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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/18948
DOI URL: http://dx.doi.org/10.21474/IJAR01/18948

RESEARCH ARTICLE

NATURAL CAFFEINE, SOURCES, EXTRACTION, USAGE, AND EFFECT OF CAFFEINE ON HUMAN HEALTH

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Manuscript Info

Manuscript History
Received: 20 April 2024
Final Accepted: 24 May 2024
Published: June 2024

Key words:-
Natural Caffeine, Extraction Caffeine, Consumption, Intake, Coffee, Tea, Cola, Energy Drink

Abstract

The primary method of absorbing natural caffeine (1,3,7-trimethylxanthine) is through the consumption of coffee.Natural Caffeine is a white crystalline purine containing methylxanthine alkaloids with a harsh flavour. It is the most often consumed bioactive substance across the world. It is a naturally occurring alkaloid found in over 60 plants, including coffee beans, tea leaves, cola nuts, and cocoa pods. Natural Caffeineis extracted from Coffee arabica beans . It can be found in various plant sources such as Coffee beans, tea leaves ,Cacao Beans , Yerba mate ,Guarana ,Kola nuts. It can have a favourable or harmful impact on human health. Natural sources of caffeine frequently include plant polyphenols (phenol-carboxylic acids, catechins) with known antioxidant properties; however, stimulant drinks and dietary supplements frequently contain sugars or artificial sweeteners, which can significantly reduce caffeine's effects on oxidative stress.C-14 testconducted for Natural Caffeine by Mangalore University and the University of California. An Inhouse testing method by HPLC has been developed by Bio-Med Ingredients Pvt. Ltd for determining Caffeine content in samples. Caffeine finds many applications, as it is used in dietary supplements ,Vitamin Premixes , Cosmetics and for energy performance benefits including improved physical endurance and reduced fatigue.

Introduction:-

Caffeine is found in various kinds of foods and drinks that we consume in daily life. (1) Caffeine is the most frequently used substance with a stimulant effect on the central nervous system. It causes various physiological effects such as relaxation of bronchial muscle, stimulation of the central nervous system, gastric acid secretion and dieresis. (2) Caffeine is a natural ergonomic aid for athletes which promotes thermogenesis aiding the body to burn calories and fat, providing prolonged energy.(3)

Figure 1;shows structure of Caffeine (1,3,7-trimethylxanthine) , which is a heterocyclic organic compound with a purine base called xanthine, consisted of a pyrimidine ring linked to an imidazole ring. [4] Caffeine is known as an alkaloid because it is a secondary plant metabolite derived from purine nucleotides, with a heterocyclic nitrogen

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atom. [4-5] However, because it does not have the incorporation of an amino acid in its biosynthesis some authors call it a pseudo-alkaloid. (6)

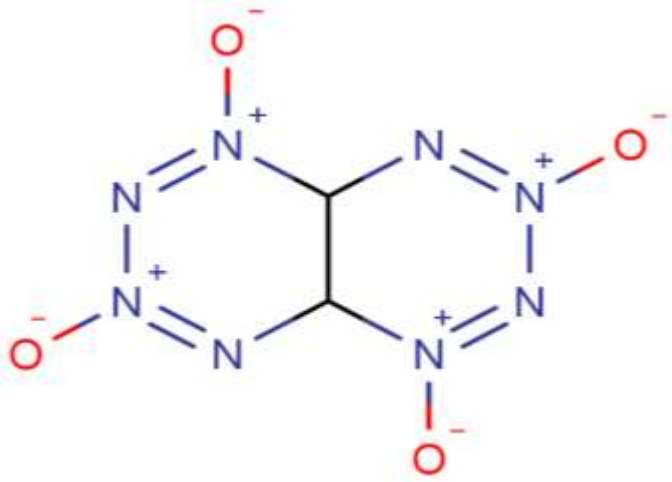


Figure 1:- Structure of Caffeine.

Sources of Caffeine

Caffeine is a naturally occurring alkaloid that is found in varying quantities in the beans, leaves, and fruits of more than 60 plants. Some common sources of caffeine are the kola nut (Cola acuminate), cacao bean (Theobroma cacao), yerba mate (Ilex paraguariensis), guarana berries (Paulliniacupana) and tea leaves (Camelia siniensis); however, roasted coffee beans (Coffea Arabica and Coffea robusta), and are the world's primary sources of dietary caffeine (Barone and Roberts 1996). It is also found in several commercial non-alcoholic beverages, powders, capsules and in association with therapeutic drugs.(7)

Natural sources of Caffeine

Coffee Beans:

Coffee is one of the most well-known natural sources of caffeine. The caffeine content can vary based on factors like the type of coffee bean and the brewing method.The two main varieties of coffee beans used are Arabica and Robusta .It is seen in Figure 2 ;Coffee Arabica beans , which are known to have lesser Caffeine content than Robusta. (8)

Figure 1:- Coffea Arabica Beans.

Tea Leaves:

Tea, especially black tea and green tea, contains caffeine. Figure 3 ; Green tea leaves shown which are known to be a natural source of natural caffeine. The caffeine content in tea can vary depending on factors like the type of tea and how it's brewed. (9-11)

Figure 2:- Green tea Leaves.

Figure 3:- Cacao Beans.

Figure 4:- Yerba Mate.

Cacao Beans:
Cacao beans, as seen in Figure 4; are used to make chocolate, also contain caffeine. However, the amount of caffeine in chocolateproducts can vary based on factors like the percentage of cacao and the type of chocolate.(12)

Yerba Mate:
Yerba mate as seen in figure 6;is a South American tea-like beverage that contains caffeine. Its popular in countries like Argentina, Uruguay, and Paraguay. (13)

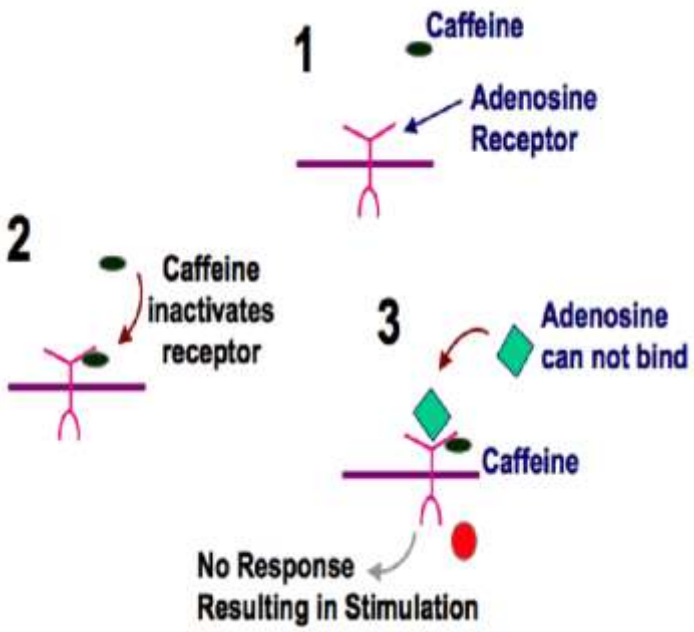
Guarana:
Guaranaas seen in Figure 7;is a plant native to the Amazon basin, and its seeds contain caffeine. It's often used as an ingredient in energy drinks and supplements.(14)

Figure 5:- Guarana.

Kola Nuts:
Kola nuts as seen in Figure 8, found in the fruit of the kola tree, are another natural source of caffeine. They are used in some traditional beverages and cola-flavoured drinks.(15)

Figure 6:- Kola Nuts.

General toxicity
Caffeine toxicity in adults can present a spectrum of clinical symptoms, ranging from nervousness, irritability and insomnia to sensory disturbances, diuresis, arrhythmia, tachycardia, elevated respiration and gastrointestinal disturbances. Caffeine toxicity in children is manifested by severe emesis, tachycardia, central nervous system agitation and diuresis. Chronic exposure to caffeine has been implicated in a range of dysfunctions involving the gastrointestinal system, liver, renal system and musculature (16-17).



Mechanism of action :
Figure 9; explains the mechanism of action of caffeine The most important mechanism of action of caffeine is the antagonism of adenosine receptors..Adenosine is a locally released purine which acts on different receptors that can increase or decrease cellular concentrations of cyclic adenosine monophosphate (cAMP). Caffeine selectively blocks adenosine receptors and competitively inhibits the action of adeno- 15 mg kg1 bw. For have been given as 1 mg kg1 bw in the USA, <3mgkg1 bw in the UK and <2.5mgkg1 bw in Denmark. (18-20)

Pharmacokinetics
Following ingestion, caffeine is rapidly and essentially completely absorbed from the gastrointestinal tract into the bloodstream. Maximum caffeine concentrations in blood are reached within 1–1.5h following ingestion. Absorbed caffeine is readily distributed throughout the entire body. It passes across the blood–brain barrier, through the placenta into amniotic fluid and the foetus, and into breast milk. Caffeine has also been detected in semen.(21-22)

The liver is the primary site of caffeine metabolism. (16,22) In adults, caffeine is virtually completely metabolized to 1- methylxanthine and 1-methyluric acid from the para- xanthine intermediate. Only 1–5% of ingested caffeine is recovered unchanged in the urine. Infants up to the age of 8–9 months have a greatly reduced ability to metabolize caffeine, excreting about 85%.

Extraction of Natural Caffeine and Standardization
Raw material :
Natural Caffeine has been extracted from the Coffee beans , **Coffea Arabica L**beans, procured from the south part of Karnataka region, India.

Extraction method :
Coffee beans were flaked by using flaker and extracted with acidic water (Water + HCl). In this process almost 80% of the caffeine is present in the beans. The extract has been filtered and neutralized by sodium bicarbonate. Filter the precipitate and extract with chloroform. Crude crystals of caffeine around 80-85% purity were obtained . These crude crystals are again crystallized by ethanol to get 95% pure crystals .

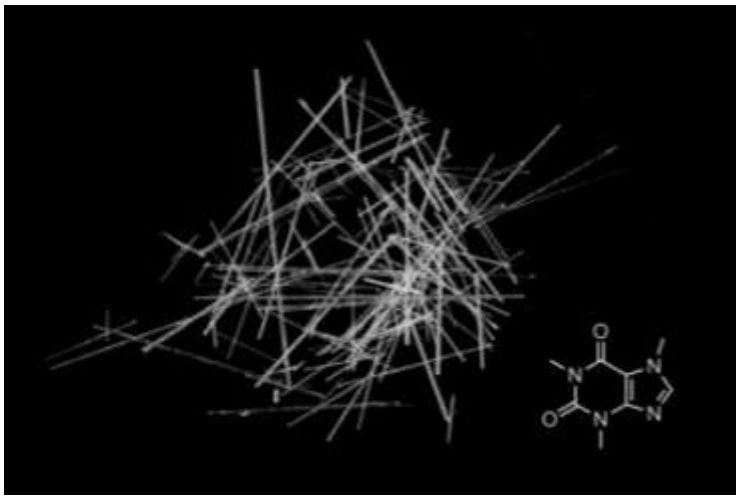


Figure 7:- Caffeine Crystals.

Crystallization:

Crude crystals 80-85% purity , were taken in a beaker , and 1:3 ratio of ethanol stirred well and temperature 50-60^{o} C. This saturated solution cooled and allowed overnight to develop pure and good crystals. Natural Caffeine crystals look like needle shaped white crystals. Mother liquor has been decanted to get pure white crystals. This process is repeated to get **95% to 99% pure crystals**

Natural Caffeine 99% Powder :

Natural caffeine powder as seen in figure 11 , that is 99% pure typically means it's a concentrated form of caffeine extracted from natural sources like coffee beans or tea leaves. It's commonly used as a supplement or ingredient in energy drinks, pre-workout supplements, and other products for its stimulant properties. It's important to use it carefully and in moderation due to its potency.

Figure 8:- Natural Caffeine 99.0% Powder.

Natural Caffeine 99% Granules:

Natural caffeine 99% granules , as represented in figure 12;typically refer to a concentrated form of caffeine derived from natural sources like coffee beans or tea leaves. This high purity level means that 95% of the substance in the granules is caffeine, with the rest likely being other natural compounds from the source material. It's often used in dietary supplements, energy drinks, and other products where a potent, natural source of caffeine is desired. Natural Caffeine granules will be of different mesh size , 20#, 40#, 60# as per USP grade

Figure 12:- Natural Caffeine 99.0% Granules.

Natural Caffeine Testing by C14 test.

C14 test :

A C14 test, or carbon-14 dating test, is a method used to determine the age of organic materials based on the decay rate of carbon-14, a radioactive isotope of carbon. This technique is commonly used in archaeology, anthropology, and other fields to date objects such as fossils, artifacts, and historical structures. The basic principle is that carbon-14 is incorporated into living organisms through the food chain, and after an organism dies, it stops taking in carbon-14. The remaining carbon-14 in the organic material decays over time, allowing scientists to estimate the age of the sample. In order to confirm the source , Natural caffeine was analysed in external laboratory and the results reported were as per figure 13 and 14.

Reference Number :CARER/2023-24/Report-42 Dated: October 31, 2023

Sl. No.	Sample Code	Percentage modern carbon (pMC) ± 2 σ	^{14}C (Bq/kg C) ± 2 σ	^{14}C (dpm/g C) ± 2 σ
1	BMI20230397	98.5 ± 3.0	222.7 ± 6.7	13.4 ± 0.40
2	BMI20230482	98.0 ± 3.1	221.5 ± 7.0	13.3 ± 0.42

Figure 9:- Table depicting C-14 Test Results from Mangalore University, Karnataka India.

Reference Number :C.A.I.S. Invoice No.: [NPI240120] Certificate#: [BIO-MEDINGREDIENTS_1_2402] Dated: August 15, 2023

Sample	**Lot**	**pMC**	**^{14}C**	**+ 1σ**	**$\delta^{13}C$**	**+ 1σ**	**δD**	**+ 1σ**
Caffeine 99%	BMI20230262	100	13.65	0.08	27.68	0.01	-162	0

Figure 14:- Table depicting C-14 Test Results from Georgia University.

Procedure For Granulation

Roller compaction is a dry granulation process used in the pharmaceutical industry to create drug granules with suitable densification, drug content uniformity and powder flowability. During the roller compaction operation of natural caffeine, the extract powder of 99% purity is passed continuously through the gap between a pair of counter rotating compression rolls to form solid ribbons or sheets or flakes which are then passed through a mill or granulator with a suitable sized size to form dry granules.

Procedure

1. Preparation of the Powder: If the natural caffeine powder is clumpy or not very fine, the material needs to be sifted through a fine sieve or mesh screen to break up clumps and ensure a smooth granule.

2. **Mix with Binder (Optional):** If using a binder, it should be mixed with the caffeine powder. Common binders include starch or cellulose. The binder helps the granules stick together. Using a ratio of around 1 part binder to 5-10 parts caffeine powder, depending on the desired consistency.

3. **Add Water (If not Using Binder):** If you're using a dry binder like starch, add a small amount of water to create a paste-like consistency. The water should be added gradually to avoid making the mixture too wet.

4. **Mix Thoroughly:** Stir the mixture well until the caffeine powder and binder are evenly distributed. The mixture should be slightly damp but not wet.

5**. Form Granules:** Preheat your oven to a low temperature, around 200°F (93°C). Line a baking tray with parchment paper. Spread the mixture evenly on the parchment paper in a thin layer.

6**. Drying in Oven:** Place the tray in the preheated oven. Let it dry for about 1-2 hours, checking periodically. The granules are ready when they are dry to the touch and easily crumble.

7. **Cool and Store:** Once dry, remove the tray from the oven and let the granules cool completely. Break up any large clumps into smaller granules if needed. Store the caffeine granules in an airtight container in a cool, dry place. It's essential to ensure the granules are completely dry before storing to prevent mold or spoilage. Experiment with different binder ratios and drying times to achieve the desired texture and consistency. Be cautious when working with caffeine powder and avoid inhaling it or getting it into your eyes. Use gloves and a mask if necessary.

Methods:-

Natural Caffeine Powder as seen in figure 15 ;was converted into natural caffeinegranules by the process of wet granulation. Granules as in Figure 16 ; can be considered as primary powder particles which adhere and form larger multi-particles entities having size range from 0.2 and 4.0 nm and are mainly dependent on the use of granules.

Granulation is known to possess several benefits such as to prevent loss of constituents from the powder mix , thereby ensuring the contents of the powdered sample to be intact. Granulation also helps improve the flow properties of the mix. Improvisation of the compaction characters of the mixture:

The granulation process is also helpful to minimizing the hazards associated with toxic dust particles during handling, transporting of powders, thus precaution should be taken. Granules generally occupy less volume per unit weight and are denser than the powder mix, thus more convenient for storage and shipment. Granulation technique helps adhesion and cake formation of hygroscopic materials. This occurs because the granules willbe able to absorb some moisture and still retain the flow-ability because of their size 3. The product appearance also is known to improve due to granulation.

Figure 10:- Natural Caffeine 99.0% Powder.

Figure 16:- Natural Caffeine 99.0% Granules.

HPLC Analysis of Caffeine:

A Shimadzu P-series HPLC with auto-sampler was operated via Lab solutions software to run the test. The machine includes a UV detector as well as PDA (Photo-Diode array) detector with a 5 µm C-18, shim-pack column of dimensions 4.6 x 250mm. The Gradient mobile phase consisted of Double distilled water, Formic acid and acetonitrile as Mobile phase A and B in varying concentrations. The Total Run time of the analysis is 25 minutes and wavelength of detection of natural caffeine is at 275 nm. Total flow rate is 1.5ml/min, with injection volume of 20 µl. Retention Time of natural caffeine reference standard observed at 7.4, whereas RT of natural caffeine powder and granules recorded at RT 7.6. Thus ,the results obtained can be visualised through a 3-D Chromatogram as seen in Figure 17 and Figure 18.Thus, the retention time of Natural Caffeine Standard, Granules and Powder can be seen as in Figure 19 , Figure 20 and Figure 21.

Materials:-

Acetonitrile was of HPLC grade obtained from MERCK, Ortho-phosphoric acid and Formic acid was of Qualigens.

Preparation of Reference standard:

Stock solution of caffeine RS was prepared by dissolving 0.01g in 50 ml of diluent, i.e 0.1% ortho-phosphoric acid. approximately 5.1ml of Acetonitrile was added and volume was made up using diluent.

Preparation of Samples:

Stock solution of Caffeine powder and granules were prepared by dissolving 0.01 - 0.025 g in 50 ml diluent, approximately 5 ml of acetonitrile was added, and volume was made up using diluent.

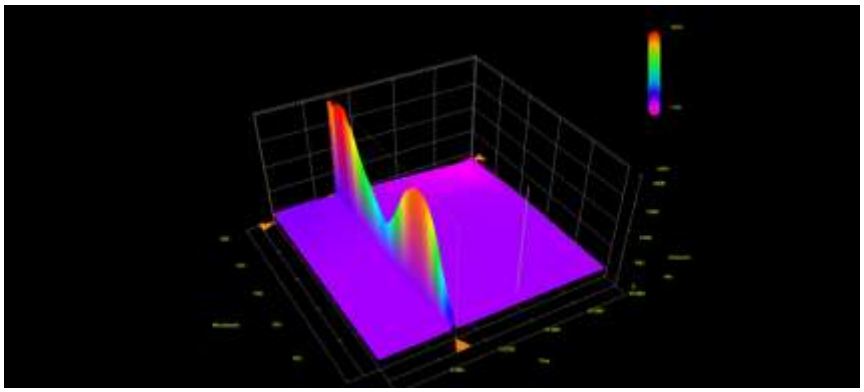


Figure 11:- Natural Caffeine powder 3D Chromatogram.

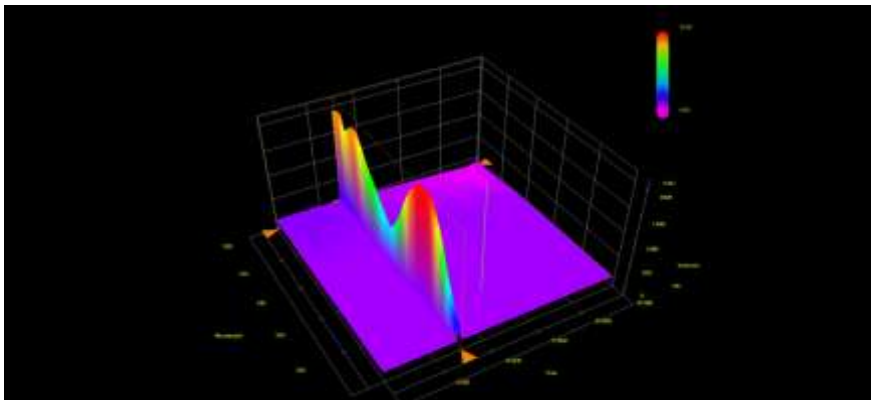


Figure 18:- Natural caffeine granules 3D Chromatogram.

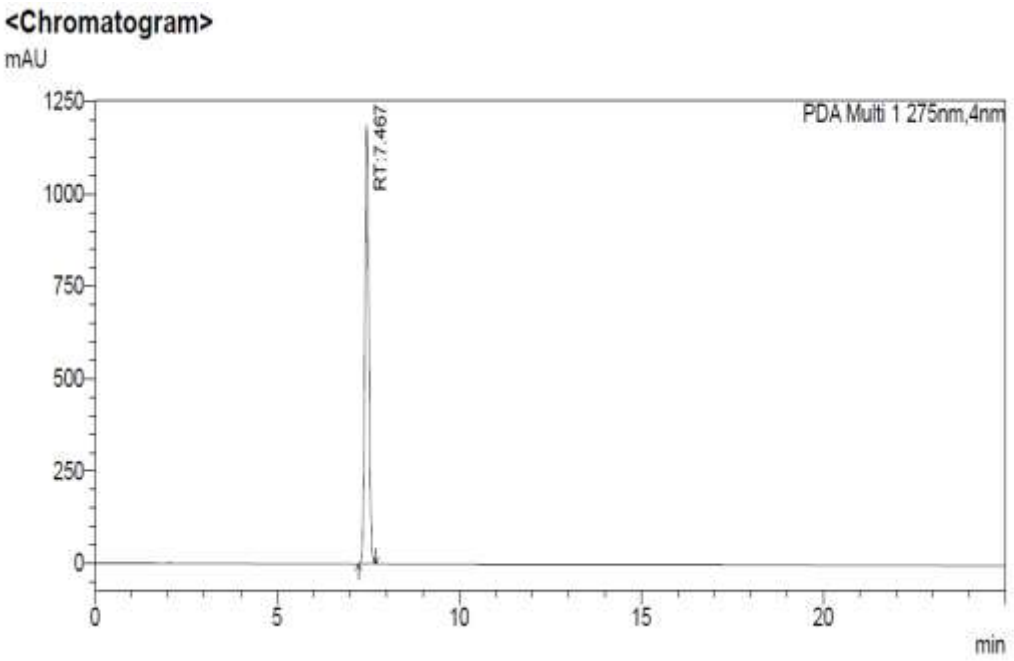


Figure 19:- Caffeine Reference standard HPLC Chromatogram.

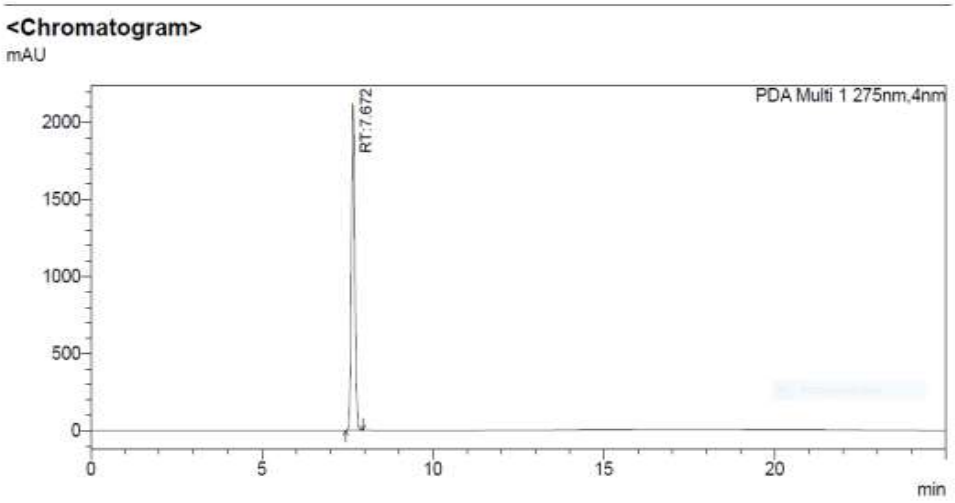


Figure 20:- Natural Caffeine powder HPLC Chromatogram.

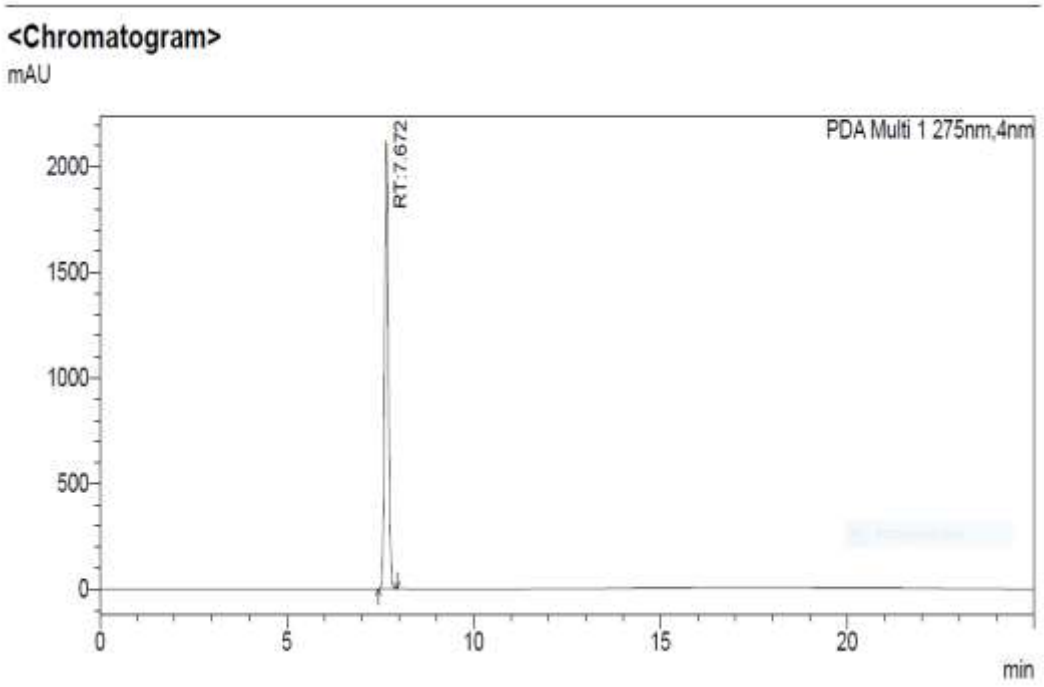


Figure 21:- Natural Caffeine Granules HPLC Chromatogram.

	Bottle/can mL (oz)	Caffeine mg/100 mL (mg/oz)	Total caffeine mg (range)
Red bull	250 (8.4)	32 (9.6)	80
Monster	473 (16)	34 (10)	160
Rockstar	473 (16)	34 (10)	160
Full throttle	473 (16)	30 (9)	144
No fear	473 (16)	37 (10.9)	174
Amp	250 (8.4)	30 (8.9)	75
SoBe	250 (8.4)	32 (9.5)	79
Tab energy	311 (10.5)	31 (9.1)	95
Cola	355 (12)	11 (3.3)	40 (30–60)
Coffee	237 (8)	36 (10.6)	85 (65–120)
Tea	237 (8)	17 (5)	40 (20–90)

Figure 22:- Natural Caffeine Content in Various Drinks.

Figure 23:- Natural Caffeine Applications as Flavouring agents.

Figure 24:- Natural Caffeine Applications in Coffee Aroma.

Figure 25:- Natural Caffeine Applications in Dietary Supplements.

Figure 26:- Natural Caffeine Applications in Cosmetic Products.

Figure 27:- Natural Caffeine Applications in Pharmaceutical Products.

Applications Of Natural Caffeine

Food and Beverage Industry:

1.Energy Drinks: Natural caffeine is a key ingredient in many energy drinks, providing a boost to alertness and energy levels.(23).Figure 22; shows levels of natural caffeine in various energy drinks.

2.Coffee and Tea: Naturally, caffeine is found in coffee beans and tea leaves, making it a primary component of these popular beverages.(23)

3.Functional Foods: Caffeine is added to some foods, such as snacks and bars, to provide an energy boost.(23)

4. Chocolate and Cocoa Products: Cacao beans contain caffeine, so chocolate products also contain some level of natural caffeine.(23)

5. Flavouring Agent: In some cases, caffeine can be used as a flavouring agent, especially in products that are designed to have a coffee or tea flavour.(23)as shown in Figure 23 and Figure 24.

Natural Caffeine in Health and Wellness Category

1. Dietary Supplements: Natural caffeine is often included in dietary supplements designed to increase energy, focus, and metabolism.(24)Figure 25 depicts supplements derived from Natural Caffeine source .

2. **Weight Loss Aids** Caffeine is a common ingredient in weight loss supplements due to its ability to boost metabolism and suppress appetite.(2)
3. **Pre-Workout Supplements**: It's often included in pre-workout formulas to enhance exercise performance and endurance.(24)
4.**Cosmetics**:Some skincare and beauty products use caffeine for its potential to reduce puffiness and improve circulation when applied topically.(24)as seen in figure 26.

Natural Caffeine in Pharmaceutical Products:
1.Natural Caffeine Medications:
Caffeine is sometimes used in medications, particularly in pain relievers like aspirin, to enhance their effectiveness as seen in Figure 27;
2.Headache Remedies: It's also a component of some headache remedies, as it can help alleviate headaches by constricting blood vessels

Conclusion:-

Natural Caffeine has been derived from various plant sources , including coffee beans, tea leaves, cola nuts, and cocoa pods.However ,Natural Caffeine is extracted from Coffee arabica beans .A C14 testwas conducted by Mangalore University and the University of California to check the origin andconfirm the naturality of the product. Nowadays many consumer products contain synthetic caffeine , which leads to several health issues. Social awareness is required to reduce the use and consumption of synthetic caffeine. Naturally derived caffeine has health benefits and also it will be safe to consume. Bio-Med Ingredients provide the 100% Pure natural Caffeine which is used in nutraceuticals, cosmetics, food , confectionery , beverages, dairy and dietary supplements. Bio-Med Ingredients has thus developed natural caffeine powder and granules by extraction of Coffea Arabica beans . Natural Caffeine Granules are more comfortable to handle and use without the much process in the various applications. Thereby , Natural Caffeine has very wide applications in food, health and cosmetics applications , with more and more research innovations required to prove the efficacy in each product category.

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