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Study of Oxidants and Antioxidants in Addicts

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Abstract

Context: This study was a systematic review that aimed to extract published articles regarding oxidant and antioxidants status in opium addiction by searching in PubMed, Google Scholar engine, SID, and Magiran databases.

Evidence Acquisition: Sixty-six published articles were investigated in this review, which were selected from studies among the Iranian society and other societies from 1976 to 2015. All articles published in different fields of descriptive-analytical, experimental, and interventional studies were considered.

Results: Several studies have shown that with increased production of free radicals and reactive oxygen species (ROS), the enzymatic and non-enzymatic antioxidants such as glutathione (GSH) and glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase activities, and also the concentration of vitamins A, E, C and total antioxidant capacity (TAC) decrease in opium addiction. Increased atherogenic indexes such as Low density lipoprotein/high density lipoprotein (LDL/HDL) ratio and malondialdehyde (MDA) may contribute to the increased risk of cardiovascular disease. However, it has also increased other markers of oxidative stress including: isoprostanes, 8-oxoguanine and protein carbonyl.

Conclusions: Oxidative stress increases in opium-addicted people. It seems that opium is capable of provoking oxidative stress and also, has harmful effects on lipid profile and antioxidant enzyme. Drug addicts were found to have antioxidant vitamin deficiency.

Keywords: Antioxidants, Oxidants, Drug Addicts

1. Context

Drug addiction is a social problem in Iran. According to the world health organization (WHO), more than 15 million people are addicted to opiate (1). Opium (known as Taryak in Farsi) contains more than 40 types of alkaloids, such as morphine, codeine and thebaine, and over 70 other components including sugars and organic acids. Opium is traditionally smoked in Iran recreationally or as a remedy for pain, diarrhea and insomnia (2, 3). Opiate abuse is related to oxidative stress that is evaluated separately through oxidants and antioxidants (4).

Free radicals or radical generating agents cause oxidative stress, which overwhelm natural radical blocking or scavenging mechanisms (5). Research has revealed that free radicals cause oxidative damage to lipid peroxidation, protein and nucleic acids. Therefore, in order to fight the damaging effects of free radicals, cells have developed a complex anti-oxidation system that includes both exogenous antioxidants and endogenous antioxidant enzymes such as Superoxide dismutase (SOD), CATALASE (CAT) and Glutathione-S-Transferase (GST) (6, 7). It was reported that drug addicts have multiple nutrient deficiencies; therefore, they are in need of taking vitamins and minerals so as to improve their health conditions (8). Drug addicts have already been reported to have some kinds of deficiency in antioxidant vitamins (9). Some food components have been identified to possess antioxidant properties; they have some specific activities and usually work synergistically in order to improve the antioxidant capability of the body (10).

Oxidative stress increases the production of free radicals and reactive oxygen species (ROS) and decreases antioxidant capacity. Measurement of the levels of ROS production, metabolites of lipid peroxidation such as Malondyaldeyde (MDA) and antioxidant capacity may give information about antioxidant status (11). Although it has been suggested that exogenous antioxidant availability affects the endogenous antioxidant defense system, the antioxidant defense system includes numerous enzymatic and non-enzymatic antioxidants. Dietary antioxidants can neutralize oxidative stress. However, non-nutrient antioxidants in plant foods can increase power of antioxidant system and protective effect of oxidative stress (12). Overall, long-term drug abuse is linked to pathological changes in some organs that are, in turn, mediated by oxidative stress.

The association between the expression of inflammation markers, oxidative stress and opium is not clearly known. However, studies have revealed that opium smokers had a low to moderate grade of inflammation, which was determined by an increase in acute phase proteins (13). Some studies conducted in Iran reported a relationship between opium and opium-derived drugs and cardiovascular diseases. The findings of a study revealed that drug abuse was an independent predictive risk factor for development of deep vein thrombosis in Kerman, Iran (14, 15). It was also reported that 45.7% of patients with ischemic stroke had opium addiction (15).

Between opium use and severity of coronary artery disease in Iranian cardiac patients significant association has been observed (16). It is estimated that prevalence of opium addiction has grown by three folds during the past 20 years. According to official reports, the current prevalence is estimated to be about 2 to 2.8% (17). Moreover, the prevalence for males and females has been reported as 3.32 and 0.55%, respectively. Estimated number of drug dependent people is about 1.2 million in Iran (18). The resultant oxidative stress impairs activities of both enzymatic and non-enzymatic antioxidants (10, 12). This review article was designed to study the oxidants and antioxidants status in individuals with addiction, who are a vulnerable group in our society.

2. Evidence Acquisition

We conducted a systematic review to extract published articles regarding oxidant and antioxidants status in opium addiction by searching in PubMed, Google Scholar engine, SID and Magiran databases. In total, sixty-seven articles published between year 1976 and 2015 were selected from studies in Iranian and other societies for this review. The following key words based on the MESH system were used in the study; oxidant and antioxidant status (enzymatic and non-enzymatic), total antioxidant status, and addicts. All articles published in the different fields of descriptive-analytical, experimental and interventional studies, were considered.

3. Results

In this article, we reviewed the current status of opium addiction in relation to condition of oxidant and antioxidants status according to published papers.

The characteristics of published studies (inside and outside of country) regarding oxidants and antioxidants status in addicts are displayed in Table 1.

4. The Impact of Opium Addiction on Oxidants

4.1. Malondialdehyde (MDA)

Malondialdehyde is a metabolite of lipid peroxidation, which is produced due to the reaction of superoxide anion (O_2^-) and polyunsaturated fatty acids. It is one of the end products of lipid peroxidation. The high levels of MDA are known as a positive indicator for lipid peroxidation. Mohammadi et al. (19) reported that MDA level significantly increased in opium-treated animals compared to controls (56.52% vs. 30.12 %). The results of the study on Syrian golden hamsters revealed that opium had the capability to stimulate oxidative stress. In addition, opium raises total cholesterol, Low density lipoprotein-cholesterol (LDL-C), triglyceride (TG) and very low density lipoprotein-cholesterol (VLDL-C) and reduces high density lipoprotein-cholesterol (HDL-C), which can act as an atherogenic indicator. It is supposed that reduction of antioxidant activity is in relation to increase of LDL oxidation (19).

It was reported that drug abuse is an independent predictive risk factor for improvement of vein thrombosis (14). Recent studies have indicated that oxidative stress and lipid peroxidation are implicated in the pathogenesis of atherosclerosis. Oxidized LDL is associated with the pathogenesis of atherosclerosis, a key in the early stage of CVD. However, oxidized LDL has a toxic effect on the vascular cells, and the cytotoxic potency of oxidized LDL is related to its content of lipid peroxidation products (20, 21). Recent findings show that oxidative stress and lipid peroxidation have a relationship with the pathogenesis of atherosclerosis. Lipid peroxidation is one of the first events, which takes place during oxidation of LDL, in relationship with many oxidants, and by major cellular components of the lesions of atherosclerosis (22). The high levels of MDA are known as a positive indicator for lipid peroxidation (23). Oxidized-low density lipoprotein (Ox-LDL) causes the development of the fatty streak and along with other factors exerts damage to the endothelium function. In the vessel wall, atherogenic lipids, especially ox-LDL, seem to be responsible for a wide range of cellular dysfunctions (24). Compared to controls, in ethanol, opium and combination of ethanol and opium treated animals, MDA showed a significant increase (30.12%, 56.52%, and 95.65%, respectively). Reactive oxygen species (ROS) and oxidizing species act on biomolecules, damaging lipids and proteins directly. In a situation where repeated and continued intranuclear ROS are generated, DNA damage may become extensive, and the hurt generates genomic instability, which contributes to carcinogenesis (25). Increase of serum total cholesterol in opium addiction was observed. It was reported that opium consumption could have aggravating

an effect in atherosclerosis formation related with hypercholesterolemia and lipid profile. The levels of MDA increased noticeably in the opium group as compared to controls (3.6 ± 0.20 vs. 2.3 ± 0.26 nmol/L). High MDA levels could be attributed to elevated production of ROS due to the severe oxidative stress in addicted animals. It has been shown that increased LDL/HDL ratio, MDA and decreased antioxidant ability may increase the risk of cardiovascular disease (26).

4.2. Isoprostanes (F2-Isoprostanes)

It was reported that the formation of prostaglandin F2 compounds and F2-isoprostanes F2-IsoPs by free radicals in vivo induces the peroxidation of arachidonic acid. The F2-IsoPs are initially formed esterified to phospholipids and then released in free forms (27). Isoprostanes are prostaglandin (PG)-like substances that are formed in vivo independently from cyclooxygenase (COX) enzymes, mainly by free radical-induced peroxidation of arachidonic acid. The formation of PG-like compounds during auto-oxidation of polyunsaturated fatty acids was determined (28, 29). Smoking may increase F2-isoprostanes level. Cigarette smoking has a direct vasoconstrictive effect. It may elevate the vasoconstrictory capacity of the arteries by increasing F2-isoprostanes and by a simultaneous decrease in the production of the vasodilatory compound, prostacyclin and nitric oxide (30).

4.3. 8-Oxoguanine

It was reported that biomarkers such as 8-oxoguanine-7 (8-oxo-7), 8-dihydro-2-deoxyguanosine (8-oxodG) and F2-isoprostanes, are important in smoking-related oxidative stress in humans (31), which are important forms in free radical induced oxidative lesions (32). The 8-OxodG is the most frequent mutation in human cancers (33). Cooke et al. (34) reported elevated concentrations of 8-oxodG in a high quantity of cases of several pre-cancerous and cancerous conditions. It was reported that indexes of oxidative damage, such as 8-OHdG, protein carbonyl group and malondialdehyde levels increased significantly ($P < 0.01$) in the livers of morphine- administered mice in comparison to controls, while the related in vivo indexes of antioxidative capacity, such as the ratio of glutathione and oxidized glutathione, activities of superoxide dismutase, catalase and glutathione peroxidase, showed a significant decrease ($P < 0.01$) (35).

4.4. Protein Carbonyl

Increase oxidative stress leads to protein carbonyl formation. Oxidation of thiols is done by nitric oxide. This can cause destruction of proteins and production of protein carbonyls (36). Oxidative stress causes lipid peroxidation, which leads to an increase in carbonyl groups in proteins that, in turn, can explain the formation of carbonyls (aldehydes and ketones) on the side chains of amino acids. This makes the amino acids susceptible to degradation by proteolytic enzymes, leading to deficiency of nitric oxide, and the formation of carbonyl protein (37). Reactive pecies are greatly reactive and can lead to oxidation of proteins and DNA, peroxidation of lipids and cell death. It has also been shown that oxidative stress can increase marker oxidant, such as protein carbonyl group in morphine-administered alone mice (35). Besides, it was reported that elevated production of ROS could be due to severe oxidative stress in addicted animals (26).

5. The Impact of Opium Addiction on the Antioxidants

The antioxidant system includes various types of functional components, which are categorized as: i) preventive antioxidants whose function is to reduce the rate of chain initiation and ii) chain breaking antioxidants, which interfere with the chain propagation. The antioxidants belonging to the first group include enzymes such as SOD, catalase and glutathione and the ones that belong to the second line of defense include vitamin C, uric acid, albumin, bilirubin, vitamin E and carotenoids (38, 39).

5.1. Enzymatic Antioxidant

5.1.1. Glutathione activity (GSH)

Glutathione, a tri-peptide composed of glutamate, cysteine and glycine, is found in plant and animal tissues. Furthermore, GSH has multiple disease preventing functions and is involved in the detoxification of chemicals and drugs. It scavenges free radicals and is then converted to GSSG or GSSCy, which is, in turn, reduced back to GSH by the enzymatic activity of GR. Glutathione protects cells against oxidative stress. The detoxification capability of GSH is directly related to its reduced thiol group. The enzymatic activity of glutathione-peroxidases and glutathione-transferases also depends on the reduced thiol group of GSH. Glutathione and other reduced thiols have an important role in enabling the body to resist oxidant stress (40). Glutathione (GSH) is an essential antioxidant for cellular detoxification in the brain. Glutathione has a relationship with neuronal cell death either in inadequate and/or excessive quantities and is related to neurodegenerative disease. Glutathione is an important and first line defense in the gastrointestinal (GI) tract against drugs, alcohol and toxic substances. It has been demonstrated that glutathione neutralizes ROS and $NO^{\bullet}$ in organisms through the scavenging mechanism (41). It has been postulated

that decreased levels of reduced GSH could be a marker for increased susceptibility to oxidant hurt and representative depletion of reserves due to oxidative stress (40). Regarding food groups, vegetables and fruits are a rich food source of glutathione. Low food sources of glutathione include potatoes, onions, garlic, spices, rice and bread. These foods do not have much of a protective effect in the gut. Glutathione supplements taken through ingestion are not usually effective. It was reported that the initial low activities of glutathione peroxidase (GPx) increased after natural dietary intervention during three months (12). It has been reported that daily consumption of five servings of fruits and vegetables provides enough antioxidants (42).

Moradi-Sardareh et al. reported that level of glutathione (GSH) significantly declined in opium-treated hamsters as compared to controls. The reduction of GSH may be due to the improved turnover for avoiding oxidative harm in addicts. Glutathione acts as a free radical scavenger and has a vital role in the recovery of biological injury due to free radicals (26).

5.1.2. Glutathione Peroxidase (GPx) Activity

Glutathione peroxidase is an internal antioxidant, which protects cells from oxidative stress attack. Maintenance of health and normal cellular action depends on antioxidants. Glutathione peroxidase can be reduced to organic peroxides (43). Chronic cocaine administration in rats resulted in significant glutathione content (GSH) depletion in the heart (37), whereas oxidized glutathione (GSSG), SOD, glutathione reductase and GPx increase, resulted in cardiac oxidative stress. It seems that the impairment of antioxidative defenses is caused by GSH-Px, SH-groups and GSH (44, 45).

5.1.3. Superoxide Dismutase (SOD)

Superoxide dismutase is a first line enzymatic antioxidant that causes the catalysis of dismutation of the superoxide anion into H_2O_2, which is, in turn, converted to H_2O by catalase (CAT) and GPx in synergy with GSH. Glutathione peroxidase can also cause the reduction of organic peroxides into their corresponding alcohols. It uses GSH as a hydrogen donor whereby GSH is oxidized (43). Superoxide dismutase (SOD) is an antioxidant enzyme that detoxifies $O^{\bullet}{}_2^-$, but may contribute to increase in H_2O_2 levels (44). An in vivo study showed that cocaine experience decreased GSH level in hepatic mitochondria, increased the activity of Mn-SOD, and the mitochondrial isoform of SOD, and decreased the activities of GPx and catalase (46, 47). On the other hand, treatment with antioxidants could prevent cocaine-induced cardiac dysfunction.

It is reported that ROS takes part in the progress of cardiomyopathy after cocaine abuse (48, 49). A significant reduction was observed in SOD in opium-treated Syrian hamsters as compared to the control group. Superoxide Dismutase is a metallo-protein enzyme, which is known as the main defense against Superoxide anion (26). Thus, SOD and catalase protect the organism from superoxide by conversion of $O^{\bullet}{}_2^-$ to H_2O_2 and by the breakdown of hydrogen peroxide to oxygen and water (50). Moreover, the decrease of SOD enzyme activity may be due to lack of enzymes activity in connection with their depletion because of peroxidation. The decrease of superoxide contents leads to the increase of SOD enzyme activity. Conversely, the increase of the contents of superoxide stops its activity (51).

5.1.4. Catalase

Catalase is an enzyme generally found in peroxisomes that converts hydrogen peroxide to water and oxygen. It was reported that hydrogen peroxide is involved in atherosclerosis pathogenesis by inducing peroxidation of lipid. In the oxidative stress situation, catalase activity will be declined (50). Under the oxidative stress situation, activity of catalase has been decreased. It was shown that the activity of catalase was significantly reduced in opium-treated Syrian Hamsters as compared with controls (27.85% vs. 47.40%) (23). In another study, catalase activity significantly decreased in opium-addicted hamsters compared to controls (27.85% reduction) (26).

5.2. Non-enzymatic Antioxidant

Non-enzymatic antioxidant includes albumin, uric acid, bilirubin, vitamin C and vitamin E, which jointly act to reduce the oxidative damage by scavenging free radicals and by detoxifying the oxidants (52).

Natural antioxidant vitamins such as E, C and A protect the body from oxidative stress. The highly reactive radicals and ROS can act as inhibitors of carcinogenesis, cause DNA damage, activate pro-carcinogens and alter the cellular antioxidant defense system (53). In one study, it was shown that in users of Pan Masala Tobacco (PMT), bilirubin significantly increased, while albumin showed a significant decrease. The compensatory system of free radical scavenging and its association with the increased formation of bilirubin can be attributed to free radicals induction of the gene for bilirubin reductase. Besides, in PMT users intoxication of liver occurs, which may be due to the increased levels of bilirubin. Uric acid, which is the last product of purine degradation, acts as an antioxidant by integrating to tightly bound iron and copper (52). An imbalance between cellular pro-oxidant and antioxidant levels results in oxidative stress that leads to tissue damage. It has been shown that aqueous extract of smokeless tobacco (AEST) in animals affects the enzymatic antioxidant system and reduces glutathione levels in different organs of the body. It

is supposed that these changes may possibly act as factors, which cause inflammation in these organs (53).

5.2.1. Vitamin A

Non-enzymatic antioxidants such as vitamin A (retinol), vitamin E (tocopherols and tocotrienols), vitamin C (ascorbic acid), carotenoids, thioredoxin, lipoic acid and ubiquinone, keep the organism against oxidant agents. They are harmful through mutagenesis and carcinogenesis (54, 55). Different studies have revealed different possible applications of antioxidant/free radical manipulations in preventing or controlling diseases. Natural products in the diet such as vegetables and fruits are known to have antioxidant activity (12, 56). However, fruit and vegetables increase erythrocyte glutathione peroxidase activity and resistance of plasma lipoproteins to oxidation, more efficiently than the vitamins and minerals of vegetables and fruits. The vitamins and minerals in fruit and vegetables cause an increase in plasma protein carbonyl formation at lysine residues (56). It has been reported that intake of vitamin A in opium-addict patients was significantly lower than non-addicts. It has also been observed that vitamin malnutrition, as judged from circulating levels, was prevalent among addicted individuals (57). Low consumption of fruit and vegetables as main sources of vitamins has also been observed in drug addicts compared to the ordinary population. Deficiency in vitamins, especially antioxidant vitamins, is observed in opium addicts (8, 58). It was shown that retinol in drug addicts was significantly lower compared to controls; this reduction was remarkably noticeable among people who had multiple drug addiction (9).

Nazrul Islam et al. reported that retinol in drug addicts was considerably low in comparison with controls and this reduction was more noticeably seen among multiple drug addicts (9). Addicts seem to have a tendency to replace foods that are rich in fat and proteins with a diet that is relatively poor in vitamins (59).

5.2.2. Vitamin E

Vitamin E plays role as a chain-breaking antioxidant, which can directly scavenge a variety of oxy-radicals, including peroxy (ROO-), hydroxyl (OH^-) and superoxide (O_2) radicals.

It seems that ascorbic acid and tocopherol have a similar role as antioxidants in Tobacco and related products collectively termed as Pan Masala Tobacco (PMT) (38). It has been reported that addicts have natural antioxidant deficiencies such as vitamins A, E, and C. They play an important role in immunity (60). Drug addiction impairs nutritional status and immunity (61). A low level of antioxidant vitamin E in the addicts compared to non-addict has been observed. Besides, an indirect correlation has been observed between drug habit and antioxidant vitamin status (9). Vitamin E and selenium administrations prevented lipid peroxidation and improved endogenous antioxidant defense systems (62).

Drugs damage neurons and change metabolism, which lead to irretrievable changes in the brain. On the other hand, malnutrition can increase the toxic effects of drugs, which can affect food intake in addicts. Besides, as compared to healthy individuals, drug addicts usually intake unhealthy diets. Nutritional status of drug users is not appropriate. It is suggested to perform nutritional interventional programs as a medical nutrition therapy (MNT) (58). It has also been demonstrated that long-term usage of tobacco products free radicals and ROS damages the antioxidant defense system (53).

5.2.3. Vitamin C

Vitamin C is a natural antioxidant, which has potent inhibitor of lipid peroxidation. It seems that supplementation with antioxidants such as vitamin C can reduce symptoms or indicators of oxidative stress. Oxidative stress causes a decrease of vitamin C in the organism. It can scavenge free radicals and remove oxidant agents. It renews the major antioxidant vitamin E. Vitamin C is depleted in PMC users. Reduction of antioxidant is a risk factor for cancer, CHD and other severe chronic diseases (52). It has been shown that the mean intake of vitamins A, C, E, B12 and folic acid in opioid-dependent abusers was lower than the values recommended by Dietary Reference Intakes (DRIs) and lower than controls (63). It was observed that serum levels of vitamin C in addicts were lower than controls. Drug addiction impairs nutritional status and immunity. It was reported that abuse of drugs causes several immunonutritional deficiencies, which are involved in the immune system. Deficiencies of these vitamins may cause the increase of immunodeficiency in the drug addicts. However, drug addicts are at high risk of human immunodeficiency virus (HIV) infection (9).

In addition, they have different degrees of malnutrition and nutritional deficiencies such as vitamin C. Nutritional deficiencies can affect different organ functions and cause several nutritional disorders (8).

6. Total Antioxidant Capacity (TAC)

Opioid drugs damage the activity of antioxidant systems as indicated by the decrease in total antioxidant capacity found in blood of human heroin addicts, when compared to detoxification and control groups (11). However, in other studies, it was found that opium increases the antioxidant capacity of the serum. It seems that opium can

be a drug with characteristics both useful and harmful depending on antioxidant and inflammatory effects, respectively. However, it has been observed that opiates exert their toxic effects mostly through induction of oxidative stress, which, in turn, occurs as a result of inflammatory response. It is postulated that opium increases the TAC of the serum. It seems that increasing levels of ferric reducing antioxidant power (FRAP) test in opium smokers is more related to their diet and socioeconomic status (13). It has been already found that morphine inhibits peroxidation of linoleic acid emulsion. Morphine had an effective reducing power, free radical scavenging, superoxide anion radical scavenging, hydrogen peroxide scavenging and metal chelating activities conversely (64). The improved status of antioxidants is confirmed by their direct relationship with total antioxidant capacity (TAC) and negative correlation with oxidant products, such as MDA (12). Decreased TAC in heroin addiction is due to neutralization of an increased free radical production and lipid peroxidation in heroin addiction (11). Malondialdehyde (MDA) is an oxidative stress marker while ferric-reducing ability of plasma (FRAP) is an anti-oxidant capacity marker.

It has been shown that morphine reduces the activity of the antioxidative defense system. It seems that oxidative stress is one of the major mechanisms behind drug abuse that is related to decrease in antioxidant activities including SOD, GST and CAT and the ratio of GSH/oxidized GSH (65). Heroin-injected mice were reported to decrease TAC in blood, increase ROS production in white blood cells, and also raise oxidative damages to proteins and lipids. Besides, exogenous antioxidants system could control oxidative stress, even diminish withdrawal syndrome (66). It was also observed that TAC had a positive and significant correlation to nitric oxide (NO) production in opium smokers; however, this correlation was not significant in the control group (13).

Further studies are necessary to make clear the mechanisms leading to these contradictory results.

7. Conclusion

In conclusion, oxidative stress is increased in opium addicts. According to different studies, opium seems to be capable to induce oxidative stress and also, has harmful effects on lipid profile and antioxidant systems including enzymatic and non-enzymatic ones. Besides, drug addicts showed antioxidant vitamin deficiency, which may be due to illicit drug use. Long-term use of the drugs could cause oxidative stress, which leads to pathological changes in the organism. Increased atherogenic index, LDL/HDL ratio, MDA and decreased antioxidant capacity may cause an increase in the cardiovascular disease risk.

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Footnote

Authors' Contribution: All authors contributed equally to study concept, design, and the literature review, and also access to references, writing and editing the final manuscript.

References

1. Soykut B, Eken A, Erdem O, Akay C, Aydin A, Cetin MK, et al. Oxidative stress enzyme status and frequency of micronuclei in heroin addicts in Turkey. *Toxicol Mech Methods.* 2013;**23**(9):684–8. doi: 10.3109/15376516.2013.843106. [PubMed: 24024663].
2. Rajabizade G, RamezaniMohammad A, ShakibiMohammad R. Prevalence of Opium Addiction in Iranian Drivers 2001-2003. *J Med Sci (Faisalabad).* 2004;**4**(3):210–3. doi: 10.3923/jms.2004.210.213.
3. Shiri R, Hassani KF, Ansari M. Association between opium abuse and comorbidity in diabetic men. *Am J Addict.* 2006;**15**(6):468–72. doi: 10.1080/10550490601000421. [PubMed: 17182450].
4. Kovatsi L, Njau S, Nikolaou K, Topouridou K, Papamitsou T, Koliakos G. Evaluation of prooxidant-antioxidant balance in chronic heroin users in a single assay: an identification criterion for antioxidant supplementation. *Am J Drug Alcohol Abuse.* 2010;**36**(4):228–32. doi: 10.3109/00952990.2010.495438. [PubMed: 20560843].
5. Block G, Dietrich M, Norkus EP, Morrow JD, Hudes M, Caan B, et al. Factors associated with oxidative stress in human populations. *Am J Epidemiol.* 2002;**156**(3):274–85. [PubMed: 12142263].
6. Simpson JA, Narita S, Gieseg S, Gebicki S, Gebicki JM, Dean RT. Long-lived reactive species on free-radical-damaged proteins. *Biochem J.* 1992;**282 (Pt 3)**:621–4. [PubMed: 1554345].
7. Vanella A, Geremia E, D'Urso G, Tiriolo P, Di Silvestro I, Grimaldi R, et al. Superoxide dismutase activities in aging rat brain. *Gerontology.* 1982;**28**(2):108–13. [PubMed: 7084675].
8. karajibani M, Montazerifar F, Shakiba M. Evaluation of Nutritional Status in Drug Users Referred to the Center of Drug Dependency Treatment in Zahedan. *int j high risk behav add.* 2012;**1**(1):16–9. doi: 10.5812/ijhrba.4176.
9. Nazrul Islam SK, Jahangir Hossain K, Ahsan M. Serum vitamin E, C and A status of the drug addicts undergoing detoxification: influence of drug habit, sexual practice and lifestyle factors. *Eur J Clin Nutr.* 2001;**55**(11):1022–7. doi: 10.1038/sj.ejcn.1601263. [PubMed: 11641753].
10. Bagchi K, Puri S. Free radicals and antioxidants in health and disease. *Eastern Mediterranean health j.* 1998;**4**(2):350–60.
11. Pereska Z, Dejanova B, Bozinovska C, Petkovska L. Prooxidative/antioxidative homeostasis in heroin addiction and detoxification. *Bratisl Lek Listy.* 2007;**108**(9):393–8. [PubMed: 18225476].
12. Karajibani M, Hashemi M, Montazerifar F, Dikshit M. Antioxidant Status before and after Dietary Intervention in Cardiovascular Disease (CVD) Patients. *Malays J Nutr.* 2010;**16**(3):327–38. [PubMed: 22691986].
13. Ghazavi A, Mosayebi G, Solhi H, Rafiei M, Moazzeni SM. Serum markers of inflammation and oxidative stress in chronic opium (Taryak) smokers. *Immunol Lett.* 2013;**153**(1-2):22–6. doi: 10.1016/j.imlet.2013.07.001. [PubMed: 23850638].
14. Masoomi M, Ramezani MA, Shahriari S, Shahesmaeeli A, Mirzaeepour F. Is opium addiction a risk factor for deep vein thrombosis? A case-control study. *Blood Coagul Fibrinolysis.* 2010;**21**(2):109–12. doi: 10.1097/MBC.0b013e32832f2b1e. [PubMed: 20083999].

15. Iranmanesh F. Prognostic value of electrocardiography and electroencephalography in patients with ischemic stroke. *Acta Neurol Taiwan.* 2008;**17**(4):228–32. [PubMed: 19280865].
16. Sadeghian S, Darvish S, Davoodi G, Salarifar M, Mahmoodian M, Fallah N, et al. The association of opium with coronary artery disease. *Eur J Cardiovasc Prev Rehabil.* 2007;**14**(5):715–7. doi: 10.1097/HJR.0b013e328045c4e9. [PubMed: 17925633].
17. Safaei N. Outcomes of coronary artery bypass grafting in patients with a history of opiate use. *Pak J Biol Sci.* 2008;**11**(22):2594–8. [PubMed: 19260339].
18. World Health Organization . ATLAS of Substance Use Disorders Resources for the Prevention and Treatment of Substance Use Disorders, Country Profile: IRAN 2010. Available from: http://www.who.int/substanceabuse/publications/atlasreport/profiles/iran.pdf.
19. Mohammadi A, Mirzaei F, Jamshidi M, Yari R, Pak S, Sorkhani A, et al. The in vivo biochemical and oxidative changes by ethanol and opium consumption in Syrian hamsters. *Int J Biol.* 2013;**5**(4):14.
20. Epstein FH, Diaz MN, Frei B, Vita JA, Keaney JF. Antioxidants and Atherosclerotic Heart Disease. *New England J Med.* 1997;**337**(6):408–16. doi: 10.1056/nejm199708073370607.
21. Karajibani M, Hashemi M, Montazerifar F, Bolouri A, Dikshit M. The status of glutathione peroxidase, superoxide dismutase, vitamins A, C, E and malondialdehyde in patients with cardiovascular disease in Zahedan, Southeast Iran. *J Nutr Sci Vitaminol (Tokyo).* 2009;**55**(4):309–16. [PubMed: 19763031].
22. Pratico D. Lipid peroxidation in mouse models of atherosclerosis. *Trends Cardiovasc Med.* 2001;**11**(3-4):112–6. [PubMed: 11685999].
23. Janero DR. Malondialdehyde and thiobarbituric acid-reactivity as diagnostic indices of lipid peroxidation and peroxidative tissue injury. *Free Radic Biol Med.* 1990;**9**(6):515–40. [PubMed: 2079232].
24. Napoli C, Ignarro LJ. Nitric Oxide and Atherosclerosis. *Nitric Oxide.* 2001;**5**(2):88–97. doi: 10.1006/niox.2001.0337.
25. Charames GS, Bapat B. Genomic instability and cancer. *Curr Mol Med.* 2003;**3**(7):589–96. [PubMed: 14601634].
26. Moradi-Sardareh H, Mohammadi N, Oubari F, Nikbakht MR, Hosseini KR, Farnoosh G, et al. Biochemical factors, MDA levels and Antioxidant activity in Opium addicted Hamsters. *In Res J Biol Sci.* 2014;**3**(2):21–4.
27. Roberts LJ, Morrow JD. Measurement of F(2)-isoprostanes as an index of oxidative stress in vivo. *Free Radic Biol Med.* 2000;**28**(4):505–13. [PubMed: 10719231].
28. Morrow JD, Hill KE, Burk RF, Nammour TM, Badr KF, Roberts L2. A series of prostaglandin F2-like compounds are produced in vivo in humans by a non-cyclooxygenase, free radical-catalyzed mechanism. *Proc Natl Acad Sci U S A.* 1990;**87**(23):9383–7. [PubMed: 2123555].
29. Pryor WA, Stanley JP, Blair E. Autoxidation of polyunsaturated fatty acids: II. A suggested mechanism for the formation of TBA-reactive materials from prostaglandin-like endoperoxides. *Lipids.* 1976;**11**(5):370–9. [PubMed: 1271974].
30. Obwegeser R, Oguogho A, Ulm M, Berghammer P, Sinzinger H. Maternal cigarette smoking increases F2-isoprostanes and reduces prostacyclin and nitric oxide in umbilical vessels. *Prostaglandins Other Lipid Mediat.* 1999;**57**(4):269–79. [PubMed: 10402220].
31. Hatsukami DK, Benowitz NL, Rennard SI, Oncken C, Hecht SS. Biomarkers to assess the utility of potential reduced exposure tobacco products. *Nicotine Tob Res.* 2006;**8**(4):600–22. doi: 10.1080/14622200600858166. [PubMed: 16920658].
32. Valavanidis A, Vlachogianni T, Fiotakis K. Tobacco smoke: involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenesis and synergistic effects with other respirable particles. *Int J Environ Res Public Health.* 2009;**6**(2):445–62. doi: 10.3390/ijerph6020445. [PubMed: 19440393].
33. Pilger A, Rudiger HW. 8-Hydroxy-2'-deoxyguanosine as a marker of oxidative DNA damage related to occupational and environmental exposures. *Int Arch Occup Environ Health.* 2006;**80**(1):1–15. doi: 10.1007/s00420-006-0106-7. [PubMed: 16685565].
34. Cooke MS, Olinski R, Evans MD. Does measurement of oxidative damage to DNA have clinical significance?. *Clin Chim Acta.* 2006;**365**(1-2):30–49. doi: 10.1016/j.cca.2005.09.009. [PubMed: 16214123].
35. Zhang YT, Zheng QS, Pan J, Zheng RL. Oxidative damage of biomolecules in mouse liver induced by morphine and protected by antioxidants. *Basic Clin Pharmacol Toxicol.* 2004;**95**(2):53–8. doi: 10.1111/j.1742-7843.2004.950202.x. [PubMed: 15379780].
36. Levine RL, Garland D, Oliver CN, Amici A, Climent I, Lenz AG, et al. Determination of carbonyl content in oxidatively modified proteins. *Methods Enzymol.* 1990;**186**:464–78. [PubMed: 1978225].
37. Lamsal M, Gautam N, Bhatta N, Toora BD, Bhattacharya SK, Baral N. Evaluation of lipid peroxidation product, nitrite and antioxidant levels in newly diagnosed and two months follow-up patients with pulmonary tuberculosis. *Southeast Asian J Trop Med Public Health.* 2007;**38**(4):695–703. [PubMed: 17883009].
38. Burton GW, Ingold KU. Vitamin E as an in vitro and in vivo antioxidant. *Ann N Y Acad Sci.* 1989;**570**:7–22. [PubMed: 2698111].
39. Carr A, Frei B. Does vitamin C act as a pro-oxidant under physiological conditions?. *FASEB J.* 1999;**13**(9):1007–24. [PubMed: 10336883].
40. Singh RJ. Glutathione: a marker and antioxidant for aging. *J Lab Clin Med.* 2002;**140**(6):380–1. doi: 10.1067/mlc.2002.129505. [PubMed: 12486403].
41. Dean O, Giorlando F, Berk M. N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action. *J Psychiatry Neurosci.* 2011;**36**(2):78–86. doi: 10.1503/jpn.100057. [PubMed: 21118657].
42. Padayatty SJ, Katz A, Wang Y, Eck P, Kwon O, Lee JH, et al. Vitamin C as an antioxidant: evaluation of its role in disease prevention. *J Am Coll Nutr.* 2003;**22**(1):18–35. [PubMed: 12569111].
43. Cheng TY, Zhu Z, Masuda S, Morcos NC. Effects of multinutrient supplementation on antioxidant defense systems in healthy human beings. *J Nutrition Biochem.* 2001;**12**(7):388–95. doi: 10.1016/s0955-2863(01)00153-x.
44. Cunha-Oliveira T, Cristina Rego A, Oliveira CR. Oxidative Stress and Drugs of Abuse. Mini-Reviews in Organic Chemistry. 2015 ;**12**(6):1–12.
45. Pacifici R, Fiaschi AI, Micheli L, Centini F, Giorgi G, Zuccaro P, et al. Immunosuppression and oxidative stress induced by acute and chronic exposure to cocaine in rat. *Int Immunopharmacol.* 2003;**3**(4):581–92. doi: 10.1016/S1567-5769(03)00050-X. [PubMed: 12689662].
46. Devi BG, Chan AW. Impairment of mitochondrial respiration and electron transport chain enzymes during cocaine-induced hepatic injury. *Life Sci.* 1997;**60**(11):849–55. [PubMed: 9076324].
47. Devi BG, Chan AW. Cocaine-induced peroxidative stress in rat liver: antioxidant enzymes and mitochondria. *J Pharmacol Exp Ther.* 1996;**279**(1):359–66. [PubMed: 8859014].
48. Boess F, Ndikum-Moffor FM, Boelsterli UA, Roberts SM. Effects of cocaine and its oxidative metabolites on mitochondrial respiration and generation of reactive oxygen species. *Biochem Pharmacol.* 2000;**60**(5):615–23. [PubMed: 10927019].
49. Moritz F, Monteil C, Isabelle M, Bauer F, Renet S, Mulder P, et al. Role of reactive oxygen species in cocaine-induced cardiac dysfunction. *Cardiovasc Res.* 2003;**59**(4):834–43. [PubMed: 14553823].
50. Madhavan V, Shah P, Murali A, Yoganarasimhan SN. In vitro and in vivo antioxidant activity studies on the roota of Toddalia asiatica (L.) Lam.(Rutaceae). *Asian J Trad Med.* 2010;**5**(5).
51. Karajibani M, Montazerifar F, Hashemi M, Bolouri A, Dikshit M. A Study on Oxidative Stress in Patients with Angina Pectoris Admitted to Coronary Care Unit. *Zahedan J Res Med Sci.* 2013;**15**(3):20–5.
52. Shrestha R, Nepal AK, Lal Das BK, Gelal B, Lamsal M. Non-enzymatic antioxidant status and biochemical parameters in the consumers of Pan Masala containing tobacco. *Asian Pac J Cancer Prev.* 2012;**13**(9):4353–6. [PubMed: 23167342].
53. Avti PK, Kumar S, Pathak CM, Vaiphei K, Khanduja KL. Smokeless tobacco impairs the antioxidant defense in liver, lung, and kidney of rats. *Toxicol Sci.* 2006;**89**(2):547–53. doi: 10.1093/toxsci/kfj041. [PubMed: 16280382].

54. Devasagayam TP, Tilak JC, Boloor KK, Sane KS, Ghaskadbi SS, Lele RD. Free radicals and antioxidants in human health: current status and future prospects. *J Assoc Physicians India.* 2004;**52**:794–804. [PubMed: 15909857].
55. Halliwell B. Biochemistry of oxidative stress. *Biochem Soc Trans.* 2007;**35**(Pt 5):1147–50. doi: 10.1042/BST0351147. [PubMed: 17956298].
56. Dragsted LO, Pedersen A, Hermetter A, Basu S, Hansen M, Haren GR, et al. The 6-a-day study: effects of fruit and vegetables on markers of oxidative stress and antioxidative defense in healthy nonsmokers. *Am J Clin Nutr.* 2004;**79**(6):1060–72. [PubMed: 15159237].
57. el-Nakah A, Frank O, Louria DB, Quinones MA, Baker H. A vitamin profile of heroin addiction. *Am J Public Health.* 1979;**69**(10):1058–60. [PubMed: 484761].
58. Himmelgreen DA, Perez-Escamilla R, Segura-Millan S, Romero-Daza N, Tanasescu M, Singer M. A comparison of the nutritional status and food security of drug-using and non-drug-using Hispanic women in Hartford, Connecticut. *Am J Phys Anthropol.* 1998;**107**(3):351–61. doi: 10.1002/(SICI)1096-8644(199811)107:3<351::AID-AJPA10>3.0.CO;2-7. [PubMed: 9821498].
59. Morabia A, Fabre J, Chee E, Zeger S, Orsat E, Robert A. Diet and opiate addiction: a quantitative assessment of the diet of non-institutionalized opiate addicts. *Br J Addict.* 1989;**84**(2):173–80. [PubMed: 2720181].
60. Brown KM, Morrice PC, Duthie GG. Erythrocyte vitamin E and plasma ascorbate concentrations in relation to erythrocyte peroxidation in smokers and nonsmokers: dose response to vitamin E supplementation. *Am J Clin Nutr.* 1997;**65**(2):496–502. [PubMed: 9022535].
61. Varela P, Marcos A, Ripoll S, Santacruz I, Requejo AM. Effects of human immunodeficiency virus infection and detoxification time on anthropometric measurements and dietary intake of male drug addicts. *Am J Clin Nutr.* 1997;**66**(2):509S–14S. [PubMed: 9250140].
62. Cemek M, Büyükokuroğlu M, Hazman Ö, Konuk M, Bulut S, Birdane YO. The Roles of Melatonin and Vitamin E Plus Selenium in Prevention of Oxidative Stress Induced by Naloxone-Precipitated Withdrawal in Heroin-Addicted Rats. *Biol Trace Element Res.* 2010;**142**(1):55–66. doi: 10.1007/s12011-010-8744-8.
63. Montazerifar F, Karajibani M, Lashkaripour K, Yosefi M, Dorzadeh H, Dashipour A. Dietary intakes of opiate abusers before and during Methadone Maintenance Treatment. *Heroin addiction and related clinical problems.* 2014;**16**(4):41–7.
64. Gulcin I, Beydemir S, Alici HA, Elmastas M, Buyukokuroglu ME. In vitro antioxidant properties of morphine. *Pharmacol Res.* 2004;**49**(1):59–66. [PubMed: 14597153].
65. Samarghandian S, Afshari R, Farkhondeh T. Effect of long-term treatment of morphine on enzymes, oxidative stress indices and antioxidant status in male rat liver. *Int J Clin Exp Med.* 2014;**7**(5):1449–53. [PubMed: 24995110].
66. Pan J, Zhang Q, Zhang Y, Ouyang Z, Zheng Q, Zheng R. Oxidative stress in heroin administered mice and natural antioxidants protection. *Life Sci.* 2005;**77**(2):183–93. doi: 10.1016/j.lfs.2004.12.025. [PubMed: 15862603].

Table 1. Characteristics of Published Studies (Inside and Outside of the Country) About Oxidants and Antioxidants Status in Addicts

No.	Author (s)	Methodology	Results
		Inside Country	
1	Ghazavi et al., 2013, (13)	Cross-sectional, case-control study; Determination of in [U+FB02]ammation markers, oxidative stress, hs- CRP (ELISA), C3, C4 (SRID method), Igs, NO, and TAC (FRAP) in opium smokers and controls.	Addicts had in [U+FB02]ammation with a low to moderate grade, which was determined by an increase in acute phase proteins. Thus, it is suggested that opium is a drug with potentially helpful (antioxidant) and harmful (in [U+FB02]ammatory) effects.
2	Mohammadi et al., 2013 (19)	Experimental study; investigation of the effect of consumption of alcohol and opium on lipid profile and oxidative stress in Syrian golden hamsters. Determination of Lipid profiles and atherogenic indexes, ALT, AST, MDA, GSH, NO, CAT and SOD levels in four treatment groups of hamsters.	Results showed that opium and ethanol are capable of provoking oxidative stress when administered alone or in combination. Opium and alcohol also harmfully increased total cholesterol, LDL-C, TG, VLDL-C, atherogenic index and non-HDL-C in animals.
3	Samarghandian et al., 2014 (65)	Experimental study; determination of biochemical indices, which changes due to long term usage of morphine in rats.	Findings showed the risk of hepatic damage due to long term usage of morphine via trouble oxidant-antioxidant balance. Besides, morphine was shown to be effective in pain treatment; its toxic effects should be kept in mind during chronic usage.
		Outside the Country:	
1	Brown et al., 1997 (60)	Interventional study: The effect of supplementation of D-alpha-tocopherol on erythrocyte vitamin E and plasma ascorbate in relation to erythrocyte peroxidation in smokers and nonsmokers.	Increased peroxidation was observed in non-smokers ($P < 0.001$). In addition, prolonged supplementation with D-alpha-tocopherol in nonsmokers caused a decline in plasma ascorbate concentration ($P < 0.02$) in association with an increasing erythrocyte vitamin E uptake ($P < 0.001$). Thus, vitamin E may have prooxidant activity in nonsmokers with high and prolonged intakes.
2	Morabia et al., 1989 (59)	Descriptive study: nutritional assessment (quantitative method); assessment of diet and anthropometric indices in non-institutionalized opiate addicts.	The results showed that BMI may not be a good indicator of the unbalanced diet in addicts. This study provided a quantitative assessment, in terms of nutrient intake of the typical craving for sweets, described by opiate addicts.
3	Himmelgreen et al., 1998 (58)	A case-control study; determination of food insecurity, nutritional status (anthropometry and dietary intake), and food preparation patterns in drug abusers and controls.	All anthropometric measurements were significantly lower in drug users. They had poor nutritional status. Nutrition interventions as part of drug treatment are needed.
4	Obwegeser et al.,1999 (30)	Descriptive-analytical study; this study evaluated the influence of smoking on F2-isoprostanes, prostacyclin and nitric oxide in human umbilical vessels. Umbilical cords of smoking mothers and non-smoking mothers were tested. Cigarette smoking increased F2-isoprostane levels and reduced the generation of prostacyclin in umbilical arteries and veins.	It is recommended that smoking might increase the vasoconstrictory capability in umbilical arteries by improved F2-isoprostanes and by a decrease in the production of the vasodilatory compounds, prostacyclin and nitric oxide.
5	Boess et al., 2000 (48)	Experimental study; study of the potential role of cocaine N-oxidative metabolites in mitochondrial respiration and ROS generation in isolated mouse mitochondria treated with cocaine and its N-oxidative metabolites-norcocaine, N-hydroxynorcocaine, and norcocaine nitroxide.	It was suggested that the effects of cocaine on mitochondrial respiration were due to its N-oxidative metabolites. Inhibition of mitochondrial respiration by the N-oxidative metabolites of cocaine may be the underlying cause for observed ATP depletion and subsequent cell death.
6	Nazrul Islam et al., 2001 (9)	Cohort study; determination of Vitamin E, C and A, and life style of male drug addicts and controls. Research instruments were a questionnaire and blood specimens.	To performance antioxidant therapy in drug addicts and to rehabilitate them to normal life.
7	Block et al., 2002, (5)	A case-control study; Determination of two biomarkers of lipid peroxidation MDA and Iso-P, in smokers and nonsmokers. The effect of antioxidant supplements on oxidative damage in parallel to dietary intake (FFQ). Plasma were assayed for CRP, cotinine, Vit.C, Vit.E, five carotenoids, cholesterol, triglycerides, and transferrin saturation levels.	Findings showed two markers of lipid peroxidation, plasma MDA and Iso-P, to be useful as markers of oxidative stress. It is suggested that both markers have potential value for future epidemiologic studies.
8	Moritz et al., 2003 (49)	Experimental study; determination of CAT, SOD, MDA and $O_2^{-\bullet}$ in rats.	The results showed cocaine administration induces early NADPH-driven $O_2^{-\bullet}$ release, which may play an important role in the development and progression of the left ventricular dysfunction observed after chronic cocaine abuse.
9	Zhang et al., 2004 (35)	Experimental study; study of oxidative damage of biomolecules in mice treated with morphine intraperitoneally. Determination of the protein carbonyl and the activities of SOD, CAT, GPx and Vit.C levels. The activity of alanine aminotransferase was also assayed. Besides, all the indexes of oxidative damage, such as 8-OHdG, protein carbonyl group and MDA content, and activity of alanine aminotransferase were measured.	These results implied that morphine caused oxidative stress in mice livers and caused hepatotoxicity. Blocking oxidative damage may be a useful strategy for the development of a new therapy for opiate abuse.
10	Kumar et al., 2006 (53)	Experimental study; evaluation of the effects of long-term use of Aqueous Extract of Smokeless Tobacco (AEST) on the antioxidant defense status and histopathological changes in liver, lung and kidney of male Wistar rats. GSH and GPx, SOD, CAT, vitamins A, C, E and lipid peroxidation (Lpx) were determined.	Decrease in the antioxidant defense system and inflammation caused by smokeless tobacco may be risk factors for induced pathogenesis.
11	Pereska et al., 2007 (11)	Descriptive, cross-sectional study; evaluation of oxidative stress by measuring of ROS, MDA, TAC and MDA in heroin addicts. The extracellular antioxidant capacity was estimated using OXY-adsorbent test.	Long-term heroin abuse stimulates a progressive systemic oxidative stress, which increases the extracellular antioxidants consumption and develops conditions for chronic heroin toxicity.
12	Kovatsi et al., 2010 (4)	Case -control study. To determine Prooxidant-Antioxidant Balance (PAB) by the ELISA method in chronic heroin abusers. This study assessed the relationship between PAB value and the duration of abuse or the presence of anti-HCV antibodies.	In heroin abusers, oxidative balance was disrupted in favor of prooxidants. Chronic heroin abusers can benefit from an antioxidant therapy, and the method currently presented can be used as an identification criterion.
13	Obwegeser et al., 1999 (30)	Descriptive-analytical study; this study evaluated the influence of smoking on F2-isoprostanes, prostacyclin and nitric oxide in human umbilical vessels. Umbilical cords of smoking mothers and non-smoking mothers were tested. Cigarette smoking increased F2-isoprostane levels and reduced the generation of prostacyclin in umbilical arteries and veins.	It is recommended that smoking might increase the vasoconstrictory capability in umbilical arteries by improved F2-isoprostanes and by a decrease in the production of vasodilatory compounds, prostacyclin and nitric oxide.
14	Shrestha et al., 2012 (52)	Case-control study; determination of the biochemical parameters and non-enzymatic antioxidant status and the lipid peroxidation products in Pan Masala Tobacco (PMT) users and controls. Plasma levels of vitamin E, vitamin C, albumin, bilirubin, uric acid, glucose, urea, creatinine, aspartate AST, ALT and MDA were measured.	Pan masala tobacco users are at risk of oxidative stress. Non-enzymatic antioxidants are depleted with subsequent alteration in the biochemical parameters.
15	Soykut et al., 2013 (1)	Case-control study; this study investigated Cu, Zn-SOD, CAT, Se-GPx and MDA levels and the frequency of Micronuclei (MN) in addicts using heroin.	A significant decrease in Cu, Zn-SOD activity and increases in MDA levels and micronuclei frequency were observed in addicts. It was observed that opiates may cause oxidative stress and that antioxidant supplementation, in addition to pharmacological and psychiatric approaches, can reduce the toxicological effects of these opiates.
16	Moradi-Sardareh et al., 2014 (26)	Experimental study; All Syrian hamsters were sacrificed after 24 hours of the final treatment. Lipid profiles and liver enzymes Atherogenic Index (AI) and LDL-C were calculated. LDL-C to HDL-C SOD, CAT, GSH activity and MDA levels were also determined by standard methods.	The plasma concentration of MDA markedly increased in the opium ($P < 0.01$) group compared to healthy hamsters. SOD, GSH and catalase levels were also markedly reduced in opium ($P < 0.05$). In conclusion, oxidative stress is increased in opium-treated animals.
17	Cunha-Oliveira et al., 2015 (44)	This review focused on evidences for oxidative damage and depletion of antioxidants upon exposure to drugs of abuse, especially amphetamines, cocaine and opiates. The sources of oxidative stress induced by drugs of abuse was also studied.	It is suggested that changes in oxidative balance induced by drug of abuse may cause toxicity and behavioral changes associated with drug addiction.