MI/R injury exacerbates fragmentation of mitochondria, leading to impaired mitochondrial function, notably mitochondrial oxidative damage, leakage adjustment port opening, and mitochondrial death, all of which contribute to MI/R injury development (Sun et al., 2020).

Opioids and their binding sites are well acknowledged for their existence in the nervous system and their capacity to reduce pain, making them important in the treatment of a range of human illnesses (Spetea & Schmidhammer, 2020). They are specifically distributed throughout the cardiovascular system and have a role in the control of cardiovascular function (Pathan & Williams, 2012). The Kappa-Opioid Receptor (KOR) is a major opioid receptor subtype found in cardiac tissue. Numerous studies have revealed that KOR activation is important in the prevention of cardiovascular illnesses such as myocardial ischemia, cardiac hypertrophy, and heart failure (Wang et al., 2020). KOR activation has been demonstrated to increase durability against MI/R damage by preventing arrhythmias and enhancing the contraction of the myocardium (Tian et al., 2019).

The study revealed that KOR engagement via U50,488H decreased infarct areas and enhanced cardiac function in the setting of MI/R damage and that the KOR antagonist nor-BNI counteracted these effects. Furthermore, U50,488H lowered cardiomyocyte apoptosis and oxidative stress in MI/R rats, and these effects were prevented by the KOR antagonist nor-BNI, suggesting that U50,488H has protective benefits in MI/R damage and that these advantages are at least partly mediated by KOR activation (Wang et al., 2020). Furthermore, results reveal that OPA1 not only regulates reactive oxygen species formation, but also limits cell death by suppressing the release of mitochondrial apoptotic proteins (Quintana-Cabrera et al., 2021). As a result, KOR activation-induced OPA1 overexpression protects the heart from MI/R damage in part by lowering oxidative stress and cardiomyocyte apoptosis.

Endoplasmic reticulum

Chronic morphine usage resulted in oxidative stress with a drop in glutathione levels, lipid peroxide MDA levels, and peroxynitrite generation, which happened simultaneously with the development of tolerance and dependence (Skrabalova et al., 2013). Antioxidants that target peroxynitrite production, such as thymoquinone, reversed biochemical alterations as well as morphine tolerance and dependency (Flieger et al., 2021). This study found that both single-dose morphine and continuous consumption of morphine for tolerance building reduce antioxidant status (TAS) in the DRG, which is consistent with previous studies. It might suggest that morphine usage lowers the antioxidant system, which could contribute to tolerance development. This study also discovered that both single-dose and long-term morphine treatment induce oxidative stress (TOS) in the DRG. Furthermore, protracted morphine treatment raised TOS levels in single-dose patients more than in DRG patients. This may be associated with the development of tolerance (Zeng et al., 2020).

Endoplasmic reticulum (ER) stress is related to neuropathic and inflammatory pain processes. Furthermore, ER stress stimulation has been found in the peripheral nerve system of nephropathy associated with diabetes rats (Inceoglu et al., 2015). Additionally, ER stress has been linked to morphine analgesia and tolerance mechanisms in a few recent investigations. It was also discovered that following tolerance, PERK/eIF2a the activation of the ER stress response pathway in the spinal cord increased. In this study, ER stress proteins (elF-2a, ATF-4, and CHOP) were shown to be increased in DRG following single-dose and chronic morphine therapy. (Liu et al., 2018). Chronic morphine treatment, on the other hand, elevated ER stress proteins in DRG more than single-dose morphine administration. Previous research has found that morphine tolerance promotes neuronal death by influencing cellular processes such as oxidative damage and ER stress (Taskiran & Avci, 2021). According to the findings of this review, Morphine tolerance triggered apoptosis in the DRG via increasing caspase-3 and bax levels. This corresponds to earlier research. Despite enhanced oxidative and ER stress, a single acute dosage of morphine did not induce apoptosis. It might be related to the fact that DRG has an apoptotic threshold (Taskiran & Avci, 2021).

The contrast of opioid withdrawal symptoms in male and female

Morphine and oxycodone serve as full agonists on Mu-Opioid receptors (MORs), and their activation results in the drugs' significant analgesic and rewarding effects (Pantouli et al., 2021). Oxycodone has a lower affinity for MORs than morphine and hence travels more freely through the blood-brain barrier. However, dependency on both medications grow fast, resulting in comparable withdrawal symptoms when they are halted. (Umukoro et al., 2021). Numerous research in the disciplines of pain and stress have been conducted to investigate the molecular and cellular processes behind sex variations in opioid responses.

According to the findings of this study, previous usage of protracted, increasing dosage morphine therapy followed by withdrawal improves male oxycodone self-administration (SA) but reduces female oxycodone SA maintenance and motivation. Repeated opioid exposure can result in opioid-induced hyperalgesia, a syndrome characterized by enhanced pain sensitivity (Mavrikaki et al., 2021). A recent study has implemented that the underpinning mechanisms of opioid-induced hyperalgesia may differ by gender; nevertheless, it is uncertain whether hyperalgesia supports or discourages opioid misuse (Wilson et al., 2021).

The overall assumption that males exhibit worse morphine withdrawal symptoms than females align with accumulating data that opioid drugs are frequently notably stronger in men (Bobzean et al., 2019). Numerous studies imply that this is due to gender differences in MOR density in different brain regions rather than pharmacokinetics. However, it would be impossible to equalize morphine dosages in order to produce comparable behavioral outcomes since each behavior is likely the result of various neurological networks and diverse arrangements of MOR concentrations and operational activity (Listos et al., 2019).

The review additionally pointed out that throughout the 8 days of maintenance, SA morphine-treated men increased, but SA morphine-treated females did not. The latter outcome in females might be attributable to a decrease in tolerance, a decrease in the rewarding effect of oxycodone, a rise in responsiveness to oxycodone reward, or an upsurge in sensibility to oxycodone's negative consequences (Dumas & Pollack, 2008). According to the study's findings, females who had previously been exposed to morphine SA less oxycodone in the dosage response and had a lower PR break threshold, reflecting a decreased willingness to work for the medicine, possibly due to greater sensitivity to the drug's negative effects. Women, for example, have lower (MOR) contributions and

function in pain and stress-related areas such as the periaqueductal grey and locus coeruleus than men, with evidence suggesting estrogen is implicated (Mavrikaki et al., 2021). In addition, chronic morphine has been related to preferential absorption of MOR in male locus coeruleus but not females, as well as an estrogen-potentiated flip of MOR coupling from Gm/o to GPS proteins in females (Mavrikaki et al., 2021).

CONCLUSION

All studies that been reviewed shows the possible effects of opioid drugs on one's body. In conclusion, oxidative stress plays a main role on disrupting the normal physiology that lead to malfunction of certain organs, such as kidney, brain, liver, heart, and reproductive as well as organelles, mainly mitochondria and endoplasmic reticulum due to the overconsumption of opioid drugs. Especially in the brain, drug addiction has major consequences for oxidative stress, which is a critical factor in the neurobiological implications of persistent drug use, including oxidative stress and neuroinflammation in the brain. Oxidative stress is caused by an imbalance between reactive oxygen species (ROS) production and antioxidant defences, while neuroinflammation is characterised by the activation of immune cells (microglia) and the production of proinflammatory chemicals, in fact both processes disturb normal brain function and contribute to addictive behaviours. These findings encourage for more researchers to come out with prevention or alternative treatment to overcome this long-term major problem that been occurred since decades ago. However, all are aware that it is a time consuming to be able to produce such outcome considering the ethical consideration and budget.

AUTHOR CONTRIBUTIONS

Thur Sina Alkesah, Muhamad Arif Shahariah and Nur Alya Syarafina Moh Salleh involved in performing literature search and drafted the manuscript. Nik Nasihah Nik Ramli, Mohamad Halim Mohamad Shariff and Ashok Kumar Jeppu supervised and revised the manuscript. All authors contributed to the manuscript and approved the submitted version.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest in this work.

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