© INTERNATIONAL JOURNAL FOR RESEARCH PUBLICATION & SEMINAR
ISSN: 2278-6848 | Volume: 13 Issue: 02 | April - June 2022
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CAFFEINE – A CRITICAL REVIEW ON THE HEALTH ASPECTS AND ITS BENEFITS

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Abstract: Caffeine is a psychoactive drug which has attracted lot of attention in the culture. This is a white crystalline substance with unpleasant taste and has got no scent. Alkaloid caffeine is contained in the leaf, nuts, & seeds of a number of plants. It belongs to the organic group of xanthine's which acts as a flavour enhancer and natural pesticide. Even though it is recognized as safe by ICMR, the excess amount can lead to several ill effects. There is an amino nitrogen in position 9 of the "caffeine (1,3,7-trimethylxanthin) heterocyclic structure", which is made up of "pyrimidinedione and imidazole ring systems". Caffeine has got numerous health impacts posing more of the positive and less negative sequel to the health. Hence, this literature survey was carried out to gain more knowledge on the caffeine's health impacts and its benefits. Caffeine has got lot of advantages in treating and altering the neurological consequences, maintaining one's mental and physical endurance, mood, time taken to fall asleep, well-being of cognitive health, keeping track on cardiovascular disease, liver disease and balancing bone calcium level. Studies have also stated that caffeine is a non-carcinogenic compound, and it has got several health impacts on reproductive system as well as on fetal growth. Therefore, Caffeine is more healthful than it is harmful.

KEY WORDS: Caffeine, health benefits, psychoactive drug, cognitive health, cardiovascular, mood, fetal growth, brain functioning, neuromodulator.

1. INTRODUCTION: While Ludwig Medicus **(1847–1915)** originally postulated a molecular structure for caffeine in 1875, it had previously been determined to be a pure molecule. Validated structures for caffeine and other methylxanthines were discovered by "Hermann Emil Fischer **(1852-1919)"** in 1882. Caffeine, one of the most extensively used medicines in the world, needs some attention. Most people across the globe ingest caffeine, which is referred to as a "ancient wonder medication" **(Smith., 2005).** Among the most commonly consumed psychoactive substances, caffeine is ubiquitous **(Nehlig., 1999).** It's a white crystal substance with a bitter taste and odourless aroma, caffeine. Caffeine may readily pass across membranes since it is fat and water soluble **(Hassan M (2013).** Caffeine, a "methylxanthine alkaloid" that is chemically connected to adenosine and works as a "psychoactive adenosine receptor antagonist", may be found in a range of South American and East Asian plants**.** Because of its ability to enhance taste, caffeine is frequently employed in the beverage business, particularly in the creation of energy drinks **(Reyes and Cornelis., 2018).** Natural pesticides are also being employed. Xanthine's, or caffeine, is one of the chemical substances of the xanthine family **(Poole and Tordoff., 2017).** Some experts believe that caffeine was once an unimportant but

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efficient pesticide since it is naturally present in around 60 types of plants **(Cappelletti et al., 2015).** Many drinks, including tea, chocolate, cola, mates, and chocolate, contain it in some form or another.

Holstege et al., (2009) said that Caffeine is a common component of many medicines, although the rationale for its inclusion is not always apparent. Premature babies with apnea of prematurity may benefit from caffeine's ability to alleviate lethargy and orthostatic hypotension. Stimulant drugs are often used to awaken the central nervous system, and this one is no exception. Excessive use of caffeine may lead to major health problems and even death, even though the FDA usually considers it safe **(Broderick and Benjamin., 2004; Kerrigan and Lindsey., 2005).**

1.1. STRUCTURE OF CAFFEINE:

Fig: 1

Source: ***Joseph., (2017)***

IUPAC name of caffeine: -1, 3, 7-trimethylpurine-2, 6-Dione

Molecular formula of caffeine: - $C_8H_{10}N_4O_2$

Molecular Weight of caffeine: -194.19 g/mol

The methylxanthines family of phytocompounds includes caffeine, which is generated from xanthine. The seeds and leaves of "coffee ***(Coffea Arabica)***", "tea ***(Camellia sinensis)***", and "cocoa ***(Theobroma cacao)***" may be used to extract the "***caffeine (Theobroma cacao L.)***". A heterocyclic structure, consisting of "pyrimidinedione and imidazole rings" with an amino nitrogen at position 9, gives ***"caffeine (1,3,7-trimethylxanthin)"*** the feature of mild acidity. In numerous physiological systems, "caffeine (1,3,7-trimethylxanthine)" acts as a non-selective antagonist of adenosine receptors **(Mitchell et al., 2014).** "Adenosine receptor antagonism", in particular at the A1 and A2A subunits, is thought to underlie the physiologic effects of caffeine, one of most widely used psychoactive stimulant in the world today. Consequently, a cup of coffee or 150 millilitres of freshly brewed coffee may contain anything from 30 to 350 milligrams of caffeine **(Nawrot P, et al., 2003, Higdon JV, Frei B, 2006).** Moreover, the 1,7-dimethylxanthin is the "primary caffeine metabolite and an isomer of theobromine (3,7-dimethylxanthin) and theophylline", which are both represented by the three methyl groups at positions 1, 3 and 7 of the "paraxanthines (1,7-dimethylxanthin)". A methyl group is not present in paraxanthine's position 3 although theobromine lacks one at position 1 and is devoid of theophylline's position 7 methyl group. Because caffeine contains all three methyl groups, it has unique physiochemical effects **(Schepici et al., 2020).** The seeds as well as leaf of the plant also used create caffeine, black tea, as well as chocolate all organically contain ingredients **(Kovacs and Mela, 2006; Friedman, 2007).** Coffee grounds, tea, cocoa beans, and kola nuts all contain caffeine as a naturally occurring alkaloid component **(Nawrot P, et al., 2003, Franco R, et al., 2017).**

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As an endogenous neuromodulator with inhibitory properties, adenosine may be countered by caffeine, which possesses stimulatory properties normally associated with caffeine. Caffeine's additional effects on the body include stimulation of the central nervous system, a rise in blood pressure as well as a rise in metabolic rate and dieresis **(Benitez J, 2000).** Increasing energy expenditure and decreasing energy intake are the two ways caffeine helps keep you in a healthy weight range. Using thermogenesis, fat oxidation, as well as calorie consumption, it enhances weight loss and maintains a healthy weight **(Tamir S, 2017).**

2. POTENTIAL HEALTH BENEFITS OF CAFFEINE:

a. Mental and physical performance:

Efficiency and attentiveness were boosted in a simulated nightshift situation and in shift workers who work the night shift by taking 300 mg of caffeine. For protracted wakefulness as well as circadian misalignment, caffeine administration is suggested to increase physiological attentiveness as well as some cognitive function by decreasing the impact of homeostatic sleep drive **(Wright et al., 1997).** In persons who are exhausted or old, caffeine's energizing benefits are more pronounced **(Cappelletti et al., 2015).**

Athletes utilize caffeine, according to **Ferrauti et al. (1997) and Davis and colleagues (2003)** by favoring effects of caffeine on moods, increased alertness, reduced weariness, and energetic excitement have been widely reported. There is an inverted dosage response curve for caffeine's ergogenic and cognitive effects, as well as a different time course based on age, sexual identity, as well as body mass. Consider the long-term consequences of caffeine on the body while making decisions about whether or not to drink it. Increasing the release of analgesic - endorphins, which caffeine increases, also seems to lower the experience of pain in humans. Caffeine's ability to improve endurance as well as coordination in stop-and-go activities (such as team sports and racket sports) as well as sports requiring prolonged high-intensity effort is well-documented **(Folmer et al., 2017).** Known for its energizing properties, coffee has a stimulant impact because of caffeine's propensity to improve mental function, including alertness as well as attention "**(Einother and Giesbrecht., 2012)".** Generally speaking, 75 mg of caffeine is required to get the desired effects, regardless of the individual's tolerance. Other coffee components, however less potent than caffeine itself, have been shown to influence ageing people's cognitive performance. Caffeine has already been demonstrated to improve rugby play by factor contributing to the growth, energy, and stamina **(Ranchordas et al., 2019).**

b. MOOD:

Caffeine's benefit on alertness is best seen when circadian attentiveness is low as well as mood is evaluated while doing difficult activities **(Liberman., 1992).** Other side effects include a rise in anxiety in some people who consume excessive amounts of caffeine **(Smith., 2002).** Increased alertness or decreased weariness may be attributed to the use of caffeine **(Wurtman et al., 1987).** Caffeine alone or in conjunction with other substances in coffee may be responsible for the shift in behavioural consequences, but no one is sure. Memory and other cognitive processes may be aided by caffeine use "**(Nehlig., 2010; Borota et al., 2014)** and mood **(Smith., 2005)".**

Single dosages of caffeine have been shown to have little or no effect on mood in several studies of 32mg **(Lieberman et al. 1987),** 100mg **(Svenningsson P et al. 1999)** or 200mg

(Swift and Tiplady 1988)". Anger/hostility scores have already been linked to higher doses of caffeine ("200, 400, or 600 mg in a single dose"), and so have the scores for tiredness and loss of coordination **(Roache and Griffiths 1987).** No matter how much coffee you consume in a day, caffeine has no effect on your ability to feel melancholy **(James 1991).**

According to several studies, persons who use a lot of caffeine are more likely to get anxious. There has been a rise in anxiety levels among patients in mental institutions who consume a lot of coffee, according to several research **(James 1991);** On the other hand, because some studies did not account for patients' alcohol as well as cigarette usage, the results may have been skewed. **James et al. (1987)** in a sample of 173 mental inpatients, the researchers corrected these methodological flaws and found no correlation between coffee use and anxiety. Patients with "generalised anxiety disorder" had a dose-dependent increase in anxiety after receiving a coffee injection **(Bruce et al. 1992).** In spite of the fact that it's only applicable to those with mental illness, it's nevertheless important to discuss **(James and Crosbie 1987).**

c. Sleep:

Increased sleep latency and shorter sleep duration have both been linked to excessive coffee use in the hours leading up to bedtime ("more than 3 mg kg1 bodyweight, or more than 210 mg for a 70 kg individual") **(Smith 2002).** Caffeine users are less likely to experience sleep difficulties than those who drink the stimulant on a regular basis "**(Snyder and Sklar 1984, Zwyghuizen-Doorenbos et al. 1990)**", implying a tolerance to the effects of coffee on this parameter. Self-limitation in caffeine use is likely to take place if caffeine consumption adversely affects the person's ability to fall asleep. To summarize, among healthy people, consuming more caffeine had no positive impact on mood or performance compared to consuming less caffeine. If you have anxiety, you may want to restrict your consumption of caffeine because of the conflicting outcomes in the research and the fact that each person's tolerance to caffeine is different **(Bovim et al. 1995).**

One of the most ingrained notions in the minds of people all over the globe is that drinking a lot of caffeine in the evening will make it harder for certain people to go asleep. Although when sleep is disrupted, there is no convincing evidence that the consequences are large enough to have a significant impact on health and well-being. Most individuals can regulate their caffeine intake, thus there is no solid evidence that excessive caffeine use is associated with sleeping difficulties **(Liberman., 1992).** A cup of coffee in the morning may help you stay awake and productive when travelling since caffeine reduces the weariness that comes with adjusting to the new time zone's circadian rhythms. A 15- to 30-minute nap followed by a dose of caffeine (50 milligrams to 200 milligrams) has been proven to improve cognitive performance in sleep-deprived individuals and during the circadian nadir, making it an excellent treatment for jet lag and travel tiredness **(Mednick et al., 2008).**

d. Cognitive health:

Additionally, polyphones appear to reduce the risk of "Alzheimer's disease" when consumed. Chlorogenic acids have been associated to the prevention of neurological illness as well as ageing in a variety of animal models **(Rogers et al., 2003).** As with Alzheimer's disease, several epidemiological studies have shown that caffeine use is inversely related to the likelihood of "Parkinson's disease" developing. Resting tremors, muscle stiffness, gait abnormalities, and a

weakened postural response are all symptoms of this neuropath logical condition. Disintegration of brain stem cells is also a result of this **(Ramassamy., 2006).**

"Parkinson's disease" seems to be slowed or perhaps prevented when caffeinated beverages are consumed. Coffee consumers had 25percent reduced risk of "Parkinson's disease" than non-coffee drinkers, according to a meta-analysis of 26 research. According to current research, this effect is caused by caffeine's capacity to block brain adenosine receptor A2 activation **(Costa et al., 2010).**

Reading comprehension, logical thinking, as well as perceptual quickness all declines beyond the age of twenty in humans. The pace and magnitude of this decrease are influenced by genetics, life experiences, and a person's way of life **(Folmer et al., 2017).** Numerous epidemiological studies show that older people who drink coffee on a daily basis show less cognitive impairment **(Corley., 2010; Arab et al., 2013).**

Caffeine ingestion, instead of coffee itself, seems to have a protective impact in several human investigations **(Santos et al., 2010).** The most common cause of dementia, which is characterized by a steady deterioration in mental abilities, is "Alzheimer's disease". There is a 27% decrease in the chance of developing "Alzheimer's disease" if you drink coffee regularly **(Folmer et al., 2017).**

e. Neurological effects:

The reticular development is directly affected by modest concentrations of coffee in the single neuron level **(Forde and Hirsh., 1976).** That caffeine raises cortical arousal and also that ascending activating circuits in the brain are responsible for this action was clearly shown in this research **(Battig., 1985).**

Watanabe et al., (1978) indicated that the inhibitory action of coffee on the "medical thalamic nuclei system" may be a factor in the stimulant's arousal effects. "Catecholamine, noradrenalin, and dopamine metabolism" in the brain was shown to be accelerated by coffee use **Chou et al., (1980).** Caffeine treatment had a better "amplitude-integrated electroencephalography score" in babies than the control group, according to the research. Premature babies who are given long-term caffeine medication are less likely to suffer from hypoxemia episodes, which may have a negative impact on their brain development. Although there were no reported side effects, this study concluded that neonatal caffeine therapy would seem to be safe up to the age of middle school at the doses used throughout the CAP trial **Moschino et al., (2019).**

f. Cardiovascular disease:

After a cup of coffee, caffeine raises blood pressure and decreases insulin sensitivity. Acute caffeine effects disappear with frequent coffee drinking owing to adaption mechanisms, while some other components of coffee, such as "chlorogenic acids and trigonelline", exhibit compensating effects on endothelial dysfunction and glucose intolerance. Other studies show that coffee's ability to reduce inflammation and improve endothelial dysfunction, as well as to lower insulin resistance, points to a role for coffee as a cardiovascular health protector **(Rebello and Van Dam., 2013).**

At the start of the study, "41836 postmenopausal women aged 55–69 years old" were tracked for 15 years. During this time, 4265 people died. In a review of the causes of death, the authors

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found that postmenopausal women who drank coffee had lower rates of cardiovascular as well as other inflammatory disorders, resulting in a reduction in their mortality. Coffee's "antioxidative as well as anti-inflammatory properties" are thought to be responsible for this impact. Researchers conducted a meta-analysis **Crippa et al., (2014)** With 997464 individuals and 121915 fatalities recorded across 21 prospective trials, we can draw some solid conclusions. Researchers found that those who drank three to four cups daily were less likely to die as a result of any cause or cardiovascular disease. Additionally, similar outcomes were seen by **Malerba et al., (2013).** Patients with ischemic heart disease or severe ventricular ectopia should not have an increased frequency or intensity of cardiac arrhythmias while taking single doses of caffeine 450mg **(Myers 1998).** According to research, heart rate variations in healthy or hypertensive people may be noticed at doses of more than 150 mg/person **("James 1991c, Green et al. 1996, Myers 1998").** A fast increase in heart rate tolerance is a common side effect of caffeine **(Green et al. 1996)** and "complicates data interpretation". A drop-in heart rate may be clinically insignificant, though **(Myers 1998).**

g. Bone and calcium balance:

"Caffeine-induced osteoporosis" is distinguished by poor bone mineral density as well as a risk of fractures, & epidemiological research have studied the relationship between caffeine and/or coffee use and this risk. Calcium homeostasis has been studied in metabolic investigations as well. Urinary calcium excretion was elevated by 150–300mg of coffee after a 10-hour fast in both adolescent boys and women **(Massey and Hollingbery 1988),** "women 22–30 years of age" **(Massey and Wise 1984, Massey and Opryszek 1990),** "men 21–42 years of age" **(Massey and Berg 1985),** and "women 31–78 years of age" consuming 5200mg caffeine day_1 **(Bergman et al. 1990).** Because persistent coffee drinking had no impact on the rise in calcium excretion connected to an acute dose of caffeine, renal effects of caffeine are not tolerant **(Massey and Opryszek 1990).** "Caffeine induced hypercalciuria was not affected by oestrogen status **(Bergman et al. 1990),** gender or age **(Massey and Wise 1992)**". **Barger-Lux et al. (1990)** Despite the fact that "fractional calcium absorption, endogenous faecal calcium, or urine calcium excretion" were unaffected by 400 mg of coffee per day in premenopausal women aged 35 to 44, the researchers detected altered bone remodelling. In the same group, higher 24-hour urinary calcium excretion has been linked to caffeine consumption of 175mg per day **(Heaney and Recker 1982).**

h. Cancer:

Esophageal mucosa is damaged by high temperatures, which results in inflammation or the formation of reactive nitrogen species. The "International Agency for Research on Cancer (IARC)" warns that consuming coffee and other hot drinks above 65°C increases one's chance of developing esophageal cancer **(Tomita et al., 1989).** Consuming hot drinks like mate, tea, or caffeine has been linked to an elevated risk of esophageal cancer in epidemiological studies. At 65°C, the temperature of the esophagus increases by 6–12°C, according to a study **(Bode and Dong., 2007).** Cancer, in its widest meaning, is the outcome of uncontrolled cell proliferation and may affect almost every human organ or tissue. "International Agency for Research on Cancer (IARC)" evaluated coffee's carcinogenicity in 1991. Depending on insufficient evidence of carcinogenicity for experimental animals and little evidence of a link with bladder cancer through case-control studies, coffee was categorized as "probably carcinogenic to humans" at the time. Whenever the effects of smoking were taken out of the equation, no increased risk of bladder cancer could be seen **(Butt and Sultan., 2011)**.

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In mice **(Bauer et al. 1977, Macklin and Szot 1980, Stalder et al. 1990)** and rats "**(Wurzner et al. 1977, Johansson 1981, Takayama and Kuwabara 1982, Mohr et al. 1984)**" Caffeine was shown to be non-carcinogenic at doses as high as 391 and 230mg/kg in a number of studies looking at oral oncogenicity as well as chronic toxicity. However, a drop in body weight has been seen without a corresponding decrease in food intake.

i. Reproductive and developmental effects:

Throughout pregnancy, this is common to see a decrease in caffeine consumption, and some even experience a temporary loss of taste for the stimulant. Depending on the situation, it also might stay high. Caffeine is used by the majority of women of reproductive age in the form of caffeinated beverages or medicines, and 72% of these women continue to do so throughout pregnancy **(James 1991).** Numerous studies were relieved to find that the majority of pregnant women drank 100–300mg of caffeine daily "**(Fenster et al. 1991, Fortier et al. 1993, Mills et al. 1993, Dominguez-Rojas et al. 1994, Rondo et al. 1996)**". A far higher dose may be consumed by a tiny subset of the general population, which includes pregnant women. Caffeine content of 5400 mg per kilogramme for these women "**(Kurppa et al. 1983, Toubas et al. 1986, Olsen et al. 1991, Armstrong et al. 1992, McDonald et al. 1992)**". Research has focused on the influence caffeine has on reproduction and the development of the foetus throughout the last two decades. Findings from this study indicate caffeine intake at 5300mg per day might negatively affect several reproductive and developmental traits at particular periods of the year **(Dlugosz and Bracken 1992). Christian and Brent (2001)** Pregnant or pregnant women who don't even drink alcohol and eat moderate amounts of caffeine (45–6 mg/kg 1 bw day 1) are unlikely to have reproductive disorders, according to the examination of known human and animal epidemiological studies. This holds true for both men and women. When pregnant women eat large quantities of caffeine or its metabolites from the mother's gastrointestinal tract, the foetus as well as neonate are swiftly absorbed, easily cross the placenta, as well as disseminated to all foetal tissues as well as systems, such as those of the "central nervous system" **(Norman p, et al., 2003).** Breast milk also flushes caffeine out of the body. When it comes to pregnant women, new-borns, and adults, caffeine has more of an effect on the foetus since it lacks enzymes that oxidise methylated xanthine's (the foetus does not have these enzymes) "**(James and Paull 1985, James 1991g, Dlugosz and Bracken 1992)**".

j. Fetal growth:

Pregnant women who use caffeine may harm their foetus's development. The inhibition of phosphodiesterase's may result in an increase in the levels of cAMP, which may interfere with the growth and development of foetal cells **(Karen 2000).** The adenosine receptors in the brain are blocked by the stimulant effects of caffeine. Hypoxia may be more likely to occur if receptors for adenosine are blocked, since it is important in maintaining the balance between tissue oxygen supply and consumption. Many studies have indicated that two cups of coffee a day may raise maternal adrenaline levels and reduce intervillous placental blood flow **(Fortier et al. 1993).** Caffeine and smoking have comparable negative physiological effects on foetal development, which should be emphasised since they are both often connected with smoking **(Fortier et al. 1993).** Studies looking at the link between caffeine use and foetal development have produced mixed results. At birth, a baby's body weight must be less than 2500 grammes to be considered underweight, and the amount of caffeine consumed must be less than 300 milligrams per day to be considered underweight, according to 18 original epidemiological research in a population-based investigation by **Fortier et al. (1993),** Caffeine use was linked

to an increased risk of intrauterine development retardation, and not even to low birth weight in a group of 7025 women in the Quebec City, Canada, region. There was an increase in the percentage of pregnant women who had kids with intrauterine development retardation in Brazilian unmatched case-control research by **Rondo et al. (1996).**

Vlajinac et al. (1997), During the third trimester of pregnancy, non-smokers' caffeine consumption increased from 71 to 5140mg, research found. A higher risk of foetal development retardation was reported in five trials after adjusting for putative confounding variables, including such as cigarette smoking and alcohol consumption (especially binge drinking). In a prospective study, excessive caffeine consumption (>300 mg/day) was linked to lower birth weight and a smaller head circumference study by **Watkinson and Fried (1985),** that also collected the data on maternal consumption of tea, coffee, artificially sweetened soft drinks, chocolates, cocoa drinks, and caffeine - containing medication. These associations persisted even after controlling for maternal caffeine usages. Babies born to 12 heavy users had an average weight of 3158 g, whereas the rest of the group had an average weight of 3537 g. An average daily caffeine consumption of 5300mg has been shown to have an adverse effect on proper foetal development, according to the research. The effects of caffeine use on "intrauterine growth retardation" were examined in a prospective research **Martin, and Bracken (1987)** Women who drank more than 300mg of caffeine a day were more likely to give birth to underweight children, with a rate of 7.3 percent compared to 4.1 percent in the control group. Consuming more than 300 milligrams of caffeine daily resulted with a 120-gram decrease in birth weight. Caffeine consumption between 151 and 300 milligrams per day was similarly linked to a smaller birth weight, although the link was weaker.

k. Liver disease:

Larsson and Wolk (2007) and Bravi et al. (2013) conducted a meta-analysis of 16 human studies, and showed that consuming caffeinated drinks reduced the incidence of liver cancer by 40%. Low levels of liver disease and other problems have been related to regular coffee use. Coffee use has not been investigated in patients with cholestatic autoimmune liver diseases, "primary biliary cirrhosis (PBC)," or primary sclerosing cholangitis. This study looked at a large North American cohort to investigate whether coffee consumption was linked to an increased incidence of PBC and PSC. Participants with PBC, PSC, and healthy controls filled out surveys that allowed researchers to learn how much coffee they had consumed throughout the course of their lives (controls). Comparing patients and controls, the "Wilcoxon rank sum test for continuous variables and c2 approach" were utilized. Coffee properties did not vary between patients with PBC as well as controls. Such data show that patients with PSC, and not PBC, consume less coffee than the controls, as compared to the general population (**Lammert et al., 2014).**

3. CONCLUSION:

However, consuming caffeine has various advantages, including an increase in mental and physical energy and a reduced risk of developing certain illnesses. Overall, the literature survey has shown that caffeine does in fact affect a person's concentration and alertness while doing schoolwork, paying attention in class or while working. As a psychoactive agent, caffeine has been shown to be one of the most attention-seeking substances in the world. It imposes lot of health impacts in the field of mood alteration, mental and physical performance, sleep timings, growth, and development of fetal, brain functioning, maintaining liver and heart related issues.

Although there are several side effects on caffeine intake, but the negative effects clearly tell us that one should be limiting their caffeine consumption.

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ISSN: 2278-6848 | Volume: 13 Issue: 02 | April - June 2022
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Refereed & Peer Reviewed