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## **Nutrition and addiction - are they linked in de-addictive process? A review**

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**Abstract**---Background: Substance abuse has become a serious issue that is faced by the world. The effects of drug abuse can be detrimental to corporeal, psychological and societal well-being of a person. Drug misuse is actually unrestrained habit of drugs leading to inspiration of reward-system in brain Substance abuse also influences the food preferences and dietary habits of the users, therefore affecting the person's nutrition. Instead of how frequently a person engages in the behavior, substance abuse and substance addiction are distinguished by how challenging it is for the person to manage without the behavior or quit it for a specific period of time. Methodology: Electronic databases were used to conduct a thorough, systematic analysis of research, which was restricted to those with

English/English abstracts and used words like "addiction," "nutrition," "lifestyle," "alcohol," "reward system," "recreational substances," etc., Conclusion: An effort has been made in this research article to highlight the effects of various addictive substances on different systems in human body with the role of adequate nutrition to fight back this addiction for the overall betterment of the society.

**Keywords**---addiction, lifestyle, nutrition, reward system, recreational substances.

## **Introduction**

Substance abuse has become a serious issue that is faced by the world. The effects of drug abuse can be detrimental to corporeal, psychological and societal well-being of a person. Drug misuse is actually unrestrained habit of drugs leading to inspiration of reward-system in brain. This organization is normally activated by adaptive behaviors. However, these drugs can directly activate the reward system, bypassing the normal physiological pathways and thereby creating a feeling of pleasure which leads to the person neglecting his /her normal routine activities. Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition has expanded substance addiction's delineation to encompass 10 distinct drug categories, comprising of alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics, and anxiolytics, stimulants, tobacco, etc., (Silvestro et al.,) About five percent of the global populace is said to be involved in consumption drugs at least one time in a day and close 0.6 percent agonize from spartan drug habit malady. Opiates are considered the most harmful and Cannabis is the maximum recurrently used drug (Anywar et al., 2022). Drug use can lead to an widespread array of adverse reactions affecting the physiology of the human body. It leads to augmented hazard of infections (Spronk et al., 2013), other medical disorders including stroke, cancer, mental disorders and systemic illnesses involving the lungs, liver and cardiovascular system (Volkow et al., 2011). Substance abuse usually leads to dys-regulation of hormones leading to altered satiety. Also, due to the cravings, users tend to devote their dough on drugs rather than on nutritive eatables (Mahtoub et al.,). Studies show that opium addiction is a peril for cardiovascular diseases (Masoomi et al., 2015) and also a self-determining jeopardy for Coronary artery disease/CAD (Masoomi et al., 2010). Substance abuse also influences the food preferences and dietary habits of the users, therefore affecting the person's nutrition. It leads to decrease in the consumption of food, absorption of nutrients and altered metabolism. As a result, this population maybe vulnerable to malnutrition. Rendering to DSM-5, alcohol abuse and alcohol dependence comes is included in the term alcohol use disorder/AUD. Alcohol abuse is the excessive consumption of alcohol that may cause damage to well-being, aptitude to exertion and decree. Uncontrolled alcohol consumption often leads to an extensive assortment of harmful possessions that includes liver cirrhosis, pancreatitis, impaired fertility, decreased immunity (NIH Guide protocol) and electrolyte and acid-base ailments like hypomagnesaemia, alkalosis (Knochel, 1988). Furthermore, like other drug addicts, alcoholics tend to skip meals and eat less

frequently. This leads to alcohol being the prime source of energy in alcoholics (Guilland et al., 1994). In tallying, consuming excess alcohol can hamper digestion and absorption of nutrients (Odeleye and Watson, 1992). This causes a decline in the energy derived from the meal, thereby decreasing dietetic value of food disbursed. Therefore, alcohol drinking has venomous consequences on nutritional status including health of the individual (Hillers and Massey, 1985).

## Methodology

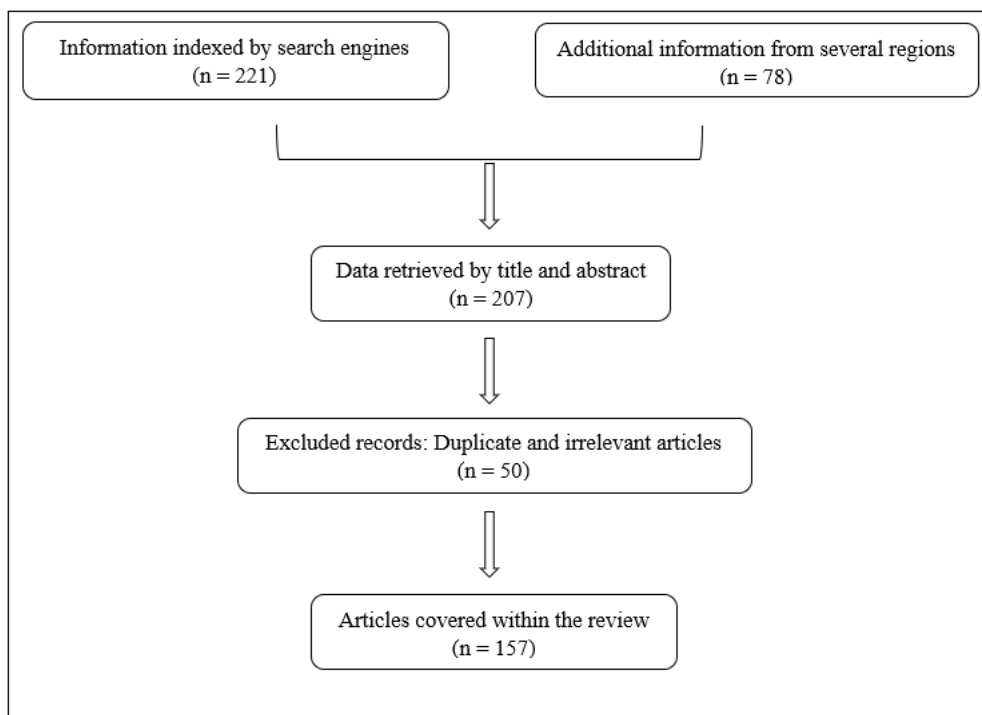


Fig I. Intangible Outline: Quest Stratagem

## Neuropeptides in addiction: A discernment

### Ghrelin

#### An overview

The 28-amino-acid peptide known as ghrelin is primarily formed and stored by gut including a number of auxiliary structures. However, some brain regions may produce some of these substances. The initial understanding of ghrelin's function in the hypothalamo-pituitary growth axis was that it encouraged growth hormone release. Consequently, substantial research has been done on the physiological roles of circulating ghrelin for food intake and appetite in rodents and humans. Moreover, ghrelin regulates when meals begin, and in healthy individuals, higher ghrelin levels are linked to greater feelings of hunger. According to studies revealing that ghrelin promotes adiposity through a process involving impaired fat consumption, ghrelin receptors, or growth hormone secretagogue receptor (GHS-

R1A), may be pharmacological boards for treating corpulence. It was later discovered that ghrelin's effects on fat storage, consumption of food, and basal metabolism were also dependent on the hypothalamic GHS-R1A receptors, despite the fact that these receptors were initially thought as, only imperative for ghrelin's ability to stimulate the production of growth hormone. It's intriguing that a lot of other physiological processes have recently been attributed to ghrelin and its receptor. Thus, among rodents, this hormone controls blood sugar levels, promotes prolactin secretion, affects sleep, operates on the cardiovascular system, and promotes gastric motility. Additionally, ghrelin enhances behavior similar to anxiety and depression in rats and affects memory formation via hippocampus GHS-R1A (Galharda, 2015).

### **The Cholinergic-Dopaminergic reward connection activation by ghrelin**

A key element of the brain's reward systems is the cholinergic-dopaminergic reward connection. The aforementioned comprises of cholinergic afferent projection onto VTA dopamine cells from laterodorsal tegmental region (LDTg) (NAc). It contains - Nucleus accumbens-to-ventral tegmental area (VTA) dopaminergic pathway of mesolimbic dopamine system. This recompense relationship is directly tied to the addictive drugs' capacity for reinforcement and natural rewards. Ghrelin may increase the salience of rewards for motivated activities since studies have demonstrated that it triggers the cholinergic-dopaminergic reward connection. According to studies, giving mice ghrelin intravenously accelerated their movement and increased accumbal dopamine release. Additional research proved that dopamine is released in the nucleus accumbens and movement is stimulated by local ghrelin injection into the VTA or LDTg. Furthermore, local ghrelin delivery into VTA raises dopamine NAc takings in animals. Given that GHS-R1A receptors are present on cholinergic cells in LDTg and dopaminergic neurons in the VTA, ghrelin can galvanise reward systems through local processes in VTA and LDTg. After peripheral or intra-LDTg ghrelin injection, discharge of the neurotransmitters acetylcholine and dopamine is gridlocked by the administration of GHS-R1A antagonist. Although ghrelin is mainly produced in the gastrointestinal system, it's likely that some circulating ghrelin can pass across the blood-brain barrier and enter the brain's reward centres. Peripheral ghrelin has been shown in studies to promote food intake and stimulate the mesolimbic dopamine pathway. A GHS-R1A antagonist can be infused into VTA to counteract these effects. Imaging evidence demonstrates that ghrelin treatment in rats stimulates a network comprising the lateral hypothalamus, NAc, and VTA in a focused manner. According to certain studies, the VTA expresses nicotinic acetylcholine receptor subtypes ( $\alpha 3$   $\beta 2$ ,  $\beta 3$  and  $\alpha 6$ ). After receiving antagonists for these receptor subtypes, heavy drinkers consume less alcohol. The results are consistent with the theory that ghrelin cannot activate cholinergic-dopaminergic reward link in VTA by increasing accumbal dopamine due to an unselective nicotinic acetylcholine receptor antagonist. Other neurotransmitters might be important for ghrelin-induced pleasure because they modulate activity of mesolimbic dopaminergic neurons. According to studies, an NMDA receptor antagonist, but not an orexin or an opioid receptor antagonist, can inhibit ghrelin's ability to promote locomotion and escalates accumbal dopamine discharge in mice. The ghrelin-induced rise in food reward is regulated in mice by NPY Y1 and opioid receptors. These conclusions demonstrate the fact

that ghrelin makes rodents and humans more prone to seek out fresh experiences. Ghrelin signalling may have an impact on rewarding and motivational qualities of addictive medications and behaviour because mesolimbic dopamine pathway raises incentive salience of motivated activities (Jerlhag et al., 2007).

### **Ghrelin Signaling and Alcohol addiction** (Leggio, 2010; Jerlhag et al., 2009)

Studies have shown that the same neurobiological mechanisms control the rewarding effects of food and drugs. Additionally, it implies that a lack of food enhances drug reinforcement. Studies also show that alcohol use disorder and compulsive overeating are frequently co-morbid in humans. Ghrelin and its receptor are crucial gut-brain hormone for addiction, and ghrelin signaling controls alcohol intake. According to studies, mice's consumption of alcohol is decreased when GHS-R1A antagonists (JMV2959 or BIM28163, respectively) are administered peripherally or centrally. Systemic administration of JMV2959 lowers alcohol intake, and this impact becomes stronger over time, in rats that had been voluntarily ingesting alcohol for two, five, and ten months. Without causing tolerance or a rebound rise in consumption once therapy is over, JMV2959 steadily reduces alcohol consumption. Additionally, it blocks the alcohol deprivation effect, which in rats mimics rebound drinking and lessens the desire to drink. In addition to alcohol consumption, it has been shown that alcohol reward is regulated when GHS-R1A activity is inhibited with a receptor antagonist, as determined by locomotor stimulation, conditioned place preference, and accumbal dopamine release in mice. Additionally, studies have shown that giving ghrelin to 3<sup>rd</sup> ventricle, VTA, or the LDTg causes an increase in rats' alcohol consumption. Data demonstrates that compared to wild-type mice, ghrelin knockout animals display reduced alcohol-induced locomotor stimulation and dopamine release in NAc. In mice who have consumed alcohol freely for only three days, peripheral ghrelin treatment barely affects alcohol intake, suggesting that ghrelin signalling is more important in rats exposed to alcohol for longer periods of time than for shorter ones. According to recent studies, circulating ghrelin in the plasma does not regulate alcohol consumption or the pleasurable effects of alcohol. Spiegelmer NOX-B11-2 (anti-ghrelin) does not reduce alcohol-induced reward in mice or alcohol consumption in rats, but it binds and neutralises active (i.e., acylated) ghrelin with high affinity in the peripheral nervous system and blocks its entrance to the brain. Contrarily, NOX-B11-2 reduced the amount of food that rats ate, indicating that circulating ghrelin regulates hunger physiologically. It's plausible that circulating ghrelin has a function in desire rather than reward given that plasma ghrelin levels are associated with alcohol craving. Previous studies have demonstrated that the cholinergic-dopaminergic reward link is necessary for ghrelin signalling to control alcohol-mediated responses, and GHS-R1A transcription in the VTA is dysregulated in mice who drink more liquor. Additionally required for ghrelin-mediated food intake is the hypothalamus GHS-R1A. It is known that GHS-R1A, through its constitutive activity and ability to heterodimerize with dopamine D1- and D2-like receptors, influences the sensitivity of the mesolimbic dopamine system. lateral ventral By hindering the ability of addictive medications to activate the mesolimbic dopamine system via such mechanisms, GHS-R1A may be involved in reward processes and the development of alcohol use disorder. The ability of GHS-R1A to regulate

reward may also be mediated by other systems or locations. It has been discovered that the mesolimbic dopamine system, including the amygdala, expresses GHS-R1A. Ghrelin modifies GABAergic transmission in the rat amygdala by raising inhibitory postsynaptic potential amplitudes in both alcohol-dependent and alcohol-naive animals. Acute alcohol infusion in several animal experiments prevents the ghrelin-induced increase in GABAergic transmission. Contrarily, in naive but not in alcohol-dependent mice, repeated alcohol infusion increased the inhibitory postsynaptic potential brought on by ghrelin. The amygdala's GHS-1b R1A was found to facilitate GABAergic transmission when GHS-R1A antagonists were administered. Additionally, studies have shown that acute central ghrelin injection enhances serotonergic turnover and the expression of serotonin receptors in the amygdala in rats, suggesting that ghrelin signalling inside the amygdala may regulate anxiety-like behaviours. It was discovered that GHS-R1A antagonists improved GABA-ergic transmission in the amygdala. Acute central ghrelin injection enhanced serotonergic turnover and serotonin receptor expression in the amygdala in rats, suggesting that ghrelin signalling inside the amygdala may control anxiety-like behaviours, according to supplementary research. Alcohol is calorie-rich rather than satisfying, therefore the orexigenic peptide might make people drink less. This seems less likely given that JMV2959, a GHS-R1A antagonist, suppresses locomotor stimulation and conditioned place preference, decreases reward from other addictive substances with no calorie content, and decreases ingestion of saccharine, a reward with no calories. Studies demonstrating variations in plasma ghrelin levels in alcohol-dependent patients demonstrate a role for ghrelin signalling in alcohol-mediated behaviour. The immediate oral alcohol effect on ghrelin production in healthy individuals was first proven. Acute oral alcohol consumption reduces ghrelin, which is interestingly unaffected by the gastroprotective sucralfate, indicating that ghrelin is not a mediator of alcohol's propensity to stimulate hunger. Ghrelin production is consistent with lower ghrelin levels caused by vigorous drinking related to alcohol dependence. Rats who favour drinking heavily have lower plasma levels of ghrelin than those who favour drinking lightly. On the other hand, several research contend that rats that favoured high or low alcohol intake did not exhibit any differences in ghrelin levels. It is clear that ghrelin may boost the motivating power of motivated behaviours because of the association between increased ghrelin levels and desire levels in people with alcohol use disorders. Early abstinence is linked to a large rise in plasma active ghrelin levels, which corresponds favourably with alcoholic desires. Exogenous ghrelin administered intravenously enhances alcohol demand in heavy drinkers, according to recent findings. A single nucleotide polymorphism in the GHS-R1A gene has also been linked to high alcohol consumption in humans, according to studies on human genetics. Both type II alcohol dependence and paternal alcohol dependence have been associated with the preproghrelin and GHS-R1A gene haplotypes. Additionally, alterations in self-transcendence and reduced self-directedness, two critical psychological traits of alcoholics, are associated with polymorphisms in the ghrelin signalling pathway.

### **Drug Dependence and Ghrelin Signaling** (Panagopoulos and Ralevski, 2014)

Numerous studies indicate that ghrelin signaling is crucial for reward in general. Administration of peripheral ghrelin to rats increases their conditioned place

preference for cocaine and the locomotor stimulation brought on by cocaine. Increased ghrelin levels positively correlate with elevated rat cocaine-seeking behaviour. The rewarding effects of cocaine and amphetamine are reduced in terms of locomotor stimulation, accumbal dopamine release, and conditioned place preference when JMV2959 suppresses GHS-R1A. Food restriction raises ghrelin levels, which in turn triggers amphetamine and cocaine to generate increased hyperlocomotion, increasing the likelihood that rats will seek out cocaine. Additionally, JMV2959 reduces nicotine's rewarding effects and stops nicotine from causing locomotor sensitization in rodents. A single nucleotide polymorphism in the GHS-R1A gene has been linked to both amphetamine dependence and smoking in humans. Ghrelin and its receptor may contribute significantly to the addictive drug's reinforcing characteristics when taken as a whole.

### **Glucagon-Like Peptide 1 (GLP-1)**

#### **GLP-1: Its role in the nervous system**

GLP-1 is produced in intestinal L cells and hindbrain in response to nutrient uptake. Evidence indicates that administration of GLP-1 in humans and rodents reduces their food intake. This incretin peptide also controls glucagon, gastric emptying, and glucose-dependent insulin secretion. Studies have demonstrated that GLP-1 receptors in the brainstem and hypothalamus were necessary for the hormone's anorexigenic and glucoregulatory actions (Gallwitz, 2012). GLP-1 has functions other than regulating glucose and food intake, and that these functions likely include reward control. GLP-1 receptors are found throughout the mesolimbic system and that neurons expressing GLP-1 directly project to the VTA and NAc.

#### **GLP-1 in Patho-physiology of Addiction** (Klavnsen et al., 2022)

To date, there are some initial reports implicating the GLP-1 receptor in the regulation of reward. Exendin-4, a GLP-1 analogue, was used to treat mice, and it reduced the rewarding effects of alcohol as indicated by locomotor stimulation and cumulative dopamine release. This study also showed that exendin-4 therapy, both acute and chronic, in mice decreased conditioned place preferences, which represent rewards for alcohol. Reduced alcohol intake was achieved using a 20% alcohol, two-bottle, intermittent access approach, and lowered alcohol-seeking behaviour using a progressive ratio test in an operant self-administration model. These new data suggest that the GLP-1 receptor may be a pharmacological target for treating alcoholism in humans. This finding suggests that exendin-4 injections into the peripheral or local VTA lower alcohol consumption and systemic injections lessen the conditioned place preference that alcohol causes in rodents.

Additionally, in both humans and rats, gastric bypass, lowers ghrelin and raises plasma GLP-1 levels, which in turn reduces alcohol consumption. GLP-1 receptors seem to be crucial for the reward from addictive drugs, in addition to alcohol. Exendin-4, in fact, reduce the locomotor stimulation caused by amphetamine and the conditioned place preference caused by cocaine in rodents. This is consistent with studies that found exendin-4 reduces the rewarding effects

of cocaine and amphetamine in rats. Exendin-4 also limits the nicotine-induced expression of locomotor sensitization in rats, and prevents nicotine reward. Exenatide and liraglutide, two GLP-1 analogues that have been authorised for the treatment of type II diabetes, may also be utilised to treat drug addiction. The chance that decreased alcohol consumption in addiction treatment is brought on more likely by nausea than by a lack of reward. To learn more about the function of her GLP-1 receptors in drug addiction, more research is required. For instance, it would be wise to look into how other GLP-1 analogues, including liraglutide and exenatide, affect alcohol reward, alcohol intake, relapse to alcohol use, and trigger relapse. Furthermore, it is yet unclear how alcohol and other drugs affect the GLP-1-scavenging enzyme dipeptidyl peptidase-4. It is important to look at how plasma GLP-1 levels relate to alcohol use disorders and cravings. Studies on human genetics are required to investigate the association between drinking and polymorphisms in genes associated to GLP-1.

### **Leptin**

The hormones leptin and ghrelin, as well as their "crosstalk," have been linked to the pathophysiology of alcoholism and both control drug and alcohol cravings. Very little is known about the neurobiological mechanisms underlying these effects. Therefore, how leptin and ghrelin affect alcoholic participants' brain reactions to alcohol, alcohol cravings, and risk of relapse, was studied (Hass et al., 2015). To measure their alcohol cravings, 70 abstinent alcoholics undertook a functional magnetic resonance imaging (fMRI) alcohol cue reactivity task. Before the fMRI session, the plasma concentrations of leptin, total, and acylated active ghrelin were assessed. Furthermore, during the three-month follow-up, recurrence data were gathered. We investigated the relationships between hormone levels, mesolimbic signaling reactivity, alcohol appetite, and the risk of relapse. Alcohol desire and striatal alcohol-induced brain responses were significantly negatively correlated with leptin levels. Furthermore, Leptin had a substantial impact on how long it took for a patient to experience their first major relapse; higher leptin levels predicted a longer time to recovery. Additionally, during the fMRI task, favourable correlations between acylated ghrelin and greater bilateral insula cue response and higher alcohol appetite were found. Alcohol craving and the responsiveness of mesolimbic signalling are both influenced differently by leptin and acylated ghrelin. We hypothesize that leptin's impact on relapse risk may be neurobiologically correlated with decreased striatal cue reactivity. The findings confirm the significance of appetite-regulating hormones in the pathophysiology of addiction and suggest that they may serve as viable targets for future treatments.

### **Other Appetite-Amendable Hormones and Drug Linked Actions**

Numerous other gut-brain hormones, in addition to ghrelin and GLP-1, which are often recognized to regulate food intake, have been proven to regulate responses to addictive substances. So, Leptin increases alcohol consumption and boosts motivation to drink during alcohol abstinence whereas inhibiting the leptin pathway decreases demand for alcohol. Early studies show that orexin receptor antagonists reduce alcohol self-administration, prevent resumption of alcoholism by olfactory and visual cues in rats those who preferred alcohol and attenuate

stress-induced resumption of alcoholism in Long-Evan rats. In rats, context-driven relapse to drinking is correlated with orexin neuron activation. Orexin's function in alcohol-induced reward, however, appears to be more complex, as previously stated (Walker and Lawrence, 2016). The central dose of orexin stops the desire for cocaine, morphine, and heroin. Plasma levels of the anorexigenic peptides leptin and orexin have been linked to nicotine craving in human studies. Both of these peptides can be administered to prevent psychostimulant reward. First, NPY-deficient mice consumed more alcohol compared to wild-type. Moreover, both naive and post-intoxicated animals' alcohol consumption is suppressed by NPY2 antagonists. Alcohol consumption is decreased after receiving a viral vector locally to overexpress NPY in the amygdala (Thorsell and Mathe, 2017). Additionally, NPY inhibits, yohimbine-induced resumption of alcoholism in rats. Adiponectin serum levels are significantly elevated in alcoholics on admission for alcohol detoxification and after 1-week withdrawal treatment. Additionally, this study demonstrated a substantial relationship between adiponectin and desires for alcohol. Cholecystokinin also limits rodent alcohol consumption. Data consistently show that selective cholecystokinin A receptor antagonists reduce alcohol consumption and specific cholecystokinin B receptor antagonists reduce cocaine intake in rats. Furthermore, galanin antagonists decrease alcohol intake in rats, while central administration of galanin, an orexigenic peptide, is increased

## **Effects of substance abuse on different organ systems: An overview**

### **Gut micro-biome and substance use disorder**

Lately, the association of gut microbiome with central nervous system is being explored with rising interest. Several studies have presented preliminary evidence for the view that gut microbiota and alcohol/substance use disorders are closely linked. A summary of available data, suggesting a possible role of substance use on gut microbiota and gut brain axis, and also the pathogenesis of substance abuse has been presented in this review. Gut microbiota is a pool of over 100 trillion microorganisms that reside in the gastrointestinal tract (Savage, 1977). Chronic alcohol consumption is associated with altered gut functions (Bode and Bode, 2003; Leggio et al., 2012). Alcohol use causes impairment of the intestinal barrier and brings about modifications in the intestinal permeability. Alcohol use also alters the gut microbiota composition. Studies in the near past that have aimed at understanding the influence of the gut-brain axis on substance use disorder, have revealed that, a bidirectional pathway of communication exists along the microbiome-gut-brain axis (Wang et al., 2020). Alongside modifying the gut microbiome, SUDs also cause its functional adaptations. Earlier reports have revealed the presence of substantial alterations of the intestinal micro-biome in subjects with various SUD. Long term opioid use caused significant dysbiosis of the gut micro-biome (Xu et al., 2017; Acharya, 2017). Acute-on-chronic intake of alcohol, modifies the gut micro-flora at various taxonomic levels along with producing loss of bacteria *Akkermansia*, indicating alcohol-induced gut dysbiosis. Following alcohol consumption, the gut microbes also influence inflammation and steatosis of liver and this points to the role, the gut-liver axis plays in producing early alcoholic liver disease. Alcohol-dependent (AD) individuals with active drinking, showed greater intestinal permeability (IP) along with enhanced plasma

concentrations of gut-derived microbial products like lipopolysaccharides and peptidoglycans (Leclercq et al., 2012; Leclercq et al., 2014; Parlesak et al., 2000). Chronic intake of alcohol can also bring about overgrowth of bacteria in the small intestine, produce mucosal damage of the large intestine, and cause consequent elevations in intestinal permeability (Keshavarzian et al., 2009). Another mechanism that influences intestinal microbiome profile in SUDs is the dietary differences. SUD can have intense impact on one's diets, and diet composition and nutritional status in turn can significantly alter gut microbiome composition (Sandhu et al., 2000). Evidences from recent preclinical research show that the gut microbiota influences the important neural pathways associated with alcohol/SUD and also with eating disorders (EDs) It also impacts behaviours connected to problematic alcohol drinking and eating (Temko et al., 2017). High fat is one among the dietary composition that has been reported to influence behaviors related to SUD. Pre-clinical research on this concept has shown that high fat diet (HFD) enhances cocaine dependence-like behavior. For example, researchers have reported an increase in behavioral patterns like cocaine seeking and self-administration as a result of regulated or binge-like feeding of HFD in adult male rats. Adolescent male rats exposed to HFD-binge intake showed enhanced cocaine self-administration during their adulthood. *ad libitum* consumption of HFD in adolescent rats through their adulthood markedly enhanced cocaine self-administration (Clasen et al., 2017). Offspring born of dams fed with HFD during gestation and lactation, were seen to have increased tendency for alcohol drinking during their adulthood whereas, adult rats fed with HFD on an intermittent schedule exhibited marked reduction in their alcohol intake (Sirohi et al., 2017; Villavasso et al., 2019; Puhl et al., 2011; Rodenas et al., 2021; Blanco and Rodriguez, 2017, Peleq et al., 2016). Studies have also revealed that, alcohol dependent subjects are characterized by low-grade intestinal inflammation and higher psychological symptomology. They showed markedly raised pro-inflammatory cytokines with enhanced depression, anxiety, and craving (Leclercq et al., 2012). These reports propose the likelihood of the altered gut microbiota composition in alcohol dependent subjects to be responsible for their behavioral symptoms (Leclercq et al., 2014). A study done investigated and reported the direct impact of gut microbiota manipulation on cocaine-related behaviors. Cocaine-reward and locomotive sensitivity was enhanced in mice, with antibiotic induced diminution of gut microbiota (Kiraly et al., 2016). Alterations in the gut microbiota initiates behavioral modifications in various models of SUDs. Recent investigations have started to explore the connection, gut microbiota has with immune signaling in pathogenesis of SUD. However, the literature available on this finding is insufficient (Hofford et al., 2019; Meckel and Kiraly, 2019).

### **Effects on the Brain**

All substances of abuse have potent influences on brain, a reason behind the elated or intensely pleasurable emotional experience of the individuals when they first consume alcohol or use other substances of abuse. These delightful emotional states is responsible for the repeat behavior that motivate them to consume such substances again and again, even with the knowledge about the potential risks involved. Over the past few years, study reports have strongly supported the concept that considers addiction as a disease of the brain (Volkow et al., 2016). Drugs of abuse, for example cocaine, nicotine, marijuana etc. seems

to influence the "reward" circuit, existing in the limbic system of the brain. These drugs affect this "reward" system, causing excessive quantities of the neurotransmitter dopamine to release into the system. This flood of dopamine is the cause for euphoria what is called as the "high", associated with drug abuse. Long-term substance abuse results in abnormal stimulation of dopaminergic neurons in these reward circuits (Koob and Le, 2001). Most of these psychoactive drugs abused by humans, and have shown to create this reward behavior in experimental animals, raise the level of dopamine in nucleus accumbens (NAc) shell (Solinasetal, 2007). These drugs have shown to activate central immune signaling, thereby enhancing the action of classical mesolimbic dopamine reward pathways (Coller and Hutchinson, 2012). Opioids have shown to alter this reward-processing neural circuits, primarily the mesocorticolimbic dopamine system. They also effect NAc via signalling at receptors like  $\mu$ - and  $\kappa$ -opioid receptors that are present at dopamine axon terminals, thereby controlling the release of dopamine (Vickers, 2017). Elevated dopaminergic activity in the VTA projections to NAc is supposed to play a common role for all drugs of abuse (Koob and Volkow, 2010). However, the dopaminergic system are only partially responsible for the behavioural impact of cannabinoids. Delta-9-tetrahydrocannabinol (THC) which is the main active component of cannabis (Gaoni and Mechoulam, 1964) causes stimulation of the dopamine neurotransmission. Cannabinoid CB1 agonists increases the burst firing of VTA dopaminergic neurons (Di et al., 2004; Koob, 2000; Gessa et al., 1998, French, 1997). Additionally, the concept of neuroinflammation being an important factor that contributes to brain dysfunction associated with addiction-like states is being considered. A dysregulated neuroimmune mechanism modifies the homeostasis and results in neuroinflammation, and this in turn appears to mediate brain pathology related to substance use disorders. It is now identified that, altered neuroimmune interactions in the brain leads to the development of SUD (Hafford et al., 2019). Drugs of abuse are known to produce relapse-like behaviours as well. Cocaine, reduces glutamate synaptic transporters (Moussawi et al., 2009) and this is believed to contribute to this behaviour (Scofield and kalivas, 2014). Another behavioural pattern associated with SUD is the self-administration behaviour. When THC was directly injected into the VTA or the nucleus accumbens of Sprague-Dawley rats, self-administration behaviour was demonstrated (Zangen et al., 2006). Similar result was seen THC was intravenously administered (Justinova et al., 2008). Irrespective of the mechanisms involved in causing addiction, relapse-like behaviours or self-administration behaviour studied through various clinical and pre-clinical studies, drug abuse does pose serious problems to brain and behavior. Such as: diminishing memory, weakening of intellectual abilities, loss of sensory and perceptual functions (Agarwal et al., 2008), decreased cognitive efficiency leading to decreased self-esteem specially affecting the adolescents and many other problems. This contributes to lack of an individuals' sense of identity, which possibly leads to enhanced tendency for substance abuse, thus creating a vicious circle (Hawkins et al., 1992; Eisentein et al., 2005). Thus, understanding the mechanisms underlying the substance abuse induced modifications in gut and brain, provides basis for effective therapeutic approach to help an individual get rid of SUD effectively.

**Substance abuse and substance addiction: Looks same but it does differ!!!**

Substance abuse is a threat to any Nation as it involves not only the person addicted to it but the society at large and in most instances leads to sufferings of her/his family as usually these people with a disturbed and confused lifestyle spend money on recreational drugs and give up spending on daily essential commodities including food (Mahboub et al., 2021). Substance abuse and substance addiction are distinct more so by the degree of difficulty an individual finds to cope up while discontinuing or stopping its use for a given duration, rather than how frequently a person engages in the activity. It is difficult to assess the quantity of a recreational drug required to causes dependence. It is expected to vary among individuals. It is possible for an individual to become dependent on marijuana without being addicted. The process of dependence and addiction take place in distinct regions of brain. However, dependence and addiction commonly develops simultaneously (Marijuana Abuse and Addiction). It is not uncommon to observe the nutritional status getting compromised, as substance abuse is known to greatly affect dietary habits compromising the food intake, eventually leading to under-nutrition. Other contributing factors for a drug user's nutritional status, is the kind of drug, frequency and duration of its use and prevalence of any infectious diseases (Escobar et al., 2018). Literature survey shows that individuals addicted to cocaine have irregular eating patterns as they depend primarily on a single late night meal which has unhealthy refined carbohydrates and fat alongside deficient in nutritious diet (Noble and Mc Combie, 1997; Ersche and Stochl, 2013; Billing and Ersche, 2015), Opiate addicted individuals consume meals high in sugar and alcohol that make up empty calories in place of protein rich meals (Jeynes and Gibson, 2017; Saeland et al., 2011; Stickel et al., 2011; Nolan and Scagnelli, 2007; Neale et al., 2012; Himmelgreen et al., 1998). Also, research have shown that short term use of opiates is associated with anorexia, reduced food intake and decreased gastrointestinal motility, all of which culminates in malnutrition combined with heightened risk of acquiring infectious diseases at latter stages (White, 2010). Heroin and cocaine users have reduced protein intake and lower energy than non-users (Myhre et al., 2015; Forrester et al., 2004). This reduction seems to progress as the drug use becomes more intense and prolonged (Escobar et al., 2018). Socioeconomic factors such as education and income also contributes to nutritional indices of the individuals who use drugs. This association parallels the well-documented fact that socioeconomic factors influence the nutritional status and self-reported homelessness in people who use drugs (Himmelgreen et al., 1998; Islam et al., 2002). Along with lower intake of nutrient-rich food in this group, the availability of important vitamins and minerals, is not up to the required dose (Tang et al., 2011) Hence, it can be summarized that the lack of nutritional balance (ratio of macronutrients to micronutrients), is occurring in drugs abusers, indicating that drug use results in intake of empty calories (Saeland et al., 2009).

Nutritional status is seen to be affected during the treatment phase of drug abusers. The nature of treatment given to the drug users like enrolment in detoxification program, staying at rehabilitation center or undergoing opioid substitution treatment could also affect their nutritional profile (Schroeder et al., 2017). At the initial period of detoxification, in which pharmacotherapy is provided, patients report reduced food intake due to nausea, anorexia, and

gastrointestinal disturbances (Forrester et al., 2005; Noble and McCombie, 1997). It is seen in scientific studies that, during the first six months of detoxification, patients prefer/ crave for table sugar and sweet foods. However, after 6 months, at the time of recovery, sugar cravings are replaced by intake of more structural food and improved appetite (Neale et al., 2012; Greenwell et al., 2003).

### **Nutrition and addiction: The deadly association**

#### **Effect of drug abuse on nutritional status: An insight**

Anthropometric measurements of malnutrition in drug users are typically not very severe, so testing serum nutrients, both macro and micro may demonstrate underlying inadequacies resulting from decreased nutrient intake. People who use drugs regularly generally lack essential nutrients. This population's low levels of selenium and potassium are a result of their lower muscle mass, which is brought on by starvation (Cowan et al., 2008). Iron deficiency and anemia, as well as low plasma levels of the vitamins A, C, D, and E, are common, especially among female drug users (Jeynes and Gibson, 2017; Diaz et al., 2004; Ross et al., 2012). The vitamin deficit is inversely related to the addictive dose and duration of usage. Additionally, the leading cause of these deficiencies is limited access to food. It is, therefore, necessary to think more deeply about the issue of vitamin and mineral supplementation in people who use drugs (PWUD) and during their rehabilitation (Hossain et al., 2007; Semba et al., 2002; Teixeira et al., 2011; Santolaria et al., 1995). Additionally, the plasma levels of several minerals are higher in drug users than in healthy people, a finding that cannot be attributed to a healthy diet but rather to PWUD-specific variables. Partial dehydration may be the cause of PWUD patients' elevated serum levels of phosphorus, salt, and magnesium (Jeynes and Gibson, 2017).

Short-term fasting and smoking raise copper and zinc serum levels, similar to inflammation (Quach et al., 2008; Jeynes and Gibson, 2017; Cowan and Devine, 2008). As a result of dopamine transporter inhibition, decreased serotonin reuptake, increased glucocorticoid synthesis, and increased expression of cocaine- and amphetamine-regulated genes, cocaine is hypothesized to suppress hunger and decrease food intake, which in turn reduces body weight (Diaz et al., 2004; Hossain et al., 2007). Compared to non-users, heroin addicts had lower BMIs and body weights. Drug administration frequency (>3 times per day) and route have an impact on this inverse connection. When smoked, heroin enters the brain more quickly than when injected, snorted, or eaten, which can have more potent reinforcing effects. By activating reward pathways, increasing the amount of dopamine receptors, squelching desire, and lowering body weight, it also engages in a mental competition with food. This mechanism may help to explain why heroin use has such a significant negative impact on body weight and BMI (Di et al., 2001; Kuhar, 2016; Mahboub et al., 2021; Volkow et al., 2007). After heroin and marijuana, methyl-amphetamine (MA), a psychostimulant, is now the second most commonly used drug. It is linked to malnutrition, neurological impairment, mood disorders, and cardiac and hepatic pathology. When compared to healthy people, MA users have a lower BMI. Cognitive impairment, aberrant metabolic activity, the length of MA use, and poor oral health that interferes with eating and chewing could all lead to lower BMI (Trimko et al., 2007; Volkow, 2006). Addicts to opium and MA had noticeably lower serum cholesterol levels

than non-users. But whereas heroin users' triglyceride levels were greater and their serum levels of high-density lipoprotein and cholesterol were noticeably lower, their triglyceride levels remained unchanged (Lv et al., 2016; Zhang et al., 2017). A decrease in serum lipid levels suggests starvation, which can lead to weight loss, especially if belly fat is lost, as well as liver disorders (Li et al., 2021). While some cocaine addicts did not relapse after detoxification, those with lower plasma cholesterol levels (160 mg/dL) did. These low cholesterol levels may suggest an increased susceptibility to developing behavioral and psychological disorders (Buydens and Brancheu, 2003). Animal studies have shown that morphine has a negative impact on blood glucose. An increase in hormones like cortisol, glucagon, adrenalin, and noradrenaline might explain the rise in blood glucose (Maccari et al., 1991; Lin et al., 2012). Morphine also causes hypoglycemia in healthy humans by decreasing the plasma counter-regulatory epinephrine response (Azod et al., 2008). Drug users have lower hemoglobin and hematocrit levels than non-users. The lowest hemoglobin and hematocrit levels are seen in multiple-drug users and those addicted for an extended period (Mahani et al., 2006). This finding was associated with under-nutrition and lower micronutrient intake, particularly iron (Carey et al., 2017). Drug-using women have lower hemoglobin and hematocrit levels when compared to men. The low hemoglobin and hematocrit might be a result of men being institutionalized for a more extended period than women, which is associated with better nutritional status (Islam et al., 2002; Escobar et al., 2018).

### **Nutritional derangements in Opiates abusers**

Opiates, including heroin, morphine, and other varieties, rank among the most widely used and effective treatments for treating chronic pain in clinical settings. However, using these compounds because of their rapid development and physical dependence has caused such persistent problems (Saeland et al., 2011). Addiction to opiates causes severe health issues, including a lower quality of life and a higher risk of developing cancer (Ross et al., 2012; Stockton and Devi, 2012; Challier et al., 2000). Despite the harmful impacts on health, opiate usage is nevertheless prevalent throughout the world, including in Southeast Asian countries. Usual methods of use include ingestion, smoking, and ingesting liquids (Torrens et al., 1999). The effects of opiates on the human central nervous system, including drowsiness, euphoria, mental blurring, mood swings, and loss of fine motor abilities, are well recognized (Virk et al., 2004). The neurotransmitter and neuropeptide systems in many brain circuits that regulate mood, behavior, and other processes are consequently impacted by chronic opiate use. All over the brain and spinal cord, opioid receptors are involved in a number of processes, including analgesia, species-regular behavior, and reward.

Research has shown three main classes of opioid receptors: kappa, delta, etc., however there are probably other types as well. Contrary to the notion that opioids occasionally activate G proteins, opioids typically act through calcium-dependent potassium channels without their participation (Suwanwela and Poshyachinda, 1986). Carbohydrates, fats, protein, vitamins, minerals, and water are the basic nutrients the body needs each day to grow and maintain normal bodily function. Studies show that despite having poor diets, many in recovery from opiate addiction are overweight and obese. The majority of opiate users

suffer from serious nutritional deficits in vital proteins, lipids, vitamins, and minerals, which interfere with their capacity to properly digest carbohydrates. Due to physical and metabolic changes brought on by drug usage, opiate addicts have nutritional deficiencies. Extreme nutritional inadequacies in drug users have been proven to produce weight loss and food pattern changes, according to studies on addiction disorders (Vainio et al., 2004; Dhawan, 1996). Changes in a certain nutrient status may result in obstacles to opiate addiction withdrawal (Lyle, 2006; Nabipour et al., 2014). Because of their environment, lack of food preparation skills, and nutritional knowledge, opiate addicts have unhealthy eating habits (Alves et al., 2011; Varela et al., 1997; Hauser and Iber, 1989). Numerous mechanisms have linked heroin use to problems with blood sugar. Heroin addicts had fasting insulin levels four times higher than control subjects. It also suggests that insulin resistance caused due to opioid use and beta cell dysfunction may go hand in hand. When fed intravenous glucose, heroin users had a 42% lower initial insulin response and an 80% lower rate of glucose elimination than control participants (Hatcher, 2004; Covan and Devine, 2008; Phillips and Lepiane, 1980; Westerink and Korf, 1976; Zancy et al., 2005). Researchers looked at the dietary and socio-demographic traits of heroin users during a detoxification programme. They discovered that these individuals consumed less fruit, vegetables, and grains than the minimum amount advised by the food pyramid, and they preferred sweets. Many studies supported these findings and suggested that heroin addicts eat foods low in vitamins (Zancy and Gu, 2003; Zancy and Lichtor, 2008). Patients undergoing treatment for opiate addiction need to eat even more protein and amino acids (Himmelgreen et al., 1998; Montazerifar et al., 2012). Proteins, important vitamins, and minerals including zinc, iron, calcium, chromium, magnesium, and potassium should be prescribed to recovering addicts throughout detoxification programmes. Zinc can support a healthy immune system and brain function (Usha et al., 2013). Calcium and magnesium shortages are the main causes of pain and nervous/muscular issues in alcoholics and addicts throughout detoxification treatments (Miller, 2010).

### **Nutritional derangements in Cocaine addicts**

Cocaine is a highly potent, habit-forming narcotic central nervous stimulant with a reputation for reducing appetite. It affects calorie intake and is linked to anorexia and eating disorders. Cocaine makes people more prone to restlessness, agitation, and stereotypic behavior. Frequent physical activity would make cocaine users require more energy. It is also seen that fidgeting increases an individual's need for energy, which may account for cocaine users' lower BMI (Nabipour et al., 2014). Even if they do not have any eating disorders, people with cocaine addictions frequently lose a significant amount of weight quickly (Payne et al., 2009). Numerous medical conditions, including mental and physical health issues, can be brought on by cocaine addiction, which includes eating disorders. In these situations, the eating disorder is developed due to consistent cocaine abuse affecting several areas of the brain, especially those that correspond with mood and behavior. When these areas are affected, a person not only becomes more likely to engage in addictive behavior but also to experience attitudes and behaviors that can contribute to developing an eating disorder. The short-term side effect of cocaine abuse usually includes loss of appetite, whereas the long-

term side effects can vary based on how the drug was ingested, but in any form of consumption, long-term cocaine abuse often leads to malnourishment and a weaker immune system (Uong et al., 2022).

### **Nutritional derangements in Alcoholics**

Alcohol hinders with protein breakdown, which leads to medical concerns, together with stumpy albumin levels, augmented fluid in abdomen, abridged blood coagulation with reduced urea fabrication (ensuing in unwarranted ammonia levels), which may upsurge the probability of transformed brain task. Alcoholism-related liver diseases alter an organ's capacity to absorb beta-carotene and/or convert it to vitamin A, resulting in illnesses including night blindness. Dietitians should exercise caution while working with alcoholics who have reduced vitamin A levels since blood levels can fluctuate depending on how much vitamin A is stored in tissues and because large dosages of vitamin A are known to be fatal. Patients with night blindness and low vitamin A levels are advised to take the recommended amount of vitamin A daily for a few weeks. Because zinc is preferred for the use of vitamin A, treatment with it may also be advantageous (Krahn, 1991). As alcohol consumption progresses, the human body passes through four stages of liver impairment: fatty liver, alcoholic hepatitis, cirrhosis, and encephalopathy/coma. Patients with alcoholic liver disease could have subsistence protein-calorie malnutrition. Alcoholics with liver disease make up (45–70%) of those who have diabetes or glucose intolerance. So, management should take into consideration, low-calorie régimes but starving should be evaded because of dietetic jeopardies and due to the likelihood that a patient might have a prevailing eating syndrome or may intersect to a new-fangled dependence with foodstuff, slenderizing or isometrics (Gold et al., 2003; Liber, 2003).

### **Nutritional imbalances in marijuana abusers**

Cannabis has been expended in several formulae for both therapeutic and frivolous commitments. Though comestible cannabis merchandises are usually used to treat several other illnesses, like, digestive and neurological conditions, good class exploration in these expanses is still deficient. Consequently, complete healing prospective of cannabis is still indefinite (Angeles et al., 2021). Although many sinsemilla farmers adhere to a mystical path of nutrition during the plant's growth and Indian Sadhus view cannabis as a mystical plant, there is no mystery to cannabis nutrition. Increased appetite and thirst is commonly seen in these drug abusers (Carson, 2012). In initial phases, an individual may understand the munchies and augmented consumption but after enduring use, hunger-inspiring effect of marijuana deteriorates. Marijuana is expensive, and those who depend on it may have less money to spend on food and less motivation to prepare it. Chronic marijuana use is also thought to restore taste sensitivity, which results in marijuana users virtually always favoring foods with increased salt and sugar content. Additionally, it has been observed that binge eaters among individuals with eating disorders had greater rates of substance addiction than those with restrictive bulimia or anorexia. Therefore, it can be concluded that using drugs or alcohol is always a roadblock to recovering harmony with your body and food (Friese et al., 2016). Cannabis users had reduced serum carotenoid levels. Compared to non-current users, marijuana users have greater rates of cigarette

smoking, soda intake, and beer consumption. According to US statistics from scientific studies, marijuana users also ingested added salt, a reduced amount of fruits and higher quantity of pork, cheese, and salty snacks. According to BMI and an examination of significant blood components, marijuana users in general did not exhibit poor nutritional condition, according to some study's findings (Belackova, 2020; Marr, Magazine).

### **Nutritional alterations in nicotine abusers**

Fresh fruit and vegetable consumption is lower and fat consumption is higher in smokers. Vitamin C, vitamin E, and beta-carotene deficits have been well-documented in terms of dietary consumption and plasma levels of vitamins and minerals. Additionally, there is some information on vitamin B12, folate, and several trace elements (Smit and Crespo, 2001). In rats treated with nicotine, there has been evidence of both an increased and decreased liking for sucrose (Nowack and Pentkowski, 1994). The naturally occurring metal cadmium in tobacco reduces selenium's bioavailability and interacts negatively with zinc, a cofactor for the antioxidant enzyme superoxide dismutase. According to the National Institutes of Health, vitamin E, the main lipid-soluble antioxidant, may not be present at optimal levels in smokers' tissues. In addition to depleting the body of vitamins and minerals, nicotine and other harmful components in cigarettes also interfere with the body's absorption of these vital elements. Smoking also affects rapidness of vitamin D which helps with absorption of calcium. Therefore, smokers have a greater peril of emerging osteoporosis. Smoking may even diminish probiotics, valuable bugs, from ones gut (Golub, 2000).

### **Role of nutrition in treatment of drug abusers**

Substance abuse usually clues to a want of good nutrition. Certain constituents, like, uppers, may subdue hungriness and dislocate metabolic and neuroendocrine regulation, causing an indecorous calorie ingestion and reduced nutrient dispensation. Other substances may cause an upsurge in hunger, leading to weight gain. Conditional to the substances diverse entities misuse, their nutritional state, weight glitches and ailments may diverge, probing to a want for a bursting valuation to regulate their discrete necessities. Medical nutrition therapy and nutrition education for this populace should mark the following areas (Jias and Ellison, 1990).

- Reconcile and nurture body's impairment by alcohol/substance abuse
- Alleviate mood and condense stress
- Decrease longings for drugs and alcohol
- Address medical situations that are co-occurring from substance abuse
- Reassure self-care and a wholesome existence.

To assist a person recuperate from the possessions of substance abuse, it is imperative to amount them with stable, calorically appropriate food. It is spirited to precise any nutritional absences and look into any medical ailments, as chronic malnutrition intensifies illness risk and yields desires for drugs/alcohol. Augmented ingestion of nutrient-dense foods and antioxidants is important as

these assist in reduction of inflammation and cell oxidation, and also affords basics of a nutritious diet. Reassuring patients to drink passable quantities of hydrating fluids also helps them in managing mood while safeguarding acceptable absorption of any medicines they take for prevention of adverse reactions from taking out or primary psychiatric disorders (Taylor and Ussher, 2005; CPE Monthly: Substance Abuse and Nutrition by Alyssa Salz, MS, RD, LD.; Mahboub et al., 2021).

### **Inference**

One of the main causes of sickness and mortality in society is alcohol use disorders, and they have a significant financial impact. Clinical investigations demonstrate that the few medications that are now approved for the treatment of alcoholism are only moderately effective. Moreover, it is a heterogeneous disease and treatment may need to be individualized. Therefore, additional, more effective agents are needed. Dependence on other recreational drugs is also a threat to society. In this editorial, we discuss the evidence indicating about gut-brain peptides like ghrelin/GLP-1 which may play more varied functions than only maintaining body weight homeostasis. In fact, as these hormones influence both alcohol- and drug-persuaded reward, the GHS-R1A and GLP-1 receptors could be engaged in growth of pharmacological therapy techniques for addictive behaviors. An effort has been made to highlight the effects of various addictive substances on different systems in human body with the role of adequate nutrition to fight back this addiction for the overall betterment of the society. Limitations of the Study - A more detailed search might facilitate to understand in depth the intricate mechanisms involved and the role of nutrition in de-addictive processes to help people who use recreational drugs to lead a better quality of life.

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No conflict of interest are declared.

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