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A Review on the Effects of Caffeine on Human Health

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Abstract: *Caffeine is one of the most commonly expended psychoactive substances around the world, basically found in coffee, tea, vitality drinks, and different solutions. Its popularity stems from its ability to stimulate the central nervous system, improving alertness, concentration, and mood. This review delves into the complex effects of caffeine on human health, emphasizing both its benefits and potential risks. Regular, moderate caffeine consumption has been linked to reduced risks of neurodegenerative diseases such as Parkinson's and Alzheimer's, enhanced cognitive performance, and improved physical endurance. It also exhibits antioxidant properties that may help combat oxidative stress and support cardiovascular and metabolic health. However, excessive intake can result in adverse effects, including sleep disturbances, heightened anxiety, gastrointestinal issues, and dependency. The impact of caffeine varies widely among individuals, influenced by factors such as genetics, age, and tolerance levels. This variability underscores the importance of personalized recommendations for caffeine consumption. This review aims to provide an in-depth analysis of caffeine's role in human health, balancing its positive and negative effects, and identifying areas for further research to better understand its long-term implications on diverse populations..*

Keywords: Caffeine, human health, cognitive performance, physical performance, neurodegenerative disorders, metabolic function, antioxidant properties, sleep disturbances, anxiety, cardiovascular health.

I. INTRODUCTION

Caffeine in one of the most widely consumed psychoactive substance globally, primarily found in coffee, tea, and various energy drinks. This review explores the extensive effects of caffeine on human health, highlighting both its benefits and potential adverse effects. The aim is to provide a comprehensive understanding of how caffeine impacts physical and mental health. 2 Caffeine is the world's most popular stimulant and psychoactive substance 3. More than 60 different plant species, including cacao beans and tea leaves, naturally contain it in varying degrees4 .Caffeine can be present in a variety of plant parts, including leaves, beans, and fruits. For instance, caffeine may go by different names depending on where it is found—guaranine in guarana berries, theine in tea plants, or mateine in yerba mate plants 5. The main dietary caffeine sources in the world are roasted coffee beans like robusta and arabica and tea leaves6. In addition to naturally occurring caffeine, it can also be artificially produced in labs and added during manufacturing. Between natural and manufactured caffeine, there is essentially no molecular difference. Caffeine is typically produced using chemicals like urea, dimethylurea, and chloro acetic acid7 where caffeine citrate and dicaffeine malate are some of the synthesized caffeine8. . Numerous manufactured products, including the majority of sodas and energy drinks, contain this produced caffeine. The most popular dietary sources of caffeine are coffee, tea, chocolates, and soft drinks 9. Main source of caffeine consumed by adults tends to be coffee, while soft drinks and tea are more predominant sources of caffeine among adolescents. Depending on the plant species and brewing technique used, the amount of caffeine in brewed beverages varies substantially 10 . Caffeine can also be consumed through prescription and over-the-counter medications used to treat headaches, colds, and allergies. These medications analgesic effects are said to be enhanced by caffeine. Apart from medication it can also be used cosmetically and is an active

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component in several cellulite-reducing treatments. Caffeine's ergogenic properties also makes it one of the widely utilized performance-enhancing supplements used by athletes from different sports modalities. 1 .

MECHANISM OF ACTION

Caffeine acts primarily as an adenosine receptor antagonist. Adenosine a nucleoside present in all cells, promotes sleep and relaxation. By blocking adenosine receptors, caffeine reduces the sensation of fatigue, enhances alertness, and improves cognitive functions. Furthermore, caffeine, influences, other neurotransmitter systems. Including the dopaminergic and serotonergic pathways, which are implicated in mood regulation.

Chemical Structure and Main Natural Sources of Caffeine

Caffeine (C8H10N4O2; Figure 1A), also known as 1,3,7-trimethylxanthine, belongs to the group of methylxanthines, which are alkaloids . Together with theobromine, its precursor (Figure 1B), both are synthetized by the fruits, leaves, and seeds of many plants and trees to protect them from diseases and predators

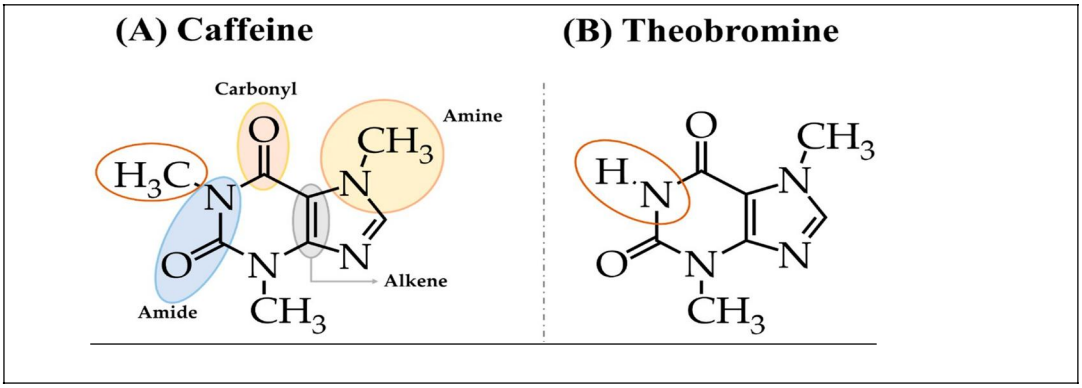

Figure 1. Chemical structure and functional groups of caffeine (A) and theobromine (B).

Regarding their structure, both compounds are carbon- and nitrogen-based molecules composed of two purine rings, a pyrimidine ring (C5-ring), and an imidazole ring (C6- ring), both of which have two nitrogen atoms 11,12 .

Their functional groups are an amide (a carbonyl group bonded to carbon and nitrogen atoms), an amine (at least one hydrocarbon group bonded to a nitrogen atom), and an alkene (an unsaturated hydrocarbon with a double bond between two carbon atoms)11 .

Caffeine serves as a hydrogen bond acceptor because three of its four nitrogen atoms are methylated 13.

Although caffeine and theobromine share similarities at the physical and chemical levels, caffeine has an additional methylene group and exerts stronger central nervous14,15 Pharmaceuticals 2023, 16, 1067 3 of 35

Regarding caffeine consumption, recent statistical data show that more than 85% of American adults consume caffeine daily (135 mg per day)17,18 In Europe, a higher caffeine consumption is observed (values ranging from 37 to 319 mg per day), especially in the Netherlands (411 mg per day), Denmark (390 mg per day), Finland (329 mg per day), Austria (300 mg per day), and Switzerland (288 mg per day) 18,19.

non-European countries, Brazil and Argentina also have a high consumption of caffeine (mean values of 40 and 100 mg per day, respectively), as well as Australia (232 mg per day) and Japan (169 mg per day) . In contrast, lower amounts of caffeine are consumed in China (16 mg per day), Angola (4 mg per day), and Kenya (50 mg per day) 19.. The main sources of caffeine are coffee and tea, energy beverages, sodas and soft drinks, and dark chocolate (see Table 1). As expected, coffee and chocolate are the most popular sources of caffeine worldwide. Among the different types of coffee (beverage), American coffee is the most caffeinated (91.7–213.3 mg per 100.0 mL) followed by Scotland espresso (66.0–276.0 mg per 13.0–90.0 mL). As for tea, black tea and Yerba Mate contain considerable amounts of this molecule (both around 40.0 mg per 236.0 mL).

Among soft drinks, Mountain Dew Rise and Diet Coke have considerable amounts of caffeine (180.0 mg per 473.0 mL and 46.0 mg for 354.0 mL, respectively) [41]. Among energy drinks, Java Monster 300 and Rockstar X Durance present the highest caffeine contents (amounts around 300.0 mg per 443.0 and 473.0 mL, respectively), followed by

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Full Throttle (160.0 mg per 473.0 mL) [41]. In addition, as expected, energy shots, such as Spike Energy Double Shot and Bang Shot, are also rich in caffeine (levels of
and 300.0 mg per 125.0 and 88.0 mL, respectively) [41]. Finally, Cran Energy juice and Water Joe also have significant amounts of caffeine (70.0 mg per 295.0 and 591.0 mL, respectively). The presence of caffeine is also reported in dark chocolate (8.0 mg per 1.0 g).

II. METABOLISM OF CAFFEINE

In the human body, caffeine is rapidly absorbed by the small intestine after oral administration into the body within 45 min and its average peak value occurs at 30 min 20 which directly depends on pH(8) and may be dragged by food input21. Its metabolic half- life is 3 – 5 h22 and it readily penetrates the blood – brain hedge21. The first step in caffeine's biotransformation is intermediated by hepatic microsomal enzymes — picky catalysis by cytochrome P450PA in mortal liver microsomes23 Caffeine is primarily metabolized in the liver via the isoenzyme CYP1A2(in about 80), which causes its 3- demethylation to major metabolite, which is 1,7- dimethylxanthine(paraxanthine). also, caffeine itself may increase CYP1A2 exertion 24 , and this isoenzyme is also responsible for the 1- and 7- demethylation of caffeine to 3,7- dimethylxanthine
(theobromine) and 1,3- dimethylxanthine(theophylline), as shown in Figure 2. These metabolites may be further primarily demethylated via CYP1A2, also acetylated via N- acetyltransferase 2, and oxidized via xanthine oxidase or CYP3A4 to yield major metabolites that are excreted primarily in the urine including 1- methyluric acid, 5- acetylamino-6-formylamino-3-methyluracil, 1- methylxanthine(e.g., after farther demethylation of paraxanthine via CYP1A2), 1,7- dimethyluric acid, and 1,7- dimethylxanthine(paraxanthine)24. A low chance(0.5 – 4.0) of an ingested cure of caffeine is excreted unchanged in urine and in corrosiveness and is also set up in slaver, semen, and bone milk23.

Benefits of Caffeine on Health

Caffeine, a natural stimulant found in coffee, tea, and various other beverages, has several potential health benefits when consumed in moderation:

1. Enhanced Alertness and Focus: Caffeine can improve attention, concentration, and reaction time by blocking adenosine, a neurotransmitter that promotes sleep.
2. Physical Performance: It may enhance physical performance by increasing adrenaline levels, making it a popular choice among athletes.
3. Antioxidant Properties: Caffeine has antioxidant effects, which help combat oxidative stress and reduce inflammation in the body.
4. Reduced Risk of Certain Diseases: Some studies suggest that regular caffeine consumption may lower the risk of diseases like Parkinson's, Alzheimer's, and certain types of cancer, such as liver and colorectal cancer.
5. Mood Enhancement: Moderate caffeine intake is associated with a lower risk of depression and may improve mood and overall well-being.
6. Metabolic Boost: Caffeine can increase metabolic rate and fat oxidation, which may aid in weight management.
7. Reduced Risk of Stroke: Some research indicates that moderate coffee consumption is linked to a lower risk of stroke.
8. Liver Health: Regular coffee drinkers may have a lower risk of liver disease and conditions like fatty liver disease.
9. Social Interaction: Drinking coffee or tea can promote social interactions, which are beneficial for mental health.

While caffeine has many potential benefits, it's important to consume it in moderation, as excessive intake can lead to negative effects such as anxiety, insomnia, and increased heart rate.

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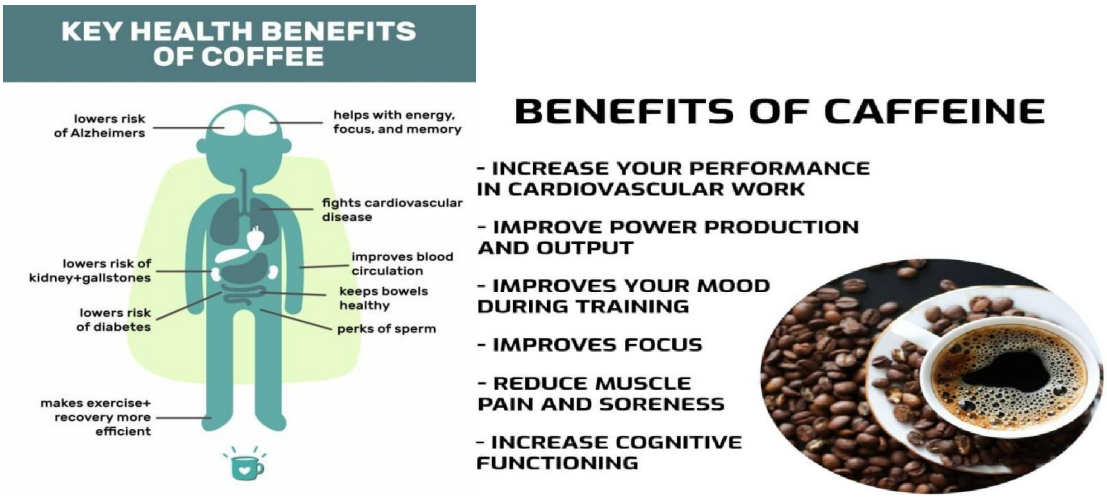

Side Effects

- When taken by mouth: Caffeine is likely safe for most healthy adults when used in doses up to 400 mg daily. This is equal to about 4 cups of coffee.
- Caffeine is possibly unsafe when used for a long time or in doses over 400 mg daily. Caffeine can cause insomnia, nervousness, restlessness, nausea, increased heart rate, and other side effects. Larger doses might cause headache, anxiety, and chest pain.
- Caffeine is likely unsafe when used in very high doses. It can cause irregular heartbeat and even death. Products with very concentrated or pure caffeine have a high risk of being used in doses that are too high. Avoid using these products.

DRUG INTERACTIONS

Major Interaction

- Do not take this combination
- Ephedrine interacts with CAFFEINE
- Stimulant drugs speed up the nervous system. Caffeine and ephedrine are both stimulant drugs. Taking caffeine along with ephedrine might cause too much stimulation and sometimes serious side effects and heart problems. Do not take caffeine-containing products and ephedrine at the same time.

Moderate Interaction

Be cautious with this combination

Adenosine (Adenocard) interacts with CAFFEINE

Caffeine might block the effects of adenosine. Adenosine is often used by doctors to do a test on the heart called a cardiac stress test. Stop consuming caffeine-containing products at least 24 hours before a cardiac stress test.

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Antibiotics (Quinolone antibiotics) interacts with CAFFEINE
The body breaks down caffeine to get rid of it. Some antibiotics can decrease how quickly the body breaks down caffeine. Taking these drugs along with caffeine might increase the risk of side effects including jitteriness, headache, increased heart rate, and others.

Cimetidine (Tagamet) interacts with CAFFEINE
The body breaks down caffeine to get rid of it. Cimetidine can decrease how quickly your body breaks down caffeine. Taking cimetidine along with caffeine might increase the chance of caffeine side effects including jitteriness, headache, fast heartbeat, and others.

Clozapine (Clozaril) interacts with CAFFEINE
The body breaks down clozapine to get rid of it. Caffeine seems to decrease how quickly the body breaks down clozapine. Taking caffeine along with clozapine can increase the effects and side effects of clozapine.

Dipyridamole (Persantine) interacts with CAFFEINE
Caffeine might block the effects of dipyridamole. Dipyridamole is often used by doctors to do a test on the heart called a cardiac stress test. Stop consuming caffeine- containing products at least 24 hours before a cardiac stress test.

Disulfiram (Antabuse) interacts with CAFFEINE
The body breaks down caffeine to get rid of it. Disulfiram can decrease how quickly the body gets rid of caffeine. Taking caffeine along with disulfiram might increase the effects and side effects of caffeine including jitteriness, hyperactivity, irritability, and others.

Estrogens interacts with CAFFEINE
The body breaks down caffeine to get rid of it. Estrogens can decrease how quickly the body breaks down caffeine. Taking caffeine along with estrogens might increase the side effects of caffeine, including jitteriness, headache, and fast heartbeat.

Fluvoxamine (Luvox) interacts with CAFFEINE
The body breaks down caffeine to get rid of it. Fluvoxamine can decrease how quickly the body breaks down caffeine. Taking caffeine along with fluvoxamine might increase the effects and side effects of caffeine.

Lithium interacts with CAFFEINE
Caffeine can increase how quickly your body gets rid of lithium. If you take products that contain caffeine and you take lithium, don't stop taking caffeine products all at once. Instead, reduce use slowly. Stopping caffeine too quickly can increase the side effects of lithium.
Medications for depression (MAOIs) interacts with CAFFEINE
There is some concern that caffeine can interact with certain medications, called MAOIs. If caffeine is taken with these medications, it might increase the risk for serious side effects including fast heartbeat and very high blood pressure.

Some common MAOIs include phenelzine (Nardil), selegiline (Zelapar), and tranylcypromine (Parnate).
Medications that slow blood clotting (Anticoagulant / Antiplatelet drugs) interacts with CAFFEINE

Caffeine might slow blood clotting. Taking caffeine along with medications that also slow blood clotting might increase the risk of bruising and bleeding.
Pentobarbital (Nembutal) interacts with CAFFEINE
The stimulant effects of caffeine can block the sleep-producing effects of pentobarbital.

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Phenylpropanolamine interacts with CAFFEINE
Caffeine can stimulate the body. Phenylpropanolamine can also stimulate the body. Taking caffeine along with phenylpropanolamine might cause too much stimulation and increase heartbeat, blood pressure, and cause nervousness.

Riluzole (Rilutek) interacts with CAFFEINE
Taking caffeine along with riluzole might decrease how fast the body breaks down riluzole. This might increase the effects and side effects of riluzole.

Stimulant drugs interacts with CAFFEINE
Stimulants, such as amphetamines and cocaine, speed up the nervous system. By speeding up the nervous system, stimulant medications can increase blood pressure and speed up the heartbeat. Caffeine can also speed up the nervous system. Taking caffeine along with stimulant drugs might cause serious problems including increased heart rate and high blood pressure.

Theophylline interacts with CAFFEINE
Caffeine works similarly to theophylline. Caffeine can also decrease how quickly the body gets rid of theophylline. Taking theophylline along with caffeine might increase the effects and side effects of theophylline.

Verapamil (Calan, others) interacts with CAFFEINE
Verapamil can decrease how quickly the body gets rid of caffeine. Taking caffeine along with verapamil can increase the risk of caffeine side effects including jitteriness, headache, and an increased heartbeat.

Medications for asthma (Beta-adrenergic agonists) interacts with CAFFEINE
Caffeine can stimulate the heart. Some medications for asthma can also stimulate the heart. Taking caffeine with some medications for asthma might cause too much stimulation and cause heart problems.

Carbamazepine (Tegretol) interacts with CAFFEINE
Caffeine might lower the effects of carbamazepine. Taking caffeine with carbamazepine can reduce its effects and increase the risk of seizures in some people.

Ethosuximide (Zarontin) interacts with CAFFEINE
Ethosuximide is used to control certain types of seizures. Caffeine might lower the effects of ethosuximide. Taking caffeine with ethosuximide might reduce its effects and increase the risk of seizures.

Felbamate (Felbatol) interacts with CAFFEINE
Felbamate is used to control certain types of seizures. Caffeine might lower the effects of felbamate. Taking caffeine with felbamate might reduce its effects and increase the risk of seizures.
Flutamide (Eulexin) interacts with CAFFEINE
The body breaks down flutamide to get rid of it. Caffeine might decrease how quickly the body breaks down flutamide. Taking caffeine along with flutamide might increase the effects and side effects of flutamide.

Phenobarbital (Luminal) interacts with CAFFEINE
Phenobarbital is used to control some types of seizures. Caffeine might lower the effects of phenobarbital and increase the risk of seizures in some patients.

Phenytoin (Dilantin) interacts with CAFFEINE
Phenytoin is used to control some types of seizures. Caffeine might lower the effects of phenytoin. Taking caffeine with phenytoin might reduce its effects and increase the risk of seizures.

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Valproate interacts with CAFFEINE
Valproate is used to control some types of seizures. Caffeine might lower the effects of valproate and increase the risk of seizures in some patients.

Water pills (Diuretic drugs) interacts with CAFFEINE
Caffeine can decrease potassium levels. "Water pills" can also decrease potassium levels. Taking caffeine along with "water pills" might make potassium levels drop too low.

Nicotine interacts with CAFFEINE
Taking caffeine along with nicotine might increase the risk for rapid heart rate and high blood pressure.

Pioglitazone (Actos) interacts with CAFFEINE
Caffeine might increase the amount of pioglitazone that the body absorbs. Taking caffeine might increase the effects and adverse effects of pioglitazone

Minor Interaction
Be watchful with this combination
Alcohol (Ethanol) interacts with CAFFEINE
The body breaks down caffeine to get rid of it. Alcohol can decrease how quickly the body breaks down caffeine. Taking caffeine along with alcohol might increase the effects and side effects of caffeine, including jitteriness, headache, and fast heartbeat. Birth control pills (Contraceptive drugs) interacts with CAFFEINE
The body breaks down caffeine to get rid of it. Birth control pills can decrease how quickly the body breaks down caffeine. Taking caffeine along with birth control pills can cause jitteriness, headache, fast heartbeat, and other side effects.

Fluconazole (Diflucan) interacts with CAFFEINE
The body breaks down caffeine to get rid of it. Fluconazole might decrease how quickly the body gets rid of caffeine. Taking caffeine along with fluconazole might cause caffeine to stay in the body too long and increase the risk of side effects such as nervousness, anxiety, and insomnia.

Medications for diabetes (Antidiabetes drugs) interacts with CAFFEINE
Caffeine can either increase or decrease blood sugar. Diabetes medications are used to lower blood sugar. Taking some medications for diabetes along with caffeine might change the effects of the diabetes medications. Monitor your blood sugar closely. The dose of your diabetes medication might need to be changed.

Mexiletine (Mexitil) interacts with CAFFEINE
Mexiletine can decrease how quickly the body breaks down caffeine. Taking Mexiletine along with caffeine might increase the effects and side effects of caffeine.

Terbinafine (Lamisil) interacts with CAFFEINE
Terbinafine can decrease how fast the body gets rid of caffeine. Taking caffeine along with terbinafine can increase the risk of caffeine side effects including jitteriness, headache, and increased heartbeat.
Medications that decrease break down of other medications by the liver (Cytochrome P450 CYP1A2 (CYP1A2) inhibitors) interacts with CAFFEINE
Caffeine is changed and broken down by the liver. Some drugs decrease how quickly the liver changes and breaks down caffeine. This could change the effects and side effects of caffeine.

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Metformin (Glucophage) interacts with CAFFEINE
Metformin can decrease how quickly the body breaks down caffeine. Taking metformin along with caffeine might increase the effects and side effects of caffeine.

Methoxsalen (Oxsoralen) interacts with CAFFEINE
Methoxsalen can decrease how quickly the body breaks down caffeine. Taking methoxsalen along with caffeine might increase the effects and side effects of caffeine.

Phenothiazines interacts with CAFFEINE
Phenothiazines can decrease how quickly the body breaks down caffeine. Taking phenothiazines along with caffeine might increase the effects and side effects of caffeine.

Tiagabine (Gabitril) interacts with CAFFEINE
Tiagabine is used to control some types of seizures. Caffeine does not seem to influence the effects of tiagabine. But long-term caffeine use might increase blood levels of tiagbine.

Ticlopidine (Ticlid) interacts with CAFFEINE
Ticlopidine can decrease how fast the body gets rid of caffeine. Taking caffeine along with ticlopidine can increase the risk of caffeine side effects.

III. CONCLUSION

Coffee is the most consumed caffeinated libation, while caffeine can also be set up in tea, soft drinks, and energy potables. Studies on the associations between coffee consumption and a range of health issues have been completed. Epidemiological studies reveal that, for the maturity of people, coffee consumption is profitable and negatively connected with threat for a number of conditions. multitudinous experimenters have lately conducted studies on the goods of caffeine on conditions similar as cancer, cardiovascular, immunological, seditious, and neurological diseases, among others, as well as in sports, suggesting that this field of study is expanding snappily. To clarify the link between caffeine consumption and specific conditions and to examine consumption patterns in relation to health issues, randomized controlled studies are needed because association does n't indicate reason. Because utmost studies have concentrated on grown-ups, little is known about the negative consequences of children and adolescents consuming particulars with

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