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Understanding The Role Of Oxidants And Antioxidants In The Prevention And Mitigation Of Diseases: A Comprehensive Review

Dr. Amit Ashok Paliwal[1], Dr Vasudha Gajananrao Asutkar[2], Dr. (Mrs). Madhu Gupta[3], Dr. Surya Prakash Gupta[4*]

[1]M.S. (Shalyatantra) Ph D, Professor, Department of Shalyatantra, Dr. D. Y. Patil Vidyapeeth, Pune (Deemed to be University), Dr. D. Y. Patil College of Ayurved & Research Centre, Pimpri, Pune-411 018 Maharashtra, India
[2]M.D (Ayurved Siddhant) Ph D (Ayurved Siddhant), Assistant professor, Department of Samhita Siddhanta and Sanskrit, Bharati Vidyapeeth (Deemed to be University) College of Ayurved, Pune 411043 Maharashtra, India
[3]Assistant Professor, Rajiv Gandhi Institute of Pharmacy, Faculty Of Pharmaceutical Science & Technology, AKS University, Satna (MP)-India-485001
[4*]Professor & Director, Rajiv Gandhi Institute of Pharmacy, Faculty of Pharmaceutical Science& Technology, AKS University, Satna (MP)-India-485001

***Corresponding Author:** Dr. Amit Ashok Paliwal
*M.S. (Shalyatantra) Ph D, Professor, Department of Shalyatantra, Dr. D. Y. Patil Vidyapeeth, Pune (Deemed to be University), Dr. D. Y. Patil College of Ayurved & Research Centre, Pimpri, Pune-411 018 Maharashtra, India.
Email ID: amit.paliwal@bharatividyapeeth.edu

Abstract

Oxidative stress, a condition characterized by an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses, is implicated in the pathogenesis of various chronic diseases. This comprehensive review explores the intricate relationship between oxidants and antioxidants, emphasizing their roles in disease prevention and management. Oxidants, including free radicals and non-radical species, can induce cellular damage through lipid peroxidation, protein modification, and DNA damage. Conversely, antioxidants, both endogenous and exogenous, neutralize these harmful effects by scavenging ROS and enhancing the body's defense mechanisms. This review synthesizes current research on the biochemical mechanisms of oxidative stress, the impact of oxidative damage on cellular function, and the protective effects of antioxidants. Special attention is given to the role of dietary antioxidants and their therapeutic potential in conditions such as cardiovascular diseases, neurodegenerative disorders, diabetes, and cancer. By elucidating the dynamic balance between oxidants and antioxidants, this review highlights the importance of antioxidant strategies in disease prevention and underscores the need for further research to optimize their efficacy and safety in clinical applications.

keywords: Oxidants, Diseases, Antioxidants, Prevention

Introduction

In recent years, biomedical researchers have speculated extensively on the involvement of oxygen-derived free radicals in a wide range of disorders. There are more than a hundred illnesses that have been linked to "reactive oxygen species" or "oxy free radicals," including diabetes, liver ailments, arthritis, cancer, AIDS, and infertility. Most, if not all, human illnesses are associated with an increase in free radical production leading to tissue harm, given the breadth of these conditions.

According to Slater (1984), any species that can stand on its own and has an unpaired electron in its outermost orbital is considered a free radical. Their charge might be neutral, positively charged, or negatively charged. A free radical may couple with or simply add an electron to a non-radical molecule by stealing an electron from another molecule. A non-radical may acquire the properties of a radical by adding one electron to it, taking one electron from it, or exchanging electrons with another radical. Reactions between free radicals and non-radicals sometimes take the form of a domino effect, with one radical producing yet another (Sies, 1985). The human body is continually producing reactive oxygen species (ROS), including free radicals. While many of them have physiological uses, producing too much of them might have harmful effects. A tissue's DNA, lipids, proteins, and carbohydrates may be damaged by an excess of reactive oxygen species (ROS) production. Detoxification is necessary for maintaining a healthy physiological balance in the body.

Protective, preventative, interceptive, and reparative measures are all tools in the arsenal against the potentially dangerous reaction set off by reactive oxygen metabolites. Cellular defense against oxidative stress is provided by substances that may neutralize free radicals, sometimes known as anti-oxidants or free radical scavengers. The variety of free radicals is comparable to that of these antioxidants (Heffeneer and Repine, 1989).

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literature review

Wilking (2012) Numerous physiological systems rely on oxygen and circadian rhythmicity to maintain homeostasis, including blood pressure, sleep/wake cycles, and cellular signaling pathways that are important in both health and illness. Internal system regulation, such as redox levels and circadian rhythms, may be compromised when the human body or cells undergo substantial stress. Disruptions in redox regulation and circadian rhythms may have far-reaching consequences, impacting both cells and organisms. These disruptions can pave the way for the development of several illnesses, including cardiovascular disease, neurological disorders, and cancer. New developments: The significance of the many species of oxidative stress components and the fundamentals of the circadian rhythm mechanism have been clarified by researchers. There has been a lot of research on the impacts of oxidative stress and dysregulated circadian rhythms ever since they were found. More recently, researchers have begun to shed light on the molecular pathways that connect the two. Important matters: Although a lot is understood about the functioning and significance of circadian rhythms and oxidative stress systems, there has been less investigation into the interface between the two. This review delves into the concept that these two systems work hand in hand, both in a healthy body and when illness strikes. Going forward, we think that if we want to effectively treat disorders that involve both the circadian rhythm and oxidative stress, we need to attack both systems at once.

Fang (2020) Chronic subjective dizziness (CSD) develops slowly from psychological and physiological imbalance; it is a neurotologic illness characterized by persistent non-vertiginous vertigo. Exposure to complex visual stimuli, such as movements, may cause a hypersensitive response known as CSD. Nevertheless, much is still unknown about the pathophysiology and mechanism of CSD. This research aimed to use blood samples from CSD patients to identify potential endogenous causes of the disease. We surveyed 199 people and split them into two groups: those with no known health issues (n = 152, 61 male, and 91 female) and those with chronic stress disorder (n = 47, 5 male, and 42 female). The levels of oxidative stress parameters, including hydrogen peroxide and reactive substances, were noticeably higher in the CSD group compared to the healthy group ($p < 0.01$ or $p < 0.001$), while the endogenous antioxidant components, such as total glutathione contents and activities of catalase and superoxide dismutase, were noticeably lower. The CSD participants showed a substantially higher level of tumor necrosis factor -α and interferon-γ in their serum ($p < 0.001$). Serum levels of emotional stress chemicals such as cortisol, adrenaline, and serotonin were also found to be unusually high in the CSD group ($p < 0.01$ or $p < 0.001$). In order to define characteristics of the redox system in CSD participants compared to a healthy population, our data demonstrated that antioxidants and oxidative stress are key contributors to the pathophysiology of the CSD.

Martemucci (2022) Overproduction of free radicals and oxidants causes biomacromolecule damage in cases of unchecked oxidative stress. This includes lipids, proteins, carbs, and DNA. Here, we take a close look at free radicals, their primary characteristics, and the ways they contribute to oxidative stress and other diseases. Many chronic noncommunicable diseases (NCDs) in clinical practice include oxidative stress, including diabetes mellitus, cardiovascular disease, inflammation, neurodegenerative illness, and tumors. In theory, taking an antioxidant supplement may halt or delay the onset of several illnesses. However, a review of the relevant literature reveals that more research is required to determine if these supplements are more effective at preventing or reversing disease development when compared to reactive oxygen species.

Jiménez-Fernandez (2020) With the goal of learning more about antioxidants and oxidative stress indicators in BD. Methods: Research comparing BD and healthy controls (HCs) using antioxidant or oxidative stress indicators may be considered until 06/30/2019 in the following electronic databases: MEDLINE, PubMed, Cochrane Library, Scopus, and TripDatabase. Three or more studies were used to determine standardized mean differences (SMD) and 95% confidence intervals (CIs). The outcomes are: The following substances were reported in forty-four studies: total nitrites, glutathione (GSH), uric acid, zinc, and antioxidant-enhancing enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and GSH-transferase (GST). The number of individuals included in the studies ranged from three thousand seven hundred to fifteen hundred. When BD was compared to HCs, it was shown that BD was related with greater GST, CAT, nitrites, TBARS, MDA, uric acid, and lower GSH levels, but there were no changes in SOD, GPX, or zinc levels. The levels of TBARS ($P <.0001$) and uric acid ($P <.0001$) were greater in BD-mania than in HCs; levels of TBARS were higher in BD-depression ($P =.02$); and levels of uric acid were higher in BD-euthymia ($P =.03$). As compared to BD sadness ($P =.002$), BD mania was associated with greater urinary acid levels, whereas BD euthymia did not. Both BD-mania and BD-depression were characterized by the same TBARS. Higher SOD ($P =.02$) and decreased GPX ($P <.0001$) were seen in medication-free BD-mania patients compared to HCs. Following therapy, there was no difference in SOD and GPX levels between BD and HCs. Final thoughts: It seems that for BD in general and disease polarity in particular, a combination of many factors is more informative than a single oxidative stress biomarker. BD is linked to an unbalanced oxidative stress, which may be treated by targeting uric acid and TBARS, with potential advantages for SOD and GPX. To further understand the relationship between oxidative stress, antioxidants, and other confounding variables, future research should collect blood from many sources at once and evaluate both oxidative stress indicators and antioxidants.

Dusak (2017) Although free radicals contribute significantly to the onset of degenerative illnesses, the body's inherent defensive systems are able to limit the damage that these reactive species may do. Superoxide dismutase (SOD),

glutathione peroxidase (GSH-Px), malondialdehyde (MDA), and glutathione reductase (GSH) enzyme activity in colon cancer patients' blood serum samples were the intended subjects of this investigation. Subject and Procedure: In this retrospective analysis, 25 patients with colon cancer and 25 healthy persons who were age- and sex-matched served as the control group. We used spectrophotometry to examine the concentrations of SOD, GSH, GSH-Px, and MDA in the serum. The results showed that there was a statistically significant difference ($p<0.05$) in the levels of SOD, GSH, GSH-Px, and MDA enzymes when compared to the control group. While the levels of MDA were significantly higher ($p<0.05$) in the colon cancer patients compared to the control group, the levels of SOD, GSH, and GSH-Px were significantly lower ($p<0.05$). The levels of malondialdehyde (MDA) were noticeably greater in the colon cancer patients compared to the control group, whereas the activities of antioxidant enzymes such as SOD, GSH, and GSH-Px were noticeably lower in these patients ($p< 0.05$). Conclusions: This is the first research to imply a link between antioxidant measures, oxidative stress, and colon cancer. Additionally, no previous research has examined the correlation between oxidative stress and the activity of antioxidant enzymes including glutathione (GSH), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px). Serum levels of glutathione (GSH), glutathione peroxidase (GSH-Px), malondialdehyde (MDA), and superoxide dismutase (SOD) may influence the development of colon cancer.

Research methodology

The medical wards of Base Hospital Srikot, VCSG Govt. IMS, Srinagar, Garhwal, Santosh Medical College &Hospital, Ghaziabad, and RMRI & Hospital, Bareilly were visited by 164 patients with clinically and histopathologically proven alcoholic hepatitis as part of this inquiry. The patients' ages range from seventeen to sixty-five. Accepted clinical, biochemical, and histological criteria were used to establish a diagnosis of alcoholism in patients after four days of hospital acclimatisation (Sherlocks and Dooley, 1997).

In heparin-containing vials rinsed with double distilled water, 5 ml of blood was collected from each participant at6, 12, 18, and 00 hours for the course of a full 24 hours. Plain vials were used to collect an additional three millilitres of blood. The samples were stored at -20 0 c until analysis, after which plasma and serum were separated. In hemolysate, the activities of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GR) were measured using the methods outlined in Aebi (1974), McCord and Fridovich (1969), pagila and Valentine (1967), and Hazelton and Lang (1985), respectively. According to Ohkawa et al. (1979) and Netalson (1971), plasma levels of malonaldehyde (MDA) and total antioxidant status were assessed.

The institutional ethics committees of santosh medical college & hospital in Ghaziabad and VCSGGIMS&R in Srinagar, Garhwal, Uttarakhand gave their stamp of approval to this research. The institutional and/or national research committee's ethical requirements, as well as the

1964 Declaration of Helsinki and its subsequent revisions or equivalent ethical standards, were followed in all studies involving human subjects.

Data analysis

According to one-way ANOVA ($P<0.001$), the average plasma MDA concentration in healthy volunteers peaked at 18:00 (with a mean of 2.83 nmol/ml plasma) and fell to a statistically significant low at 06:00. In healthy Indians, consinor rhythmometry demonstrated a statistically significant circadian rhythm in lipid peroxide levels ($P<0.001$), with an acrophase occurring at around 16.21. There was also a statistically significant ($P<0.05$) variance in MDA concentration across individuals within the 24 hour series included in this investigation. By contrast, lipid peroxide levels were 3.36 (n mole MDA/ml plasma) at 12:00 and 2.53 (n mole MDA/ml plasma) at 00:00, in contrast to healthy participants. There were substantial differences ($P<0.01$) at various collection hours throughout a 24-hour cycle. There is a clear circadian rhythm in the plasma MDA levels of alcoholic hepatitis patients, with a notable amplitude and acrophase around 13:21 ($F=35.19$; $P< 0.01$), as confirmed by cosinor rhythmometry in terms of MESOR (2.90±0.03), amplitude (0.43 n mole/ml plasma; 95% CI:0.31-0.56), and acrophase (-2000 from local midnight, with 3600 =24 hours; 95% CI: -1840 to -2170). Patients with alcoholic hepatitis have a 450-or 3-hour-earlier acrophase compared to healthy controls.

In healthy individuals, the maximum SOD activity, which was measured at 21.32 (Units/ml RBCs), dropped significantly over the day, hitting a low point at 18:00. The differences at various collection times during a 24-hour period were statistically significant ($P<0.001$). Additionally, there was a difference in mean SOD activity among healthy persons ($P<0.05$). A strong diurnal rhythm in SOD activity was verified by consignor analysis in healthy Indians, with an amplitude and acrophase at 07:22 ($P<0.001$). Additionally, SOD activity varied among healthy subjects from one person to another ($P<0.05$). Patients with alcoholic hepatitis had their SOD activity measured at its highest at 06:00 and then steadily decreased over the next 24 hours, reaching a low point at 00:00. The differences between the sample hours were statistically significant ($P<0.01$). Significant variability among individual individuals were also shown by ANOVA ($P<0.05$). According to consinor rhythmometry, there is a noticeable fluctuation in SOD activity in alcoholic hepatitis patients with a substantial amplitude and acrophase at around 08:05 ($P<0.01$), as measured by MESOR (16.05±0.09), amplitude (1.09; 95% CI:0.74 to 1.45) and acrophase (-1210; 95% CI:-990 to -1410).

At 6:00 in the morning, the mean CAT activity was 15.81 U/ml RBCs. Which dropped regularly at 18:00 in healthy participants. There were substantial fluctuations ($P<0.001$) at various sample hours throughout a 24-hour cycle. A

substantial regularity in CAT activity was established in healthy volunteers using population mean consignor analysis in terms of MESOR, amplitude, and acrophase, with a peak at 08:04 (P<0.001) for both variables. In alcoholic hepatitis patients, the peak CAT activity was at 06:00, with a mean of 12:19 (Unit/ml RBCs). From there, it steadily fell during the balance of the 24-hour cycle, reaching a minimum at 00:00. These changes were statistically significant at various collection times (P<0.01). As compared to healthy volunteers, there was significant heterogeneity in CAT activity across individuals among patients (P<0.05).

statistically significant difference from zero was seen in the amplitude (0.84 Units/ml RBCs; 95% CI: 0.53 -1.16). The acrophase occurred at 08.36 in patients with alcoholic hepatitis, showing a substantial circadian regularity in CAT activity under these circumstances (P=0.01). At all sample hours, the activity remained lower in alcoholic hepatitis patients compared to healthy people, indicating a drop in CAT activity.

In healthy participants, the mean GPx activity peaked at 18:00 (n mole NADH oxidized/min/mg protein) and then dropped dramatically at 00:00. GPx activity varied significantly between collecting hours, according to ANOVA. Cosinor rhythmometry verified that healthy Indians' GPx activity routinely varies throughout the day, with a notable amplitude and acrophase around 16:15 (P<0.001). Similarly, GPx activity peaked at 18:00 and dipped to a low at 00:00 in alcoholic hepatitis patients, but it remained lower than in healthy people during the whole sampling period. The differences at various collection times during a 24-hour period were statistically significant (P<0.01). In addition, patient-to-patient variation in GPx activity was also statistically significant (P<0.05). The circadian rhythm in the GPx activity of alcoholic hepatitis patients was confirmed by cosinor rhythmometery in terms of MESOR (2.88±0.03 n mole NADH oxidized/min/mg protein), amplitude (0.46; 95% CI:0.34-0.59), and acrophase (-2410 from local midnight, with 3600 = 24 hour; 95%CI; - 2250). The amplitude was significantly different from zero, and the acrophase occurred around 16:07 (P<0.01).

In healthy individuals, the GR activity peaked at 06:00 with an average of 5.97 (n mole NADH oxidized/min/mg protein) and fell to its lowest at 00.00. This difference was found to be statistically significant using one-way ANOVA (P<0.01) and ccosinor rhythmometery, which confirmed the existence of a circadian rhythm of GR activity in healthy Indians (P<0.01) with an acrophase at approximately 08:13. In addition, healthy participants showed inter-individual differences (P<0.05). Just like the healthy participants, alcoholic hepatitis patients showed the highest GR activity at 06:00 and the lowest at 00:00. At various sample hours, there were substantial fluctuations in GR activity, as shown by ANOVA (P<0.001). As compared to healthy subjects, those with alcoholic hepatitis showed reduced activity throughout all sample hours. A significant rhythm in GR activity was observed in alcoholic hepatitis patients using cosinor rhythmometry in terms of MESOR, amplitude, and acrophase at 09:39 (P<0.01). In contrast, there was a large difference in MESOR (2.22) and circadian amplitude (0.33) between the patients and normals, with the acrophase delayed by 21.0 minutes, or approximately 1 hour and 26 minutes.

In healthy individuals, the mean total antioxidant status (TAS) was found to be at its highest around 18:00 and lowest at 06:00. There was a statistically significant difference between the hours of sampling for these variables (P<0.001). Additionally, single-cosinor analysis demonstrated that healthy Indians had a steady rhythm with a notable amplitude and acrophase at around 16:67 (P= 0.001). The Total Antioxidant Status (TAS) concentration in alcoholic hepatitis patients was lowest at 00.00 mmol/l and highest at 12:00, with a mean value of 1.00 mmol/l. The statistical significance of these variations was confirmed by cosinor rhythmometry and one-way ANOVA (P<0.01). These methods showed that alcoholic hepatitis patients compared to healthy subjects had a significantly different circadian rhythm, with increased MESOR and an advanced acrophase (by 280). The acrophase, with an amplitude that was statistically significant (P=0.001), was detected at around 14:12.

Table- 1. Mean of Catalase Control versus Alcoholic patients in different time intervals.

S. No.	Sample	6.00 (hrs)	12.00 (hrs)	18.00 (hrs)	00.00 (hrs)
1.	Control	15.81	15.05	13.63	13.73
2.	Alcoholic Patients	12.75	12.18	11.49	10.47

Table- 2. Mean of SOD Control versus Alcoholic patients in different time intervals

S. No.	Sample	6.00 (hrs)	12.00 (hrs)	18.00 (hrs)	00.00 (hrs)
1.	Control	21.32	20.43	18.64	19.42
2.	Alcoholic Patients	16.66	15.71	15.91	15.31

Table- 3. Mean of MDA Control versus Alcoholic patients in different time intervals.

S. No.	Sample	6.00 (hrs)	12.00 (hrs)	18.00 (hrs)	00.00 (hrs)
1.	Control	1.91	2.40	2.83	1.98
2.	Alcoholic Patients	1.98	3.97	2.87	2.98

Table- 4. Mean of glutathione peroxidase Control versus Alcoholic patients in different time intervals.

S. No.	Sample	6.00 (hrs)	12.00 (hrs)	18.00 (hrs)	00.00 (hrs)
1.	Control	3.67	4.27	4.99	3.62
2.	Alcoholic Patients	3.12	3.02	3.29	3.52

Table- 5. Mean of glutathione Reductase Control versus Alcoholic patients in different time intervals.

S. No.	Sample	6.00 (hrs)	12.00 (hrs)	18.00 (hrs)	00.00 (hrs)
1.	Control	6.02	5.53	4.58	4.01
2.	Alcoholic Patients	5.51	5.02	4.07	3.49

Table- 6. Mean of TAS Control versus Alcoholic patients in different time intervals.

S. No.		6.00 (hrs)	12.00 (hrs)	18.00 (hrs)	00.00 (hrs)
1.	Control	1.9	2.0	1.8	1.6
2.	Alcoholic Patients	1.4	1.5	1.7	1.3

Table-7 One way ANOVA and single cosinor analysis of mean catalase (Units/ml RBCs) activity in normal and alcoholic hepatitis patients.

Source of variation	Normals Among circadian stages	Normals Among normals	Alcoholic hepatitis patients Among circadian stages	Alcoholic hepatitis patients Among patients
Degree of freedom (DF)	03	59	03	49
Sum of squares (SS)	201.20	39.19	57.90	60.28
Mean Squares (MS)	67.00	0.63	19.30	2.07
F	154.96	1.45	48.11	5.18
P	<0.001	>0.05	<0.01	<0.05

At the sampling time of 06:00, 12:00, 18:00 and 00:00; the mean catalase activity was 15.81, 15.05, 13.63, 13.73 in healthy participants and 12.75, 12.18, 11.49 and 10.47 respectively in alcoholic hepatitis patients.

Single Cosinor Analysis

Variable	No.	MESOR± SE	Double amplitude	Acrophase Degree	Acrophase Time	F(nDF)	P value
Normals	82	14.55±0.04	2.54	-121.21	08:04	172.96(2,60)	<0.001
Alcoholic hepatitis patients	164	11.18±0.08	1.68	-129.20	08:36	24.59(2,50)	<0.01

POPULATION –MEAN COSINER

GROUP	P	N	MESOR±SE	AMPLITUDE	ACROPHASE(Ø)*
Normal (N)	0.001	82	14.55±0.04	1.72(1.54 1.89)	-121^0 (-115^0 -128^0)
Patients (P)	0.01	164	11.18±0.08	0.84(0.53 1.16)	-121^0 (-106^0 -150^0)

Conclusion

The current findings provide light on the role of free radicals in patients with liver cirrhosis, and understanding their circadian nature might be crucial for clinical evaluation of disease progression and improved therapy. Nevertheless, additional research is required to establish a connection between lipid peroxide levels, free radical scavengers, the type, status, and rhythm following the administration of recognised dietary and therapeutic antioxidants in these pathological conditions. This will lead to new insights into the disease's aetiology.

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