Review Article

Bioactive Building Blocks and Potential Pharmacological Perspectives of Green Coffee: A Review

ABSTRACT

Coffee is known to be one of the popular beverages today on the globe. Due to its easy availability and preparation, it is consumed by the population of almost all countries. This wonder crop was discovered in the 6th century in Ethiopia. Since then, people have also used various brewing methods to extract hundreds of the bioactive compounds present in these aromatic seeds. No doubt, excessive consumption of the same can be harmful too. As a functional food, coffee is known to have multiple health benefits. Coffee beans contain vitamins, minerals, caffeine, chlorogenic acid, and various other biologically active ingredients. This review briefly describes the major biologically active compounds present in these seeds – caffeine, trigonelline, diterpenes, and chlorogenic acid (CGA). It also aims to describe various bioactive activities such as antioxidant, antiproliferative, antibacterial, antiviral, etc., against variable hallmarks. Thus, explaining different pharmacological effects for the welfare of the human population.

KEYWORDS: Green coffee, Origin, Caffeine, Diterpenes, CGA, Pharmacology

ABBREVIATIONS

BCC	Basal Cell Carcinoma
CETP	Cholesterol Ester Transfer Protein
CFA	Feruloylquinic Acid
CGA	Chlorogenic Acid
CQA	Caffeoylquinic Acid
diCQA	Dicafeolquinic Acid
GCB	Green Coffee Beans
LDL	Low Density Lipoprotein
TRG	Trigonelline
T2DM	Type 2 Diabetes Mellitus

1. INTRODUCT0ION

Coffee, an evergreen arbor, has derived its name from 'Keffa' province, where shepherds from Abyssinia/Ethiopia discovered it in the 6th century [1]. This member of the genus Coffea and family Rubiaceae is native to Ethiopia. It expanded first to India and then to other countries Indonesia, Brazil, Columbia, and Central America [2 and 3]. As of now, it got a lay hold in the human community for 1200 years [4].

Green coffee beans are now known to be produced in more than 70 countries [5]. Coffee encompasses about 90 different numbers of species [6, 7, and 8]. Among various species such as *Coffea canephora*, *Coffea liberica*, *Coffea excels*, and *Coffea stenophylla*; only *Coffea arabica* (Arabica) and *Coffea canephora* (Robusta)are of commercial importance [1, 6 and 8] and accounts for about 60% and 40% to the global coffee market, respectively [9, 10, 11 and 12]. Arabica and Robusta may seem similar, but there are various note-worthy differences among them [1].

Robusta is primarily used in the formation of prompt coffee infusions. Green (raw) Robusta coffee beans have elevated levels of caffeine and chlorogenic acids (CGA) and a lower trigonelline content than Arabica [13, 14, and 15]. In

contrast, Arabica coffee is higher ranking than Robusta due to its organoleptic characteristics and, therefore, is more costly [16]. Also, Arabica requires a variable environmental condition and produces less coffee per hectare than Robusta, increasing the growth cost [1].

What is known as 'coffee' is a liquid refreshment made by infusions of roasted and grounded green beans. The plant of *Coffea* gives rise to red cherry-like fruits having two seeds [17]. Each grain is segregated either by wet or dry processing of coffee fruits. First, the processing is needed to remove the fruit tissue (flesh) [18 and 19]. Then, these seeds are stuffed in sacks and conveyed to the countries consuming them. Once collected, they are mingled with green coffee beans from another emergence. Afterward, they are roasted to construct the predictable savor and shade associated with coffee beverages [20].

Coffee is known to be the most favored beverage on the planet, with about 400 billion cups consumed in a year. One of the most consumed beverages – either roasted or instant infusion and in global commodity. This is due to the 700 compounds that are together accountable for its aroma, pleasant taste, stimulant effect, physiological effects, and health benefits[17, 21, and 22].

Many people among the population living on this globe can't even start their day without having a cup of coffee at the beginning of the day. This well-liked beverage contains immense energy needed to raise and make it through the whole day.

Moreover, a portion of food that asserts to upgrade health or well-being by supplying benefits beyond that of the conventional nutrients it carries is known to be a 'functional

food'. Food items containing the biologically active ingredients are observed as functional because of their alliance with various corporal benefits associated with the prevention and elimination of several chronic diseases [23]. For example, coffee as an available food has multiple health benefits. Coffee beans contain vitamins, minerals, caffeine, chlorogenic acid, and various other biologically active ingredients [24]. Also, coffee has multiple chemical compounds rich in biological activity (caffeine, trigonelline, and chlorogenic acids). All these compounds together make it a potential functional food product [25 and 26].

Natural bioactive compounds have shown various antimicrobial, antiviral and anti-inflammatory, and antiproliferative properties. As a result, they are gaining considerable attention as an eco-friendly alternative to synthetic compounds or agents [27].

Various studies, including the clinical studies, have validated that utilization of several cups of coffee daily prevents and fights cancer too. Findings also demonstrate that coffee compounds are anti-cancerous and present at a therapeutic concentration [28].

The purpose of this article is to interpret the various researches on the bioactive ingredients found in coffee and their potential pharmacological approaches.

Studies suggest that GC has a very loaded composition of chemicals, including saccharides, lipids, fatty acids, sterols, polyphenols, phenolic acids, alkaloids, free amino acids, proteins, vitamins, and minerals [7 and 29]. In addition to all these, it is considered to be a source rich in compounds exhibiting various antioxidants and free radical scavenging activities such as CGA, caffeine, hydroxycinnamic acids, and caffeic acid[7 and 30]. Moreover, the chemical

composition and the biological activity of the green beans are affected during the process of roasting. As a result, many biologically active compounds are mainly degraded, which degrades its various pharmacologically essential activities. This results in the fact that Green Coffee Beans (GCB) seems to be a superior source for taking the benefits from the same [31].

2. BIOACTIVE INGREDIENTS PRESENT IN COFFEE

activity [43] and activity against respiratory viruses [44]. Undoubtedly, coffee is admired and known for its fragrance and flavour, and its caffeine content is likely to play a crucial role in its vogue. It's a fact that coffee is the primary source of caffeine in many populations and is a combination that is reported to have more than a thousand different chemical substances, including lipids, nitrogenous compounds, carbohydrates, minerals, amino acids, alkaloids, and various phenolic compounds [32 and 33]. Moreover, multiple combinations of biological activity present in this aromatic functional food correlate with several advantageous effects [34 and 35]. Not limited to but yes these include, antioxidant capacity [1], antiproliferative effect against human cancer cell line [34 and 36], role in controlling oxidative and inflammatory stress conditions [37], reduction in blood pressure [38], reduced risk of developing Basal Cell Carcinoma (BCC) [39], reduced risk of Hypertension and epithelial ovarian cancers [40 and 41], protective effects against human low-density lipoprotein oxidation [42], effect on fasting blood glucose and insulin concentration (diabetic), antimicrobial

2.1. Caffeine

(Guaranine; Methyltheobromine; 1, 3, 7 – Trimethylxanthine; Theine)

(Molecular formula – $C_8H_{10}N_4O_2$)

Caffeine contains two fused rings with molecular formula *C8H10N4O2* [21]. It is a type of alkaloid, occurring naturally in coffee beans. It's among the common stimulants consumed worldwide. It occurs naturally in coffee beans. Among the numerous compounds present in coffee, only caffeine is known to be thermostable. This means this is one such chemical composition of coffee that is not destroyed by roasting (even excessive roasting) [46].

Caffeine is a type of xanthine (methylxanthine) constituting about 4 % of the total compounds present in beans of the fruits. This percentage may vary according to the species. For example, robusta is found to have an average of about 2.2% caffeine while Arabica about 1.2% only [47].

Caffeine is known to be found in numerous natural and manufactured products counting green tea[48 and 49], chocolates[50], various drinks (caffeinated-beverages and energy drinks) [51, 52 and 53], and of course coffee (Arabica and Canephora) [47, 54 and 55].

The concentration of caffeine may vary in coffee beverages and can be found up to 30 mg in a standard cup of coffee [33 and 56].

Studies suggest that caffeine is rapidly (more or less)absorbed in digestive issues such as the stomach and intestine and diffuses to all body tissues, including parts of the nervous system such as the brain. Also, it's been suggested that caffeine is primarily metabolized in the body's liver [33].

2.2. Diterpenes

(Diterpenoids)

(Molecular formula – $C_{20}H_{32}$)

Diterpenes are a constitutionally varied category of Carbon-20 (C20) compounds occurring naturally. They are extensively distributed in Mother Nature. The condensation of isoprene units derived from mevalonate pathways is responsible for these carbon compounds' origination [57]. Also, they may occur in the Carbon (20) backbone, where these units of isoprene are combined in various configurations to give an arrangement of diterpenes such as membrane, guanacastepene, abietane, jatropha, quinonoid, cafestol, and kahweol types [58, 59, 60, 61, 62 and 63].

They are generally found as metabolites (secondary) in organisms [64]. Coffee, the complex mixture of chemicals, is also found to have diterpenes [65]. The typical bean of coffee arabica contains a structural analog of cafestol in a concentration up to 0.17mg/ml in coffee [66 and 67]. The most influential diterpenes in coffee beans are found in higher concentrations in unfiltered coffee (6-12 mg) [47], as they are mostly removed with the help of filter papers from coffee [33].

Studies also suggest that diterpenes are absorbed intestinally only [68].

2.3. Trigonelline

(TRG; 1-methylpyridinium-3-carboxylate; Nicotinic acid N-methypyridinium-3-Carboxylate; Coffearine; Gynesine)

(Molecular formula – $C_7H_7NO_2$)

Trigonelline is an alkaloid (bitter) in coffee that seems to produce the vital aroma compounds present. Trigonelline is also named N-methyl nicotinic acid as it is derived from the nitrogen atom by its methylation of the compound Nicotinic acid or Niacin. Therefore also known as a pyridine alkaloid [69, 70, and 71].

In terms of concentration, trigonelline is higher for arabica than robusta. It may range from about 0.6-1.3% and 0.3-0.9%, respectively. But when compared to green coffee - there is an overall net increase of about 10 x from green to roasted [72]. It has also been suggested that trigonelline in coffee Arabica and Coffee Robusta can also be used as a roasting level discriminator [73].

2.4. Chlorogenic Acid

(CGA; 3-(3,4-Dihydroxycinnamoyl) acid; 3- Caffeoylquinate; 3-CQA; Chlorogenate; Heriguard)

(Molecular formula – $C_{16}(H_2O)_9$)

The esterification of trans-cinnamic acids and quinic acid results in the formation of CGAs, which may even exist in different isomeric forms depending on the place of the ester bond [74]. They may also be named 5-caffeoylquinic acid (5-CQA) [75 and 76]. They have nothing to do with chlorine, as the name suggests [34]. Among many types of chlorogenic acids, caffeine-like acids (CQA) is most important. They represent approximately 80% of the chlorogenic acid content. This content of CQA is followed by dicafeolquinic acid (diCQA), feruloylquinic acid (CFA) etc [77 and 78].

Coffee is one of the richest dietary sources containing caffeic acid (cinnamic acid) and chlorogenic acids for those who drink it daily. The CGA content of a 200 ml (7-oz)cup of coffee has been reported up to 350mg, which would provide up to 75mgofcaffeicacid[33]. Colostomy studies suggest that about 33% of the CGA I and 95% of the intestinally absorbed caffeic acid. Therefore, 2-3 of the CGA ingested reaches the colon, which is metabolized by the microflora [79 and 80].

This polyphenolic compound is abundant in many plants, including tobacco, mulberry, and, of course, coffee [81, 82, 83, and 84]. The astringent taste of the brews of the coffee is because of this phenolic compound only [85 and 86].

3. POTENTIAL PHARMACOLOGICAL EFFECTS OF THE BIOACTIVE INGREDIENTS

3.1 CAFFEINE

Studies suggest that consumption of caffeine shows a positive influence in various animal and human experiments. Furthermore, it was also found that its consumption exhibits an ergogenic effect [87].

Persons with Parkinson's disease were also tested with the stimulatory effects of caffeine which gave promising results. It showed that it could be used to manage non-motor as well as motor symptoms [88]. It's also been suggested that caffeine appears to exert most of its biological effects through the antagonism of the A1 and A2A subtypes of the adenosine receptor [89]. Caffeine is also known to stimulate the human nervous system (central), to increase the blood flow by the dilation of peripheral vessels, to enhance the breathing rate, and it is also known to aid the digestion of the food in the stomach [90]. Studies also report the enhancing effect of caffeine [91], generating a very keen exchange of views

between researchers [47]. The individuals who generally consume 3-5 cups of coffee a day show a very low prevalence of Alzheimer's disease compared to all those who do not have coffee daily [92, 93, and 94].

3.2 DITERPENES

Diterpenes have attracted recognition because of its gripping biological and pharmacological activities [57].

Study shows that (in vitro) utilization of even small amounts of cafestol (10 -10 to 10-6 M) may offer a considerable increase in insulin and glucose concentration secretion, in the effect of the same. It's also been noted that coffee (filtered) having a low amount of this compound can still have a preventative action of Type 2 Diabetes Mellitus (T2DM)[95]. Apart from this, these compounds have shown a very productive activity in modulating multiple enzymes involved in detoxification, especially of the carcinogens known to cause malignant hepatoma[96].

The mode of action of diterpenes on the metabolism of lipoproteins is not yet transparent. Still, utilization of these mentioned diterpenes in coffee (French press) has been found to result in a consistent increase in cholesterol ester transfer protein (CETP) activity in human beings, which may even contribute to the rise in the concentration of Low-density lipoprotein (LDL) cholesterol [97].

Even some antimicrobial activities are also found in recent studies [98]. Studies also suggest that these two subdue the feasibility of mesothelioma cells, induce apoptotic cell death in MSTO-211H cells [65], suppress the specificity of protein 1 in MSTO-211H cells.

3.3 TRIGONELLINE

Trigonelline has been reported to exert diverse pharmacological activities, for example, antihyperglycemic and antihyperlipidemic [99].

There is no doubt that TRG has a demonstrated anti-diabetic effect; its execution to rats (models) with diabetes mellitus has shown a reduction in blood glucose concentrations on testing for oral glucose tolerance[100]. Displaying peripheral neuropathy (a condition of the nervous system, for which no effective drug is there) was one more beneficial effect seen in rats [101]. Studies also suggest that it may function as a holdback for Nrf2 gene transcription, which causes the pancreas to become more susceptible to apoptotic death [102]. TRG content of Robusta extracts (at a MIC of 0.8 mg/ml) has also shown a positive decrease in the formation of biofilm through bacteriostatic action (*Streptococcus mutans*) [103].

3.4 CGA

Many constructive effects have been accredited to CGA [34]. CGA and caffeic acid alliance have anticancer, antimutagenic, anti-inflammatory, and antioxidant effects [47]. Several studies performed on animals reported that CGA had anti-diabetic[104] and anti-obesity properties [105 and 106] with advantageous effects on insulin resistance [107]. A recent narrative review also indicates that supplements of green coffee supplements may help reduce blood pressure. Chlorogenic

acid has also been known to show potent antioxidant properties [108]. CGA's also have other medicinal values apart from antioxidant properties, including antiviral, anti-inflammatory, hypoglycaemic, and hepatoprotective properties [109]. The same's antioxidant activities were also seen in the exhibit in case of re-oxygenation injury [110]. It has also been observed that hepatitis (viral) patients who had coffee every day experienced a diminution in the frequency of the HCC just because of the antioxidant properties of the same [111].

Recent studies also suggest that CGA's may have potential antiproliferative activity and may also possess the ability to persuade the process the apoptosis and damaging the DNA (cellular) without even affecting the fibroblast of normal lungs in case of lung cancer [112]. Apart from this, CGA and decaffeinated coffee were also found to suppress lung metastasis in a dose-dependent manner, which resulted in a reduction of the number of tumor nodules [113].

CGA's hypo-lipidemic effect was also known to reduce weight in experimental mice [114 and 115].

Different microbial species are also found to be susceptible to this phenolic's anti-microbial activities. Thus, CGA is not only found to be active in opposition to the viral proteins, but it also has anti-bacterial and anti-fungal functions [34]. As far as viruses are concerned, CGA has shown anti-hepatitis B virus vigor in a duckling model [116] and anti-H1N1 influenza virus [117].

No doubt that CGA and caffeic acid both have shown antioxidant activity in vitro [118]. Yet, it is not clear that the percentage of contribution to this antioxidant activity is (in vivo) because they are metabolised extensively. The metabolites often show lower antioxidant activity than the compounds from which they are derived (parent compound).CGA's

may be a potential novel medicinal option for curing lung cancer. In tumour angiogenesis, the effect of CGA is good, but the mechanisms of action are yet not found [119].

Studies also suggest that CGA can even exert a clashing dual action as an antioxidant and pro-oxidant. But, at present, it isn't known how CGA can manage to act as either a pro-oxidant or an antioxidant [120].

4. THE GREEN PHARMACY IN YOUR CUP

An infusion of coffee is known to contain 'n' number of complex compounds whose composition and concentration depend again on the 'n' number of parameters. A solvent used to prepare the coffee infusion plays a vital role in the extraction of the biologically active compounds [1]. These extracted compounds comprise many agents, including anti-cancer, anti-genotoxic, antioxidant, pro-oxidant and anti-inflammatory agents. Many inhibitors were responsible for cell proliferation and cell cycle progression. Modulators involved in aberrant metabolism and also angiogenesis, invasion and metastasis inhibitors [121].

5. SUMMARY AND CONCLUSION:

Bioactive ingredients existing in green and roasted coffee brews are considerably biologically active, showing various types of actions in the welfare of the human population. 'N' no. of pharmacological activities including anti-oxidant, proliferative, diabetic, obesity, inflammatory, tumour and viral too; have been shown by these phenolic compounds present in the coffee. Reviews highlight the cellular and molecular

mechanisms that explain the pharmacological benefits of ingesting green coffee beverages.

COMPLIANCE AND ETHICAL STANDARDS

Human and Animal Rights

This article does not contain any studies related to humans and animals.

REFERENCES

1. Kaur, M., Tyagi, S., & Kundu, N. (2018). Effect of Brewing Methods and Time on Secondary Metabolites, Total Flavonoid and Phenolic Content of Green and Roasted coffee Coffea arabica, Coffea canephora and Monsooned Malabar. *European Journal of Medicinal Plants*. https://doi.org/10.9734/ejmp/2018/40565

2. Saura-Calixto, F., & Goñi, I. (2006). Antioxidant capacity of the Spanish Mediterranean diet. *Food Chemistry*. https://doi.org/10.1016/j.foodchem.2004.11.033

3. Illy, A., & Viani, R. (1995). *Espresso Coffee: The Chemistry of Quality*. *Academic Press*.

4. Bonita, J. S., Mandarano, M., Shuta, D., & Vinson, J. (2007). Coffee and cardiovascular disease: In vitro, cellular, animal, and human studies. *Pharmacological Research*. https://doi.org/10.1016/j.phrs.2007.01.006

5. Iwasa, K., Setoyama, D., Shimizu, H., Seta, H., Fujimura et al(2015). Identification of 3-Methylbutanoyl Glycosides in Green Coffea arabica Beans as Causative Determinants for

the Quality of Coffee Flavors. *Journal of Agricultural and Food Chemistry*. https://doi.org/10.1021/jf5054047

6. Weldegebreal, B., Redi-Abshiro, M., & Chandravanshi, B. S. (2017). Development of new analytical methods for the determination of caffeine content in aqueous solution of green coffee beans. *Chemistry Central Journal*. https://doi.org/10.1186/s13065-017-0356-3

7. Şemen, S., Mercan, S., Yayla, M., & Açıkkol, M. (2017). Elemental composition of green coffee and its contribution to dietary intake. *Food Chemistry*. https://doi.org/10.1016/j.foodchem.2016.07.176

8. Pohl, P., Stelmach, E., Welna, M., & Szymczycha-Madeja, A. (2013). Determination of the Elemental Composition of Coffee Using Instrumental Methods. *Food Analytical Methods*. https://doi.org/10.1007/s12161-012-9467-6

9. Dong, W., Tan, L., Zhao, J., Hu, R., & Lu, M. (2015). Characterization of fatty acid, amino acid and volatile compound compositions and bioactive components of seven coffee (Coffea robusta) cultivars grown in Hainan Province, China. *Molecules*. https://doi.org/10.3390/molecules200916687

10. Rodrigues, N. P., Salva, T. D. J. G., & Bragagnolo, N. (2015). Influence of Coffee Genotype on Bioactive Compounds and the in Vitro Capacity To Scavenge Reactive Oxygen and Nitrogen Species. *Journal of Agricultural and Food Chemistry*. https://doi.org/10.1021/acs.jafc.5b00530

11. International Coffee Organization. Coffee Market Report—September 2014. Available online: http://dev.ico.org/documents/cy2013-14/cmr-0914-e.pdf (accessed on 24 October 2014).

12. Schievano, E., Finotello, C., De Angelis, E., Mammi, S., & Navarini, L. (2014). Rapid authentication of coffee blends and quantification of 16-O-methylcafestol in roasted coffee beans by nuclear magnetic resonance. *Journal of Agricultural and Food Chemistry*. https://doi.org/10.1021/jf505013d

13. Corso, M. P., Vignoli, J. A., & Benassi, M. de T. (2016). Development of an instant coffee enriched with chlorogenic acids. *Journal of Food Science and Technology*. https://doi.org/10.1007/s13197-015-2163-y

14. Nogueira, M., & Trugo, L. C. (2003). Distribuição de isômeros de ácido clorogênico e teores de cafeína e trigonelina em cafés solúveis brasileiros. *Ciência e Tecnologia de Alimentos*. https://doi.org/10.1590/s0101-20612003000200033

15. Hatzold T (2012) Introduction. In: Chu YF (ed) Coffee: emerging health effects and disease prevention, 1st edn. Blackwell, London, pp. 1–20.

16. Alonso-Salces, R. M., Serra, F., Reniero, F., & HÉberger, Ká. (2009). Botanical and Geographical Characterization of Green Coffee (Coffea arabica and Coffea canephora): Chemometric Evaluation of Phenolic and Methylxanthine Contents. *Journal of Agricultural and Food Chemistry*, 57(10), 4224–4235. https://doi.org/10.1021/jf8037117

17. Buffo, R. A., & Cardelli-Freire, C. (2004). Coffee flavour: An overview. In *Flavour and Fragrance Journal*. https://doi.org/10.1002/ffj.1325

18. Kramer, D., Breitenstein, B., Kleinwächter, M., & Selmar, D. (2010). Stress Metabolism in Green Coffee Beans (Coffea arabica L.): Expression of Dehydrins and Accumulation of

GABA during Drying. *Plant and Cell Physiology*, *51*(4), 546–553. https://doi.org/10.1093/pcp/pcq019

19. Bytof, G., Knopp, S. E., Kramer, D., Breitenstein, B., Bergervoet, J. H. W., et al. (2007). Transient occurrence of seed germination processes during coffee post-harvest treatment. *Annals of Botany*. https://doi.org/10.1093/aob/mcm068

20. Vincent J. 1987. Coffee, vol 2: Technology. Elsevier: London.

21. Tewabe Gebeyehu, B. (2015). Determination of Caffeine Content and Antioxidant Activity of Coffee. *American Journal of Applied Chemistry*. https://doi.org/10.11648/j.ajac.20150302.16

22. Chu YF (2012). Coffee: Emerging health effects and disease prevention (1st ed.). Oxford: Wiley – Blackwell.

23. Alkhatib, A., Tsang, C., Tiss, A., Bahorun, T., Arefanian, H., Barake, R., et al (2017). Functional foods and lifestyle approaches for diabetes prevention and management. In *Nutrients*. https://doi.org/10.3390/nu9121310

24. Jeszka-Skowron, M., Sentkowska, A., Pyrzyńska, K., & De Peña, M. P. (2016). Chlorogenic acids, caffeine content and antioxidant properties of green coffee extracts: influence of green coffee bean preparation. *European Food Research and Technology*. https://doi.org/10.1007/s00217-016-2643-y

25. Dórea, J. G., & da Costa, T. H. M. (2005). Dorea, da Costa- (2005) Is coffee a functional food?- The British journal of nutrition. *The British Journal of Nutrition*. https://doi.org/10.1079/BJN20051370

26. Ribeiro, V. S., Leitão, A. E., Ramalho, J. C., & Lidon, F. C. (2014). Chemical characterization and antioxidant properties of a new coffee blend with cocoa, coffee silverskin and green coffee minimally processed. *Food Research International*. https://doi.org/10.1016/j.foodres.2014.05.003

27. Namrata, Yash Sharma, & Tripti Sharma. (2017). Anti-Microbial, Anti-Oxidant Activity and Phytochemical Screening of Polyphenolic Flavonoids Isolated from Peels of Ananas Comosus. *International Journal of Engineering Research And*. https://doi.org/10.17577/ijertv6is090176

28. Gaascht, F., Dicato, M., & Diederich, M. (2015). Coffee provides a natural multitarget pharmacopeia against the hallmarks of cancer. In *Genes and Nutrition*. https://doi.org/10.1007/s12263-015-0501-3

29. Yilmaz, P. K., Hacibekiroğlu, I., & Kolak, U. (2014). Effect of roasting on antioxidant and anticholinesterase capacities of coffee. *Journal of Food and Nutrition Research*.

30. Del Castillo, M. D., Gordon, M. H., & Ames, J. M. (2005). Peroxyl radical-scavenging activity of coffee brews. *European Food Research and Technology*. https://doi.org/10.1007/s00217-005-1209-1

31. Brezová, V., Šlebodová, A., & Staško, A. (2009). Coffee as a source of antioxidants: An EPR study. *Food Chemistry*. https://doi.org/10.1016/j.foodchem.2008.10.025

32. Higdon, J. V., & Frei, B. (2006). Coffee and health: A review of recent human research. *Critical Reviews in Food Science and Nutrition*. https://doi.org/10.1080/10408390500400009

33. Higdon, J. V., & Frei, B. (2006). Coffee and health: A review of recent human research. *Critical Reviews in Food Science and Nutrition*. https://doi.org/10.1080/10408390500400009

34. Nuhu, A. A. (2014). Bioactive Micronutrients in Coffee: Recent Analytical Approaches for Characterization and Quantification. *ISRN Nutrition*. https://doi.org/10.1155/2014/384230

35. Mussatto, S. I., Carneiro, L. M., Silva, J. P. A., Roberto, I. C., & Teixeira, J. A. (2011). A study on chemical constituents and sugars extraction from spent coffee grounds. *Carbohydrate Polymers*. https://doi.org/10.1016/j.carbpol.2010.07.063

36. Tai, J., Cheung, S., Chan, E., & Hasman, D. (2010). Antiproliferation effect of commercially brewed coffees on human ovarian cancer cells in vitro. *Nutrition and Cancer*. https://doi.org/10.1080/01635581.2010.492083

37. Liang, N., & Kitts, D. D. (2015). Role of chlorogenic acids in controlling oxidative and inflammatory stress conditions. In *Nutrients*. https://doi.org/10.3390/nu8010016

38. Revuelta-Iniesta, R., & Al-Dujaili, E. A. S. (2014). Consumption of Green Coffee Reduces Blood Pressure and Body Composition by Influencing 11 β-HSD1 Enzyme Activity in Healthy Individuals: A Pilot Crossover Study Using Green and Black Coffee. *BioMed Research International*. https://doi.org/10.1155/2014/482704

39. Caini, S., Cattaruzza, S., Bendinelli, B., Tosti, G., Masala, G., Gnagnarella, P., et al (2017). Coffee, tea and caffeine intake and the risk of non-melanoma skin cancer: a review of the literature and meta-analysis. In *European*

Journal of Nutrition. https://doi.org/10.1007/s00394-016-1253-6

40. Chei, C. L., Loh, J. K., Soh, A., Yuan, et al (2018). Coffee, tea, caffeine, and risk of hypertension: The Singapore Chinese Health Study. *European Journal of Nutrition*. https://doi.org/10.1007/s00394-017-1412-4

41. Leung, A. C. Y., Cook, L. S., Swenerton, K., Gilks, B., Gallagher, R. P., Magliocco, A., et al (2016). Tea, coffee, and caffeinated beverage consumption and risk of epithelial ovarian cancers. *Cancer Epidemiology*. https://doi.org/10.1016/j.canep.2016.10.010

42. Gómez-Ruiz, J. Á., Ames, J. M., & Leake, D. S. (2008). Antioxidant activity and protective effects of green and dark coffee components against human low density lipoprotein oxidation. *European Food Research and Technology*. https://doi.org/10.1007/s00217-007-0815-5

43. Bharath, N., Sowmya, N. K., & Mehta, D. S. (2015). Determination of antibacterial activity of green coffee bean extract on periodontogenic bacteria like Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum and Aggregatibacter actinomycetemcomitans: An in vitrostudy. *Contemporary Clinical Dentistry*. https://doi.org/10.4103/0976-237X.156036

44. Sinisi, V., Stevaert, A., Berti, F., Forzato, C., Benedetti, F., Navarini, L., et al (2017). Chlorogenic Compounds from Coffee Beans Exert Activity against Respiratory Viruses. *Planta Medica*. https://doi.org/10.1055/s-0042-119449

45. Mullaicharam, A., El-Khider, M., & Amaresh, N. (2011). Chemistry and pharmacology of caffeine in different types

of tea leaves. *International Journal of Nutrition, Pharmacology, Neurological Diseases*. https://doi.org/10.4103/2231-0738.84198

46. Mussatto, S. I., Machado, E. M. S., Martins, S., & Teixeira, J. A. (2011). Production, Composition, and Application of Coffee and Its Industrial Residues. In *Food and Bioprocess Technology*. https://doi.org/10.1007/s11947-011-0565-z

47. Alkhatib, A., Tsang, C., Tiss, A., Bahorun, T., Arefanian, H., Barake, R., et al (2017). Functional foods and lifestyle approaches for diabetes prevention and management. In *Nutrients*. https://doi.org/10.3390/nu9121310

48. Wang, L., Gong, L. H., Chen, C. J., Han, H. B., et al (2012). Column-chromatographic extraction and separation of polyphenols, caffeine and theanine from green tea. *Food Chemistry*. https://doi.org/10.1016/j.foodchem.2011.09.129

49. Vuong, Q. V., & Roach, P. D. (2014). Caffeine in green tea: Its removal and isolation. *Separation and Purification Reviews*. https://doi.org/10.1080/15422119.2013.771127

50. Oba, S., Nagata, C., Nakamura, K., Fujii, K., Kawachi, T., Takatsuka, N., et al (2010). Consumption of coffee, green tea, oolong tea, black tea, chocolate snacks and the caffeine content in relation to risk of diabetes in Japanese men and women. *British Journal of Nutrition*. https://doi.org/10.1017/S0007114509991966

51. Bhupathiraju, S. N., Pan, A., Malik, V. S., Manson, J. A. E., Willett, W. C., Van Dam, R. M., et al (2013). Caffeinated and caffeine-free beverages and risk of type 2 diabetes. *American Journal of Clinical Nutrition*. https://doi.org/10.3945/ajcn.112.048603

52. Reissig, C. J., Strain, E. C., & Griffiths, R. R. (2009). Caffeinated energy drinks-A growing problem. *Drug and Alcohol Dependence*. https://doi.org/10.1016/j.drugalcdep.2008.08.001

53. Keast, R. S. J., Sayompark, D., Sacks, G., Swinburn, B. A., & Riddell, L. J. (2011). The influence of caffeine on energy content of sugar-sweetened beverages: The caffeine-calorie effect′. *European Journal of Clinical Nutrition*. https://doi.org/10.1038/ejcn.2011.123

54. Mazzafera, P., & Silvarolla, M. B. (2010). Caffeine content variation in single green Arabica coffee seeds. *Seed Science Research*. https://doi.org/10.1017/S0960258510000140

55. Tello, J., Viguera, M., & Calvo, L. (2011). Extraction of caffeine from Robusta coffee (Coffea canephora var. Robusta) husks using supercritical carbon dioxide. *Journal of Supercritical Fluids*. https://doi.org/10.1016/j.supflu.2011.07.018

56. McCusker, R. R., Goldberger, B. A., & Cone, E. J. (2003). Caffeine content of specialty coffees. *Journal of Analytical Toxicology*. https://doi.org/10.1093/jat/27.7.520

57. Lanzotti, V. (2013). Diterpenes for therapeutic use. In *Natural Products: Phytochemistry, Botany and Metabolism of Alkaloids, Phenolics and Terpenes*. https://doi.org/10.1007/978-3-642-22144-6_192

58. Córdova-Guerrero, I., Andrés, L. S., Leal-Orozco, A. E., Padrón, J. M., Cornejo-Bravo, J. M., & León, F. (2013). New strategy toward the diverted synthesis of oxidized abietane diterpenes via oxidation of 6,7-dehydroferruginol methyl

ether with dimethyldioxirane. *Tetrahedron Letters*. https://doi.org/10.1016/j.tetlet.2013.06.048

59. Yang, B., Zhou, X.-F., Lin, X.-P., Liu, J., Peng, Y., Yang, X.-W., et al. (2012). Cembrane Diterpenes Chemistry and Biological Properties. *Current Organic Chemistry*. https://doi.org/10.2174/138527212800672583

60. Gampe, C. M., & Carreira, E. M. (2012). Cyclohexyne cycloinsertion in the divergent synthesis of guanacastepenes. *Chemistry – A European Journal*. https://doi.org/10.1002/chem.201202222

61. de Araújo Rodrigues, P., de Morais, S. M., de Souza, C. M., Silva, A. R. A., de Andrade, G. M., Silva, M. G. V., et al. (2010). Gastroprotective effect of barbatusin and 3-beta-hydroxy-3-deoxibarbatusin, quinonoid diterpenes isolated from Plectranthus grandis, in ethanol-induced gastric lesions in mice. *Journal of Ethnopharmacology*. https://doi.org/10.1016/j.jep.2009.11.031

62. Devappa, R. K., Makkar, H. P. S., & Becker, K. (2011). Jatropha Diterpenes: a Review. *Journal of the American Oil Chemists' Society*, *88*(3), 301–322. https://doi.org/10.1007/s11746-010-1720-9

63. Lee, K. A., Chae, J. Il, & Shim, J. H. (2012). Natural diterpenes from coffee, cafestol and kahweol induce apoptosis through regulation of specificity protein 1 expression in human malignant pleural mesothelioma. *Journal of Biomedical Science*. https://doi.org/10.1186/1423-0127-19-60

64. Ashour, M., Wink, M., & Gershenzon, J. (2010). Biochemistry of Terpenoids: Monoterpenes, Sesquiterpenes and Diterpenes. In *Biochemistry of Plant Secondary*

Metabolism: Second Edition. https://doi.org/10.1002/9781444320503.ch5

65. Lee, K. A., Chae, J. Il, & Shim, J. H. (2012). Natural diterpenes from coffee, cafestol and kahweol induce apoptosis through regulation of specificity protein 1 expression in human malignant pleural mesothelioma. *Journal of Biomedical Science*. https://doi.org/10.1186/1423-0127-19-60

66. Arab, L. (2010). Epidemiologic evidence on coffee and cancer. In *Nutrition and Cancer*. https://doi.org/10.1080/01635580903407122

67. Ranheim, T., & Halvorsen, B. (2005). Coffee consumption and human health - Beneficial or detrimental? - Mechanisms for effects of coffee consumption on different risk factors for cardiovascular disease and type 2 diabetes mellitus. In *Molecular Nutrition and Food Research*. https://doi.org/10.1002/mnfr.200400109

68. De Roos, B., Meyboom, S., Kosmeijer-Schuil, T. G., & Katan, M. B. (1998). Absorption and urinary excretion of the coffee diterpenes cafestol and kahweol in healthy ileostomy volunteers. *Journal of Internal Medicine*. https://doi.org/10.1046/j.1365-2796.1998.00386.x

69. Zhou, J., Chan, L., & Zhou, S. (2012). Trigonelline: A Plant Alkaloid with Therapeutic Potential for Diabetes and Central Nervous System Disease. *Current Medicinal Chemistry*. https://doi.org/10.2174/092986712801323171

70. Allred, K. F., Yackley, K. M., Vanamala, J., & Allred, C. D. (2009). Trigonelline Is a Novel Phytoestrogen in Coffee Beans. *The Journal of Nutrition*. https://doi.org/10.3945/jn.109.108001

71. Sánchez-Hernández, L., Puchalska, P., García-Ruiz, C., Crego, A. L., & Marina, M. L. (2010). Determination of trigonelline in seeds and vegetable oils by capillary electrophoresis as a novel marker for the detection of adulterations in olive oils. *Journal of Agricultural and Food Chemistry*. https://doi.org/10.1021/jf100550b

72. Trigonelline in Coffee. https://www.coffeechemistry.com/chemistry/alkaloids/trigonelline-in-coffee#:~:text=Trigonelline%20is%20a%20bitter%20alkaloid,to%20produce%20important%20aroma%20compounds.&text=During%20roasting%20trigonelline%20partially%20degrades,of%20its%20original%20trigonelline%20content.

73. Bicho, N. C., Leitão, A. E., Ramalho, J. C., & Lidon, F. C. (2011). Identification of chemical clusters discriminators of the roast degree in Arabica and Robusta coffee beans. *European Food Research and Technology*. https://doi.org/10.1007/s00217-011-1518-5

74. Morisco, F., Lembo, V., Mazzone, G., Camera, S., & Caporaso, N. (2014). Coffee and liver health. *Journal of Clinical Gastroenterology*. https://doi.org/10.1097/MCG.0000000000000240

75. Narita, Y., & Inouye, K. (2013). Degradation kinetics of chlorogenic acid at various pH values and effects of ascorbic acid and epigallocatechin gallate on its stability under alkaline conditions. *Journal of Agricultural and Food Chemistry*. https://doi.org/10.1021/jf304105w

76. Górnas, P., Neunert, G., Baczyński, K., & Polewski, K. (2009). Beta-cyclodextrin complexes with chlorogenic and caffeic acids from coffee brew: Spectroscopic,

thermodynamic and molecular modelling study. *Food Chemistry*. https://doi.org/10.1016/j.foodchem.2008.09.048

77. Aguiar, J., Estevinho, B. N., & Santos, L. (2016). Microencapsulation of natural antioxidants for food application – The specific case of coffee antioxidants – A review. In *Trends in Food Science and Technology*. https://doi.org/10.1016/j.tifs.2016.10.012

78. Panusa, A., Zuorro, A., Lavecchia, R., Marrosu, G., & Petrucci, R. (2013). Recovery of natural antioxidants from spent coffee grounds. *Journal of Agricultural and Food Chemistry*. https://doi.org/10.1021/jf4005719

79. Olthof, M. R., Hollman, P. C. H., & Katan, M. B. (2001). Chlorogenic Acid and Caffeic Acid Are Absorbed in Humans. *The Journal of Nutrition*. https://doi.org/10.1093/jn/131.1.66

80. Olthof, M. R., Hollman, P. C. H., Buijsman, M. N. C. P., van Amelsvoort, J. M. M., & Katan, M. B. (2003). Chlorogenic Acid, Quercetin-3-Rutinoside and Black Tea Phenols Are Extensively Metabolized in Humans. *The Journal of Nutrition*. https://doi.org/10.1093/jn/133.6.1806

81. Upadhyay, R., & Mohan Rao, L. J. (2013). An Outlook on Chlorogenic Acids-Occurrence, Chemistry, Technology, and Biological Activities. *Critical Reviews in Food Science and Nutrition*. https://doi.org/10.1080/10408398.2011.576319

82. Zhao, M., Wang, H., Yang, B., & Tao, H. (2010). Identification of cyclodextrin inclusion complex of chlorogenic acid and its antimicrobial activity. *Food Chemistry*. https://doi.org/10.1016/j.foodchem.2009.11.044

83. Memon, A. A., Memon, N., Luthria, D. L., Bhanger, M. I., & Pitafi, A. A. (2010). Phenolic acids profiling and antioxidant potential of mulberry (Morus laevigata W., Morus nigra L., Morus alba L.) Leaves and fruits grown in Pakistan. *Polish Journal of Food and Nutrition Sciences*.

84. Joët, T., Salmona, J., Laffargue, A., Descroix, F., & Dussert, S. (2010). Use of the growing environment as a source of variation to identify the quantitative trait transcripts and modules of co-expressed genes that determine chlorogenic acid accumulation. *Plant, Cell and Environment*. https://doi.org/10.1111/j.1365-3040.2010.02141.x

85. Joët, T., Salmona, J., Laffargue, A., Descroix, F., & Dussert, S. (2010). Use of the growing environment as a source of variation to identify the quantitative trait transcripts and modules of co-expressed genes that determine chlorogenic acid accumulation. *Plant, Cell and Environment*. https://doi.org/10.1111/j.1365-3040.2010.02141.x

86. Moon, J. K., Hyui Yoo, S. U. N., & Shibamoto, T. (2009). Role of roasting conditions in the level of chlorogenic acid content in coffee beans: Correlation with coffee acidity. *Journal of Agricultural and Food Chemistry*. https://doi.org/10.1021/jf900012b

87. Laurence, G., Wallman, K., & Guelfi, K. (2012). Effects of caffeine on time trial performance in sedentary men. *Journal of Sports Sciences*. https://doi.org/10.1080/02640414.2012.693620

88. Prediger, R. D. S. (2010). Effects of caffeine in Parkinson's disease: From neuroprotection to the management

of motor and non-motor symptoms. *Journal of Alzheimer's Disease*. https://doi.org/10.3233/JAD-2010-091459

89. James, J. E. (2004). Critical Review of Dietary Caffeine and Blood Pressure: A Relationship That Should Be Taken More Seriously. In *Psychosomatic Medicine*. https://doi.org/10.1097/10.PSY.0000107884.78247.F9

90. Frost-Meyer, N. J., & Logomarsino, J. V. (2012). Impact of coffee components on inflammatory markers: A review. In *Journal of Functional Foods*. https://doi.org/10.1016/j.jff.2012.05.010

91. Borota, D., Murray, E., Keceli, G., Chang, A., Watabe, J. M., Ly, M., Toscano, J. P., & Yassa, M. A. (2014). Post-study caffeine administration enhances memory consolidation in humans. *Nature Neuroscience*. https://doi.org/10.1038/nn.3623

92. Chu, Y. F., Chang, W. H., Black, R. M., Liu, J. R., Sompol, P., et al. (2012). Crude caffeine reduces memory impairment and amyloid β1-42 levels in an Alzheimer's mouse model. *Food Chemistry*. https://doi.org/10.1016/j.foodchem.2012.04.148

93. Vila-Luna, S., Cabrera-Isidoro, S., Vila-Luna, L., Juárez-Díaz, I., Bata-García, J. L., Alvarez-Cervera, F. J., et al (2012). Chronic caffeine consumption prevents cognitive decline from young to middle age in rats, and is associated with increased length, branching, and spine density of basal dendrites in CA1 hippocampal neurons. *Neuroscience*. https://doi.org/10.1016/j.neuroscience.2011.11.053

94. Qi, H., & Li, S. (2014). Dose-response meta-analysis on coffee, tea and caffeine consumption with risk of

Parkinson's disease. *Geriatrics and Gerontology International*. https://doi.org/10.1111/ggi.12123

95. O'Keefe, J. H., Bhatti, S. K., Patil, H. R., Dinicolantonio, J. J., Lucan, S. C., & Lavie, C. J. (2013). Effects of habitual coffee consumption on cardiometabolic disease, cardiovascular health, and all-cause mortality. In *Journal of the American College of Cardiology*. https://doi.org/10.1016/j.jacc.2013.06.035

96. Mellbye, F. B., Jeppesen, P. B., Hermansen, K., & Gregersen, S. (2015). Cafestol, a Bioactive Substance in Coffee, Stimulates Insulin Secretion and Increases Glucose Uptake in Muscle Cells: Studies in Vitro. *Journal of Natural Products*. https://doi.org/10.1021/acs.jnatprod.5b00481

97. De Roos, B., Van Tol, A., Urgert, R., Scheek, L. M., Van Gent, T., Buytenhek, R., et al (2000). Consumption of French-press coffee raises cholesteryl ester transfer protein activity levels before LDL cholesterol in normolipidaemic subjects. *Journal of Internal Medicine*. https://doi.org/10.1046/j.1365-2796.2000.00728.x

98. Greay, S. J., & Hammer, K. A. (2015). Recent developments in the bioactivity of mono- and diterpenes: anticancer and antimicrobial activity. In *Phytochemistry Reviews*. https://doi.org/10.1007/s11101-011-9212-6

99. Zhou, J., Chan, L., & Zhou, S. (2012). Trigonelline: A Plant Alkaloid with Therapeutic Potential for Diabetes and Central Nervous System Disease. *Current Medicinal Chemistry*. https://doi.org/10.2174/092986712801323171

100. Yoshinari, O., & Igarashi, K. (2010). Anti-Diabetic Effect of Trigonelline and Nicotinic Acid, on KK-Ay Mice.

Current Medicinal Chemistry. https://doi.org/10.2174/092986710791299902

101. Zhou, J. Y., & Zhou, S. W. (2012). Protection of trigonelline on experimental diabetic peripheral neuropathy. *Evidence-Based Complementary and Alternative Medicine*. https://doi.org/10.1155/2012/164219

102. Arlt, A., Sebens, S., Krebs, S., Geismann, C., Grossmann, M., et al (2013). Inhibition of the Nrf2 transcription factor by the alkaloid trigonelline renders pancreatic cancer cells more susceptible to apoptosis through decreased proteasomal gene expression and proteasome activity. *Oncogene*. https://doi.org/10.1038/onc.2012.493

103. Antonio, A. G., Moraes, R. S., Perrone, D., Maia, L. C., Santos, K. R. N., Iório, N. L. P., et al. (2010). Species, roasting degree and decaffeination influence the antibacterial activity of coffee against Streptococcus mutans. *Food Chemistry*. https://doi.org/10.1016/j.foodchem.2009.05.063

104. Meng, S., Cao, J., Feng, Q., Peng, J., & Hu, Y. (2013). Roles of chlorogenic acid on regulating glucose and lipids metabolism: A review. In *Evidence-based Complementary and Alternative Medicine*. https://doi.org/10.1155/2013/801457

105. Ong, K. W., Hsu, A., & Tan, B. K. H. (2013). Anti-diabetic and anti-lipidemic effects of chlorogenic acid are mediated by ampk activation. *Biochemical Pharmacology*. https://doi.org/10.1016/j.bcp.2013.02.008

106. Cho, A. S., Jeon, S. M., Kim, M. J., Yeo, J., et al(2010). Chlorogenic acid exhibits anti-obesity property and improves lipid metabolism in high-fat diet-induced-

obese mice. *Food and Chemical Toxicology*. https://doi.org/10.1016/j.fct.2010.01.003

107. Ma, Y., Gao, M., & Liu, D. (2015). Chlorogenic acid improves high fat diet-induced hepatic steatosis and insulin resistance in mice. *Pharmaceutical Research*. https://doi.org/10.1007/s11095-014-1526-9

108. Onakpoya, I., Terry, R., & Ernst, E. (2011). The use of green coffee extract as a weight loss supplement: A systematic review and meta-analysis of randomised clinical trials. In *Gastroenterology Research and Practice*. https://doi.org/10.1155/2011/382852

109. Marinova, E. M., Toneva, A., & Yanishlieva, N. (2009). Comparison of the antioxidative properties of caffeic and chlorogenic acids. *Food Chemistry*. https://doi.org/10.1016/j.foodchem.2008.11.045

110. Sato, Y., Itagaki, S., Kurokawa, T., Ogura, J., Kobayashi, M., Hirano, T., et al. (2011). In vitro and in vivo antioxidant properties of chlorogenic acid and caffeic acid. *International Journal of Pharmaceutics*. https://doi.org/10.1016/j.ijpharm.2010.09.035

111. Arab, L. (2010). Epidemiologic evidence on coffee and cancer. In *Nutrition and Cancer*. https://doi.org/10.1080/01635580903407122

112. Bothiraj, K. V., Murugan, & Vanitha, V. (2020). Green coffee bean seed and their role in antioxidant–a review. In *International Journal of Research in Pharmaceutical Sciences*. https://doi.org/10.26452/ijrps.v11i1.1812

113. Bułdak, R. J., Hejmo, T., Osowski, M., Bułdak, Ł., Kukla, M., et wl(2018). The impact of coffee and its selected

bioactive compounds on the development and progression of colorectal cancer in vivo and in vitro. In *Molecules*. https://doi.org/10.3390/molecules23123309

114. Ong, K. W., Hsu, A., & Tan, B. K. H. (2013). Anti-diabetic and anti-lipidemic effects of chlorogenic acid are mediated by ampk activation. *Biochemical Pharmacology*. https://doi.org/10.1016/j.bcp.2013.02.008

115. Cho, A. S., Jeon, S. M., Kim, M. J., Yeo, J., Seo, K. Il, Choi, M. S., et al(2010). Chlorogenic acid exhibits anti-obesity property and improves lipid metabolism in high-fat diet-induced-obese mice. *Food and Chemical Toxicology*. https://doi.org/10.1016/j.fct.2010.01.003

116. Wang, G. F., Shi, L. P., Ren, Y. D., Liu, Q. F., Liu, H. F., Zhang, R. J., et al (2009). Anti-hepatitis B virus activity of chlorogenic acid, quinic acid and caffeic acid in vivo and in vitro. *Antiviral Research*. https://doi.org/10.1016/j.antiviral.2009.05.002

117. Kuwata, K., Urushisaki, T., Takemura, T., Tazawa, S., Fukuoka, M., et al (2011). Caffeoylquinic acids are major constituents with potent anti-influenza effects in brazilian green propolis water extract. *Evidence-Based Complementary and Alternative Medicine*. https://doi.org/10.1155/2011/254914

118. Iwai, K., Kishimoto, N., Kakino, Y., Mochida, K., & Fujita, T. (2004). In vitro antioxidative effects and tyrosinase inhibitory activities of seven hydroxycinnamoyl derivatives in green coffee beans. *Journal of Agricultural and Food Chemistry*. https://doi.org/10.1021/jf040048m

119. Farah, A., & Donangelo, C. M. (2006). Phenolic compounds in coffee. In *Brazilian Journal of Plant Physiology*. https://doi.org/10.1590/S1677-04202006000100003

120. Tea, Coffee and Health Benefits.**https://link.springer.com/referenceworkentry/10.1007%2F978-3-319-78030-6_14**

121. Gaascht, F., Dicato, M., & Diederich, M. (2015). Coffee provides a natural multitarget pharmacopeia against the hallmarks of cancer. In *Genes and Nutrition*. https://doi.org/10.1007/s12263-015-0501-3

LIST OF FIGURES:

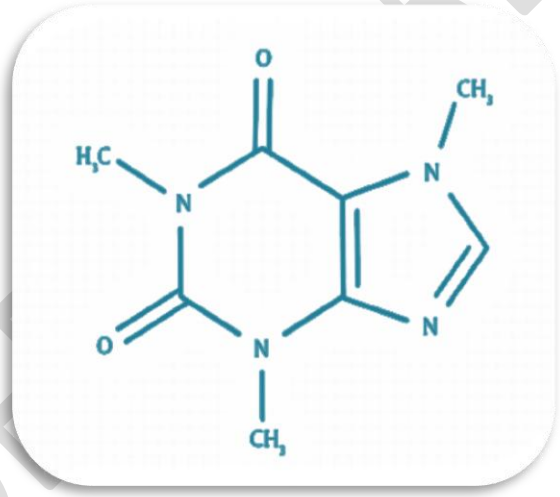

Figure 1

Fig 1: General structure of Caffeine

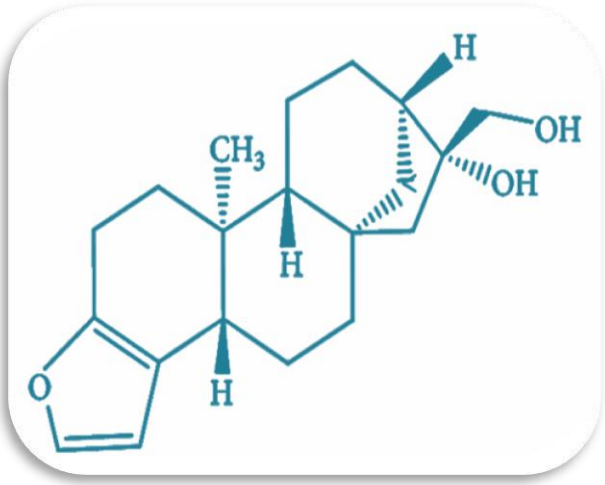

Figure 2

Fig 2: General structure of Diterpenes

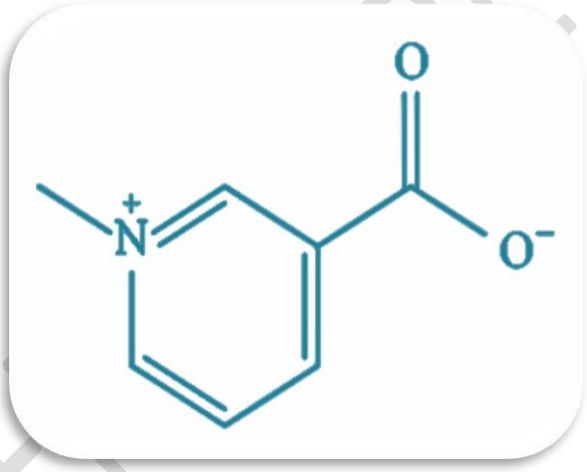

Figure 3

Fig 3: General structure of Trigonelline

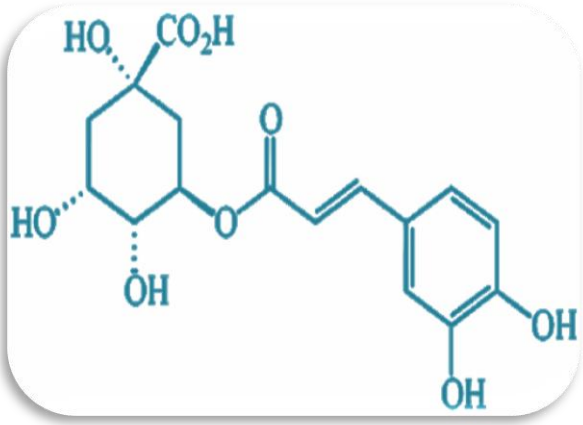

Figure 4

Fig 4: General structure of Chlorogenic Acids

Figure 5

Fig 5: Pharmacological effects of Caffeine

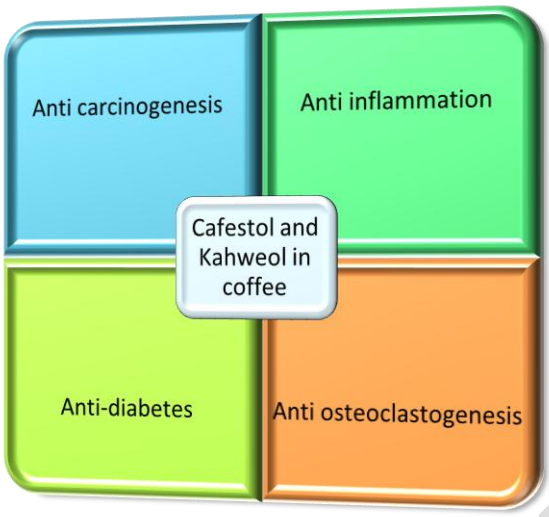

Figure 6

Fig 6: Pharmacological effects of Diterpenes

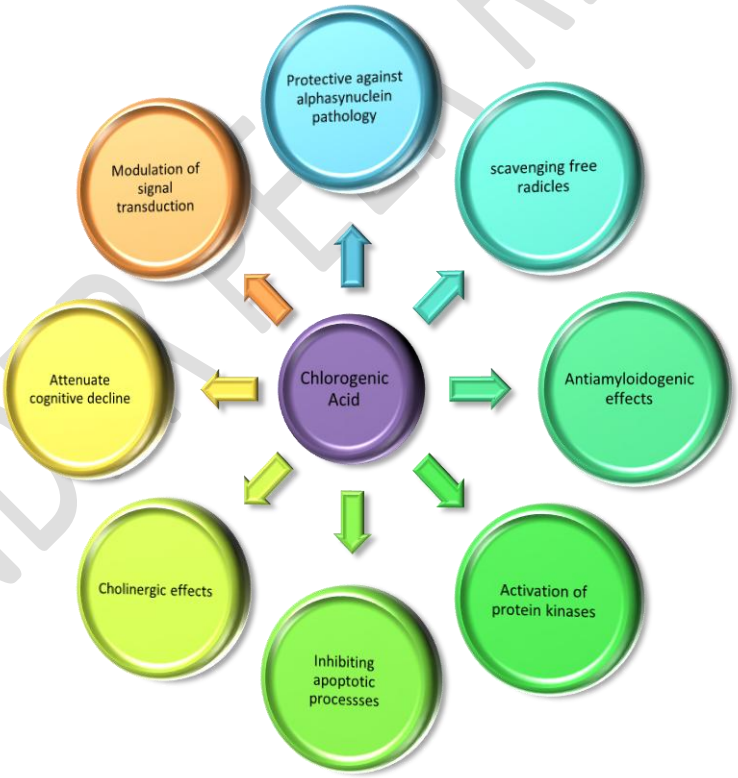

Figure 7

Fig 7: Pharmacological effects of Chlorogenic Acids

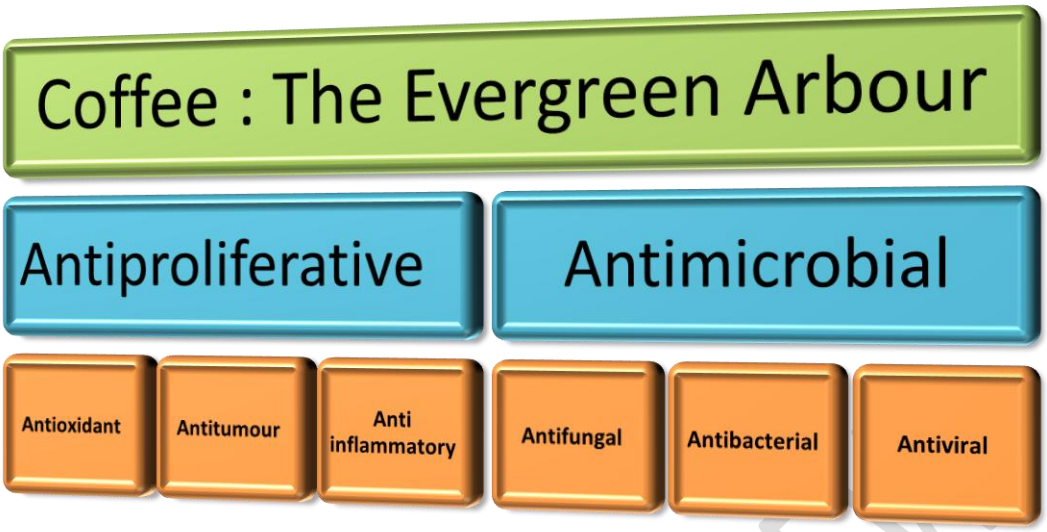

Figure 8

Fig 8: Effective pharmacological effects of Coffee