REVIEW ARTICLE

EFFECT OF CAFFEINE ON THE HUMAN BODY: A REVIEW
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ABSTRACT
Caffeine (1,3,7-trimethylxanthine) is the widely consumed substance all over the world. It is found in coffee, tea, cocoa, etc. Caffeine (CF) is rapidly and completely absorbed from the gastrointestinal tract; peak plasma concentration reaches in about 15 to 120 min after oral ingestion in humans without any significant first-pass effect. There are some drugs which are responsible for the inhibition of metabolism of CF. It also exerts its effect in higher doses on different body organs like neuro, gastrointestinal, renal, respiration, skeletal muscle, cardiovascular systems. Those who are regular consumer of tea, coffee, or CF containing beverages are at the higher risk for the development of CF toxicity which can lead even to death of an individual. The dependence and withdrawal side effects of CF include anxiety, insomnia, restlessness, nervousness, tremors, gastrointestinal upset, tachycardia, psychomotor agitation, etc.

Keywords: Caffeine, pharmacokinetics, metabolism, toxicity.

1. INTRODUCTION
Caffeine (CF) is an alkaloid like theophylline and theobromine and belongs to the class of methylxanthines. The only difference between these three substances is the presence of methyl groups on two positions in their chemical structure (Fig. 1). In humans, CF acts as a central nervous system (CNS) stimulant. It is a widely used psychoactive drug in the world and is most frequently consumed for alertness and wakefulness. It can interfere in the transmissions based on acetylcholine, epinephrine, norepinephrine, serotonin, dopamine and glutamate. CF also possesses diuretic effects and helps in reducing weight and provides boosting energy. In analgesic preparations, CF is added in small doses to enhance the analgesic effect because it is a weak stimulant. The amount of CF in 2 to 4 cups of coffee a day is not harmful, however, more than 4 cups per day (~250-300 mg) may cause hypercalcemia. Hundreds of brands of energy drinks are now available in the market containing CF. Excessive amount of CF can also cause restlessness, anxiousness, irritation, headaches, abnormal heart rhythms, blood pressure or other problems. The use of CF during pregnancy in a concentration of 300 mg or more per day has been associated with the chances of spontaneous abortions and fetal growth retardation predominantly in women who smoke. Infertility in both male and female is also reported by the intake of CF. CF may interact with various drugs such as aspirin, antibacterials, antihypertensive, benzodiazepines, lithium, nicotine, oral contraceptives, etc. and thus produce synergistic and/or antagonistic effects.

2. SOURCES
CF and other xanthenes like theophylline, theobromine, and paraxanthine are obtained from dietary sources.

Fig. 1. Structures of methylxanthines.

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especially coffee, tea, cocoa, etc. An average cup of coffee or tea contains approximately 100 mg of CF. The source, origin, country where it is produced, consumed form by the humans and amount of CF taken by the human are given in Table 1.

**Table 1. Sources of CF.**

<table>
<thead>
<tr>
<th>Source</th>
<th>Origin</th>
<th>Producing country</th>
<th>Consumed form</th>
<th>CF content (% total weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coffea arabica</strong></td>
<td>Seed, fruit</td>
<td>Brazil, Colombia</td>
<td>Coffee</td>
<td>1.1</td>
</tr>
<tr>
<td>(Coffee bean)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Coffea robusta</strong></td>
<td>Seed</td>
<td>Indonesia</td>
<td>Coffee</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Coffea liberica</strong></td>
<td>Seed</td>
<td>Regions in Africa</td>
<td>Coffee</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Camellia sinensis</strong></td>
<td>Leaf</td>
<td>China, India</td>
<td>Tea</td>
<td>3.5</td>
</tr>
<tr>
<td>(Tea)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cola acuminata</strong></td>
<td>Seed</td>
<td>West Africa</td>
<td>Soft drinks, Chewing nuts, Kola tea</td>
<td>1.5</td>
</tr>
<tr>
<td>(Kola nut)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. **PHARMACOKINETICS OF CF**

CF is rapidly absorbed after oral administration and has a bioavailability of almost 100%. It is widely distributed in the body including CNS and saliva. It can cross the placenta and small amounts are excreted in breast milk. The metabolism of CF is dose dependent and the metabolic reactions include N-demethylation, acetylation, and oxidation to uric acid derivatives. The cytochrome P450 isoenzyme CYP1A2 is mainly responsible for the metabolism of CF in liver and its conversion to paraxanthine. CF is frequently used as an important substance to investigate the effects of medicines on this isoenzyme. It has a plasma half-life of about 2 to 10 hours but various factors can alter its rate of excretion. The plasma half-life of CF is decreased by smoking and exercise whereas an increase is reported in diseases like cirrhosis and viral hepatitis. Conditions like old age or obesity are not known to affect its plasma half-life; however, an increase in its elimination is reported during pregnancy. Drug interactions can also affect its pharmacokinetics. Around 1% of CF is excreted in the urine unchanged whereas the remaining up to 40% of the dose as 1-methyluric acid, 10 to 15% as 1-methylxanthine, up to 35% as 5-acetylamino-6-formylamino-3-methyluracil and 5-acetylamino-6-amino-3-methyluracil. Other metabolites excreted in the urine include theophylline, 1,7-dimethylxanthine (paraxanthine), 7- methyl-xanthine and 1,3-dimethyluric acid. In neonates, the major amount of CF is excreted unchanged in the urine. This is due to the reduced capacity of neonates until approximately 6 months of age. It is also reported that pharmacokinetic and pharmacological effects of CF are same either taken as in coffee or beverages.

3.1. **Inhibitors of Caffeine Metabolism**

There are a number of drug substances that are well known as inhibitors of the cytochrome P450 isoenzyme CYP1A2, for e.g., fluvoxamine, idroclamide, clinafloxacin, enoxacin, cimtidine, fluconazole, verapamil, disulfiram, lomefloxacin, pipemidic acid, ciprofloxacin, and enoxacin. It has been observed that some carcinogenic
compounds are made by the catalysis of isozyme P-450 1A2 which in result inhibits the primary metabolism of CF and shows toxic effects\textsuperscript{20} for example, a study was conducted to evaluate the effect of estrogen in the presence of CF, the results showed that estrogen inhibits the CYP1A2-mediated caffeine metabolism\textsuperscript{23}. Grape fruit juice and naringenin are also known to inhibit CF metabolism by inhibiting CYP1A2 activity in man\textsuperscript{22}. Similarly 5-methoxyxpsoralen, an agent used in the treatment of psoriasis, when co-administered with caffeine causes CYP1A2-dependent inhibition of caffeine N-demethylation\textsuperscript{23}. Andersson et al.\textsuperscript{24} found that three proton pump inhibitors (omeprazole, lansoprazole, and pantoprazole) when administered with CF causes a polymorphic change in the isozyme CYP1A2 into CYP2C19 and thus inhibits CF metabolism. Therefore, it is suggested that the concomitant intake of CF in any form (beverages, herbs, etc.) with such drugs should be avoided\textsuperscript{4}.

4. EFFECTS ON BODY ORGANS
4.1. Neuro and Endocrine Effect
CF is a CNS stimulant due to nonselective adenosine receptor antagonism\textsuperscript{25}. It acts on the cerebral cortex and cerebellum of the brain and stimulates the secretion of serotonin. High doses of CF trigger the stress like condition in the pituitary-adrenal axis\textsuperscript{26-28}. Recently, it has been found that CF also plays an important role in the treatment of Parkinson’s disease\textsuperscript{29}.

4.2. Gastrointestinal System
CF stimulates gastric secretion and can produce emesis. In normal doses CF and theophylline stimulate pancreatic hormone secretions. Some studies have reported the occurrence of indigestion, heartburn, abdominal pain and symptoms due to gas or constipation as adverse effects of CF intake\textsuperscript{28,30}.

4.3. Cardiovascular System
CF may produce slight elevation in blood pressure for non habitual coffee drinkers. The high intake of CF is often associated with tachycardia and extrasystoles\textsuperscript{31-33}.

4.4. Respiratory System and Skeletal Muscle
CF affects the contractility of skeletal muscles and stimulates respiration, therefore, it is used in the treatment of apneic spells (premature infant disease). However, continuous or prolonged intake may induce tremors\textsuperscript{28,34}. It is also used in the treatment of bronchial asthma\textsuperscript{35}.

4.5. Renal System
Methylxanthines are well known for their diuretic effects specially CF and theophylline are the most potent diuretics as they activate the release of rennin from the kidneys\textsuperscript{28,31}. Hashimoto et al.\textsuperscript{36} reported that CF intake increases glomerular filtration rate (GFR). On the other hand, the effect of CF intake on urinary glucose excretion in patients who take sodium glucose transporter 2 (SGLT-2) inhibitors is yet unknown.

5. TOXICITY OR OVERDOSE
The regular consumers and abstainers of CF in the form of coffee, soft drinks, energy drinks and tea are at the highest risk of CF overdose\textsuperscript{1}. There are some particular symptoms that appear as a direct result of CF consumption such as anxiety, insomnia, restlessness, nervousness, tremors, gastrointestinal upset, tachycardia, psychomotor agitation, etc.\textsuperscript{37} and in some cases death is also reported\textsuperscript{38-40}. The use of caffeinated energy drinks in adolescent and children may increase the risk of CF intoxication\textsuperscript{7} which may result in seizures\textsuperscript{41}, stroke\textsuperscript{42} or acute mania\textsuperscript{43}. Deaths attributed to energy drink consumption have been reported in Australia, Ireland and Sweden\textsuperscript{7}.

6. DEPENDENCE AND WITHDRAWAL OF CF
The use of CF is associated with the development of dependence syndrome\textsuperscript{7}. Similarly, its withdrawal also develops certain sign and symptoms that have been reported in the medical literature\textsuperscript{44,45}. Headache is the most frequent withdrawal effect which begins within 12-24 hours after the last dose of CF\textsuperscript{45-48}. The other general CF withdrawal side effects include drowsiness, fatigue, difficulty in concentrating / decreased cognitive performance, dysphoric mood (e.g., miserable, decreased well-being / contentedness), nausea, vomiting, irritability
depression, and muscle aches / stiffness\textsuperscript{45,49,50}.

7. CONCLUSION

CF is a plant secondary metabolite with a significant impact on multiple processes and regulatory pathways in the body. Though major part of the population intake CF via coffee, tea or chocolate, it has also an important role in pharmacology and it is used as a supplementary substance in medicaments. CF is a pharmacologically promising substance that deserves big consideration in the current research and development.

REFERENCES

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