



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

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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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:	Dicafeoylquinic Acid
GCB:	Green Coffee Beans
LDL:	Low Density Lipoprotein
TRG:	Trigonelline
T2DM:	Type 2 Diabetes Mellitus

1. INTRODUCTION

Coffee, an evergreen arbour, 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 i.e., Indonesia, Brazil, Columbia, and Central America [2,3]. 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 [6,7,8]. 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 [1,6,8] and accounts for about 60% and 40% to the global coffee market, respectively [9,10,11,12]. 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 [13,14,15]. 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) [18,19]. Then, these seeds are stuffed in sacks and conveyed to the countries consuming them. Once collected, they are mingled with green coffee beans from other emergence. Afterward, they are roasted to construct the predictable savour and shade associated with coffee beverages [20].

Coffee is known to be the most flavoured 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 [17,21,22].

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 [25,26].

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 [7,29]. 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 [7,30]. 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

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 [32,33]. Moreover, multiple combinations of biological activity present in this aromatic functional food correlate with several advantageous effects [34,35]. Not limited to but yes these include, antioxidant capacity [1], antiproliferative effect against human cancer cell line [34,36], 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 [40,41], protective effects against human low-density lipoprotein oxidation [42], effect on fasting blood glucose and insulin concentration (diabetic), antimicrobial activity [43] and activity against respiratory viruses [44].

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 $C_8H_{10}N_4O_2$ [21]. It is a type of alkaloid, occurring naturally in coffee beans. It's among the common stimulants consumed worldwide [45]. 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 [48,49], chocolates [50], various drinks (caffeinated-beverages and energy drinks) [51,52,53] and of course coffee (Arabica and Robusta) [47,54,55].

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

Studies suggest that caffeine is rapidly (more or less) absorbed in digestive tissues 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 (C_{20}) 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, jatropa, quinonoid, cafestoland kahweol types [58,59, 60,61,62,63].

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 [66,67]. 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-methylpyridinium-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. 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 [69,70,71].

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-Caffeoylquinic acid; 3-CQA; Chlorogenate; Heriguard)
(Molecular formula – $C_{16}(H_2O)_9$)

The esterification of trans-cinnamic acid 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) [75,76]. 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 [77,78].

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 75 mg of caffeic acid [33]. Colostomy studies suggest that about 33% of the CGA is intestinally absorbed as caffeic acid. Therefore, 2-3 of the CGA ingested reaches the colon, which is metabolized by the microflora [79,80].

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

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] is 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, 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 secretion and glucose concentration. 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 were 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 [105,106] with advantageous effects on insulin resistance [107]. A recent narrative review also indicates that supplements of green coffee may help to 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 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 [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 [114,115].

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 vigour 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 anti-cancerous, anti-genotoxic, antioxidant, pro-oxidant and anti-inflammatory agents. Many inhibitors are also responsible for cell proliferation and cell cycle progression. Modulators involved in aberrant metabolism and also angiogenesis, invasion and metastasis inhibitors [121].

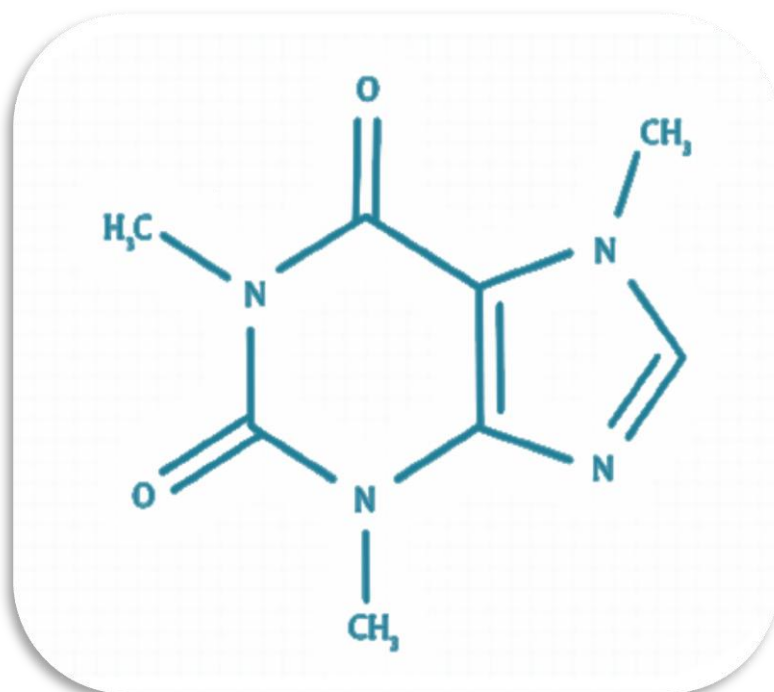


Fig. 1. General structure of Caffeine

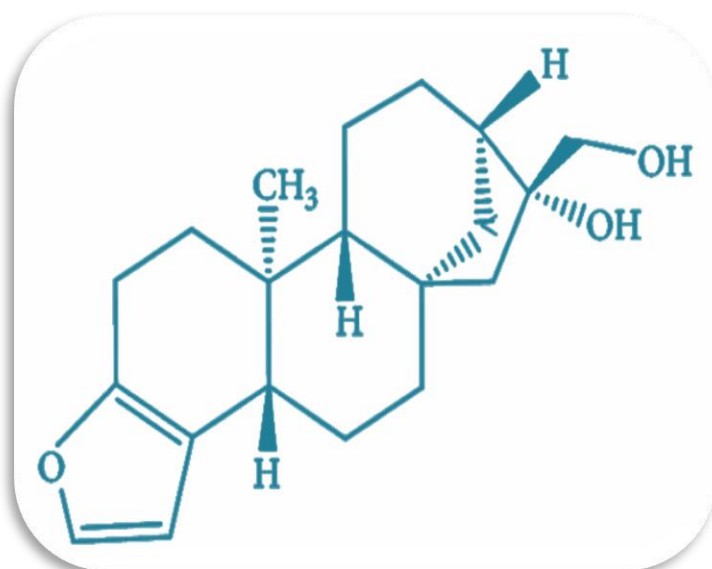


Fig. 2. General structure of Diterpenes

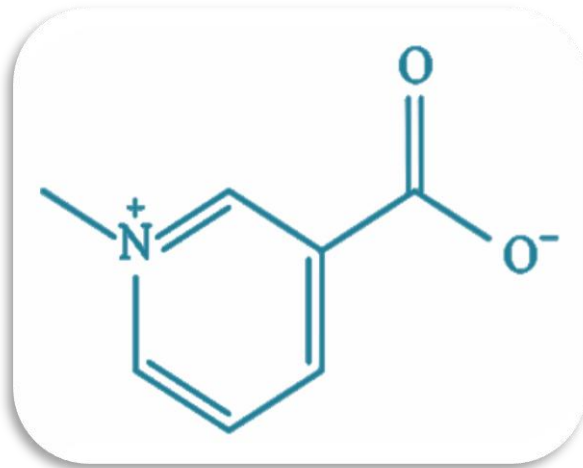


Fig. 3. General structure of Trigonelline

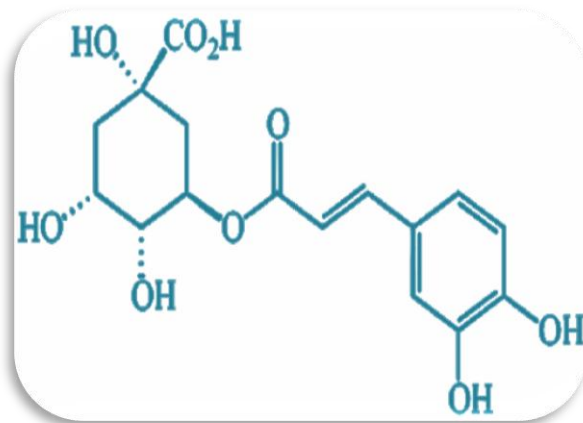


Fig. 4. General structure of Chlorogenic Acids



Fig. 5. Pharmacological effects of Caffeine

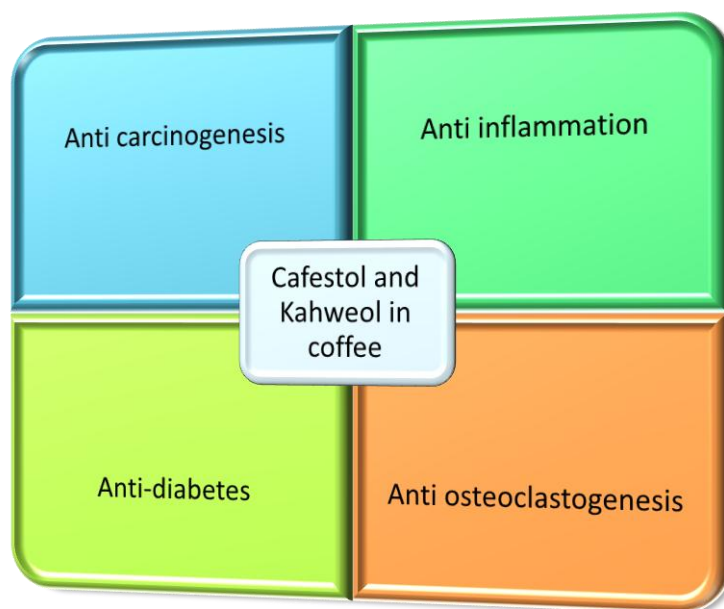


Fig. 6. Pharmacological effects of Diterpenes

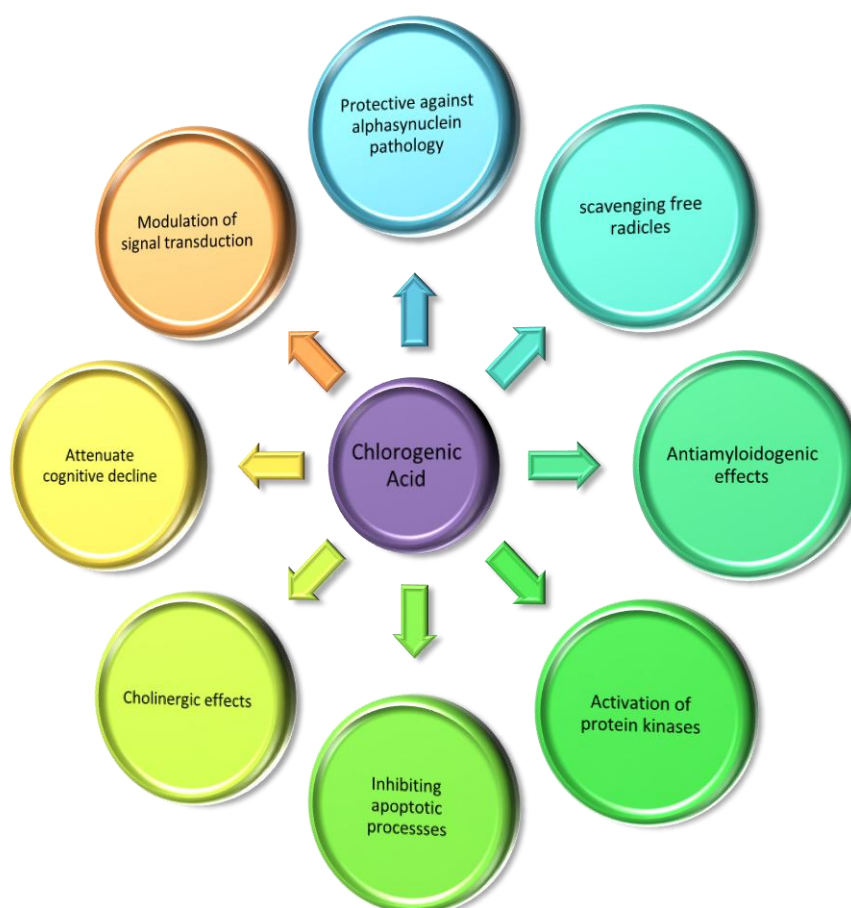


Fig. 7. Pharmacological effects of Chlorogenic Acids

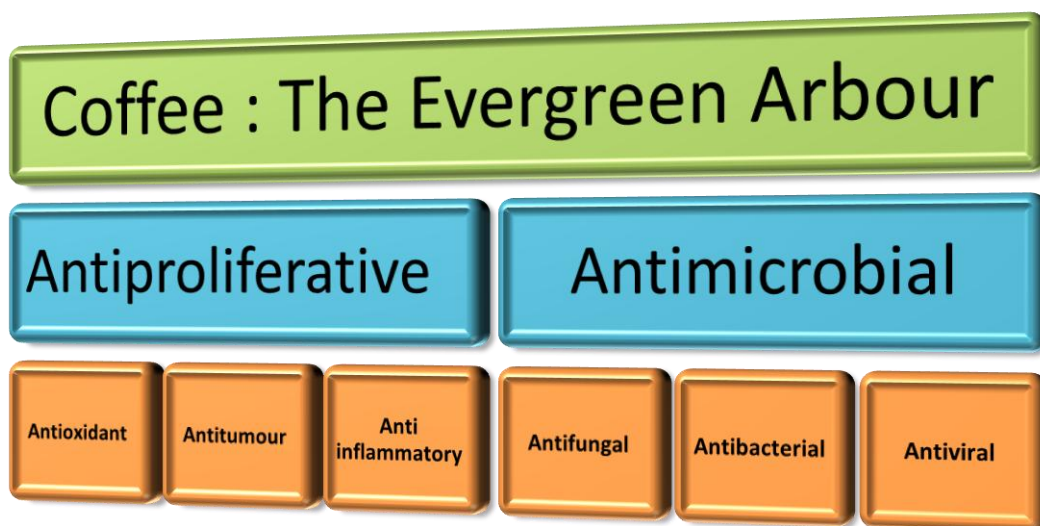


Fig. 8. Effective pharmacological effects of Coffee

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.

CONSENT

It is not applicable.

COMPLIANCE AND ETHICAL STANDARDS

Human and Animal Rights:

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

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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