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UPDATED PHARMACOLOGICAL, CLINICAL AND PHYTOCHEMICAL PROSPECTS OF GREEN COFFEE : A REVIEW

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Abstract

Over the several decades, consumption of green coffee increased due to its health benefits. Multiple studies have been done due to its antioxidant property. Many compounds like phenols, diterpenes, polysaccharides, proteins, melanoids, lipids are identified in the green coffee. Chlorogenic acid and Caffeine are important chemical constituents. Among all the species *Coffea arabica* is the main species which has more chlorogenic acid. Due to its antioxidant properties green coffee reduced the incidence of cancer, diabetes and liver diseases. Green coffee is the famous weight loss supplement marketed under different brand. Green coffee oil is used in cosmetic industry due to antioxidant property. The main aim of this review is focused on the phytochemical and pharmacological activities of green coffee extract.

Keywords: Green coffee extract, chlorogenic acid, caffeine, antioxidant property.

Introduction

After water coffee is the most consumed drink all over world. Consumption of coffee is around 255 kg per second or 8 million tonnes per year world-wide (International Coffee Organization, 2018). The family of coffee is Rubiacea & belongs to the genus coffea. In all over world there are more than 80 coffee species identified (Clarke, 2003). Among 80 species only two species of coffee are economically and therapeutically important *Coffea arabica* another name is Arabica coffee & *Coffea Canephora var. robusta* also known as Robusta coffee. But *Coffea arabica* is the most famous in the global coffee market (International Coffee Organization, 2009; Brazilian Association of Coffee Industry, 2011). Coffee is the main cultivated as crop in Brazil, Vietnam, Colombia and Indonesia (MEC Moreira 2013). Among all the countries Brazil is the main producer of coffee (Damatta and Ramalho, 2006). More than 700 compounds are present in coffee responsible for its aromatic and unique flavours (International Coffee Organization, 2013). Growth of the coffee also depends upon altitude and temperature. The altitude for the growth must be 1000 to 2100m with 18 to 22°C temperature for the Arabica coffee whereas Robusta coffee needs 100 to 1000m altitude and hotter temperature 22°C to 26°C (Toledo *et al.*, 2016; Bertrand *et al.*, 2012). Traditionally alcohol as solvent is used for the extraction of green coffee extract from green coffee beans. As a weight loss supplement, green coffee extract is marketed as "coffee slender" and "Svetol" under different brand names (Shimoda *et al.*, 2006; Cho *et al.*, 2010). Due to antioxidant activity property of the green coffee extract reduces the risk of cancer, diabetes and liver disease. Green coffee extract can also use against Parkinson's disease (Bhupatiraju *et al.*, 2013; Marquina *et al.*, 2013). Green coffee extract has a property of reducing the blood pressure (Suzuki *et al.*, 2002). Hormone secretions and glucose tolerance in humans can also be modified by the green coffee extract (Johnston *et al.*, 2003).

Ethanopharmacology

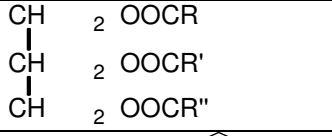
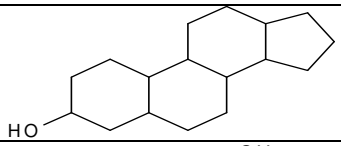
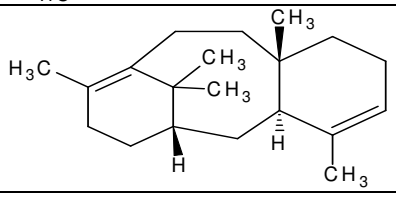
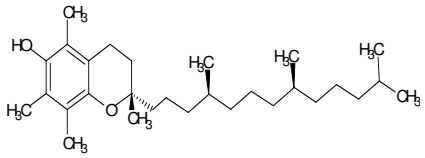
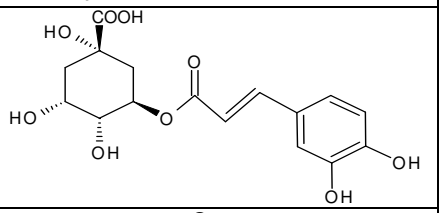
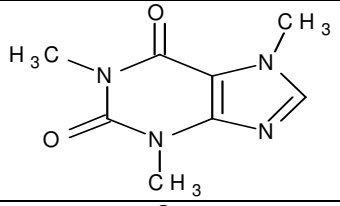
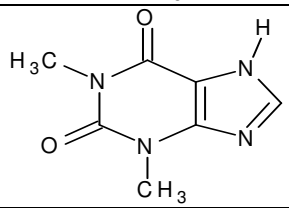
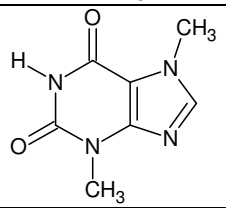
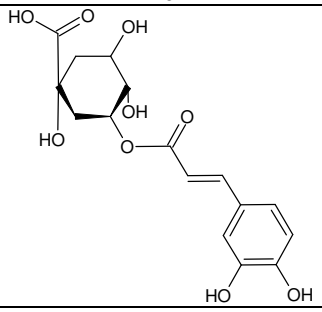
Green coffee is used traditionally by various methods like decoction of seeds used orally in treatment of influenza in Brazil (Stehmann and Brandao, 1995). In Cuba, hot water extract of green coffee seed is used orally for treatment of aphrodisiac in males (Roig and Mesa). Decoction of fruit and leaf of green coffee is used orally for treatment of anaemia, oedema, asthenia and rage in Haiti (Weniger *et al.*, 1986). The leaves of green coffee prepared through cataplasm and used in treatment of fever (Zamora and Pola, 1992). The hot water extract of dried fruit of green coffee is used in treatment of sleepiness, drunkenness & as antitussive in flu in Peru (Ayensu, 1994; Duke and Martinzez, 1994). In Thailand, hot water extract of dried seed is used as cardiotonic and neurotonic (Wasuwat, 1967).

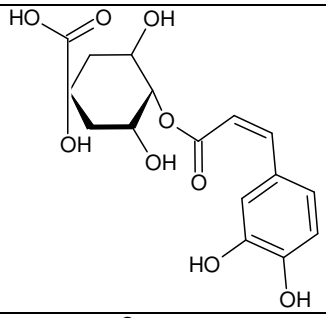
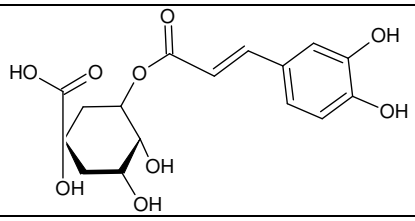
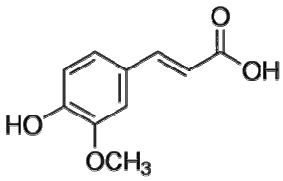
Phytochemical Analysis

Green coffee contains carbohydrates, phenolic species (caffeine, chlorogenic acid), polysaccharides, proteins, polyphenols, melanoids, lipids and minerals (Bicchi *et al.*, 1995; Fischer *et al.*, 2011; Naido *et al.*, 2008). Many other elements like Ca, K, Mg, Cu, Fe, Mn are also present in the green coffee beans (Suzuki *et al.*, 2002). Green coffee oil which is prepared from the cold pressing of unroasted green beans rich in lipids i.e. triacylglycerol, cafestol, Kahweol, sterols, tocopherols and diterpenes (Kaurene family) (Speer, 2006). Green coffee beans are rich in chlorogenic acid, caffeine, theophylline, trigonelline and theobromine (Franca *et al.*, 2005; Ruiz *et al.*, 2007; Gornas *et al.*, 2014; Skowron *et al.*, 2015; Kuhnert *et al.*, 2011; Perrone *et al.*, 2008). There are three major chlorogenic acids present in green coffee beans sample i.e. 3-CQA (3-O-caffeoylquinic acid), 4-CQA (4-O-caffeoylquinic acid), 5-CQA (5-O-caffeolquinic acid) (Ky *et al.*, 2001). Okubo and Kurata reported non-destructive classification analysis of the area which produces green coffee bean with the help of NIR spectra were found to be good. This analysis was carried out by SIMCA. Anyhow the model results were similar to that of SIMCA (Okubo and Kurata, 2019).

Driscoll studied that by using ultra performance liquid chromatography and mass spectrometry, 5-caffeoylquinic acid represented retention time of 4.49 and caffeic acid represented retention time of 7.71. In this study it was observed that the ionization was achieved at both positive and negative polarity for some compounds (Driscoll, 2014). Many compounds have been have been isolated from green coffee extract (Table 1) which has their own activity.

Table 1 : Isolated Compounds of Green Coffee

Constituent	Use	Structure
Triacylglycerol	These are the major dietary fat in the body. They are basically stored in the adipose tissues. These acts as the main energy source of the body.	
Sterol	These agents help in decreasing the cholesterol levels and prevent heart diseases.	
Diterpene	These are bitter tasting terpenoids that have shown activities to treat hypertension and respiratory tract disorders. Some analogues have also promising effect on tumour inhibition.	
α – Tocopherol	Also known as Vitamin E (which dissolves fats), this constituent has shown efficacy towards treatment of various nervous disorders like Alzheimer's Disorder, Parkinson's Disorder, Huntington's Chorea etc. It can also be used in the treatment of Vitamin E deficiency syndrome.	
Chlorogenic Acid	One of the new constituent that has been extracted has the action towards treating hypertension, inflammation and possibly can treat few respiratory allergies.	
Caffeine	This is one of the major constituent of green coffee. It is mostly used to improve the mental alertness. But the use of caffeine is not limited till here. Caffeine has promising effects in treating pain and headache (migraine) when used with other agents. Other than this caffeine helps in treatment of disorders like asthma, diabetes etc.	
Theophylline	This agent helps in the treatment of various respiratory disorders like asthma & COPD (Bronchitis, Emphysema).	
Theobromine	Theobromine has proven its efficacy in reducing blood pressure & strengthening the tooth enamel. As it belongs to the same class of caffeine, it also has a mild stimulant activity.	
3 – CQA (Caffeoylquinic Acid)	Same as Chlorogenic Acid	

4 – CQA	Same as Chlorogenic Acid	
5 – CQA	Same as Chlorogenic Acid	
Ferulic Acid	This compound is best known for its skin care benefits. It also has effects on curbing high cholesterol and high blood pressure. It is also helpful in conditions like diabetes, menopausal symptoms and osteoporosis.	

Pharmacological Activities

Green Coffee extract has many health and medicinal benefits (Table 2) as per the ethnobotanical claim. The isolated phytocomponents are tabulated (Table. 1) which have reported their own activities.

Table 2 : Pharmacological Activity of Components present in Green Coffee.

Active component	Biological activity
Caffeine	Activation of thermogenesis effect (Yoshioka *et al.*, 1990; Kogure *et al.*, 2002)
Chlorogenic acid	Glucose absorption in intestine delays, antagonise liver glucose-6-phosphatase, glucose muscle uptake increases. (Welsch *et al.*, 1989; Hemmerle *et al.*, 1997; Prabhakar and Doble, 2009)
Chlorogenic acid (5-Caffeoylquinic acid)	Antioxidant action (Bakuradze *et al.*, 2010)
Diterpenes (cafestol, kahweol)	Antioxidant action (Lee and Jeong, 2007)
N-Methyl-2-methylpyridinium-iodide	Antioxidant action; prevention of DNA oxidation (Bakuradze *et al.*, 2010)
Diterpenes	Anticancer, Hepatoprotective (Wattenberg, 1983; Cavin *et al.*, 2002; Lee *et al.*, 2007)
Caffeine	CNS stimulant, Adenosine receptor antagonist (Shlonsky *et al.*, 2003)
Trigonelline	Inhibit the cancer cells (Hirakawa *et al.*, 2005)
Ferullic acid	Anti-Hypertensive (Suzuki *et al.*, 2002)
Linolenic acid	Sun Protection

A study reported that after fermenting the green coffee beans for 24 hrs by utilizing yeast, the antioxidant activity, total phenolic content and total flavonoids content (TPC & TFC significantly increased which led to forfeiting the functionality of coffee. The phenolic compounds that are bound to the coffee beans are released due to yeast fermentation after roasting (Kwak *et al.*, 2018). Another study stated that there is a reduction in visceral fat pad accumulation and there is an increase in insulin resistance, when green coffee bean extract is administered in mice fed with high fat diet. It has been suggested that the constituents is green coffee like 5-CQA & polyphenols are effective in reducing weight and increasing insulin sensitivity. One meta-analysis on RCT also proved the effective loss of weight on consumption of green coffee extract (Song *et al.*, 2014).

Anti-Cancer Activity

Gouthamchandra *et al.* studied the anti-cancer activity of green coffee extract on mouse and human without any toxicity. In this research, decaffeinated water-soluble green coffee bean extract used on human and mouse cancer cell lines. They found that the chlorogenic acid complex (CGA 7) induced apoptosis by DNA fragmentation, PARP-1 cleavage, caspase-9 activation, and down regulation of Bcl-2, an anti-apoptotic protein and up regulation of pro-apoptotic protein BAX (Goutamchandra *et al.*, 2017).

Anti-Fungal Activity

Quiroz *et al.* studied the anti-fungal activity of the green coffee extract. The anti-fungal property found due to 5-O-Caffeoylquinic acid and alkyl ester (methyl, butyl, octyl and dodecyl) present in green coffee extract. They tested antifungal property on *Aspergillus* genus (*Aspergillus flavus*, *Aspergillus nominus*, *Aspergillus ochraceus*, *Aspergillus parasiticus, Aspergillus westerdijkiae*) by lipophilization method. The two esters octyl (78.4%) and dodecyl (54.5%) showed the maximum percentage inhibition on aspergilli.

Lipophilization method can be used to improve the antifungal activity of drugs (Quiroz *et al.*, 2013).

Anti-Inflammatory Activity

Hwang *et al.* studied the anti-inflammatory activity in lipopolysaccharide stimulated RAW264.7 murine cells. In this research they found that due to chlorogenic acid production of NO, COX-2, iNOS is inhibited without the cell toxicity. Proinflammatory cytokines (IL-1β &TNF-α) and other inflammatory cells are also inhibited by chlorogenic acid (Hwang *et al.*, 2014).

Anti-Hypertensive Activity

Suzuki *et al.* studied the anti-hypertensive activity of water-soluble green coffee bean extract on spontaneously hypertensive rats. They found that 5-CQA decrease the blood pressure and reduction in blood pressure occurred due to ferulic acid (50mg/kg P.O) which is a metabolite of 5-CQA. After the injection of atropine sulphate (5mg/kg SC) the depressor effect of FA (50 mg/kg, P.O) was attenuated which suggested that the hypotensive effect of FA in SHR might be mediated via the muscarinic acetylcholine receptors (Suzuki *et al.*, 2002). Ochiai *et al.* studied that green coffee extract improves the vasoreactivity in human. They did clinical trial on 20 healthy males in which 10 males were ingested with green coffee extract (GCE) for 4months and 10 were ingested with placebo drink which revealed that ingestion of GCE decreased the homocysteine level (Ochiai *et al.*, 2004).

Anti-Bacterial Activity

Djajal *et al.* investigated the anti-bacterial activity on salmonella *enterictidis* and *staphylococcus aureus* by using four concentration 20%, 15%, 10%, 5% in which green coffee extract shows inhibitory concentration at 20% by disc diffusion activity (Djajal *et al.*, 2018).

Use in Periodontal Disease

Bharath *et al.* found that pure green coffee extract can be used against periodontogenic bacteria like *Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans.* Anti-bacterial activity of green coffee extract determined by the minimum inhibitory concentration (MICS) and minimum bactericidal concentration by dilution and culture media method. MICS values of Pg, Pi, Aa were 0.2 µg/ml and Fn were at concentration of 3.125 µg/ml (Bharath *et al.*, 2015).

Activate Thermogenesis Effect

Yoshioka *et al.* investigated the effect of caffeine on brown adipose tissue (BAT) thermogenesis. They measured the guanosine-5'-diphosphate (GDP) binding which is a thermogenic indicator of BAT and oxygen consumption in BAT mitochondria. GDP is also measuring indicator in BAT temperature and resting metabolic rate (RMR) in mice. The dose of caffeine (60mg/kg I.P) significantly elevated BAT temperature with less effect on core temperature and increased significantly GDP binding and oxygen consumption in BAT mitochondria and RMR (Yoshioka *et al.*, 1995).

Anti-Obesity Activity

Choi *et al.* studied that mice fed with green coffee bean extract decreased the body fat mass and suppressed the high dietary fat induced obesity. The mice fed with green coffee beans extract at 50, 100, and 200 mg/kg with high fat diet which showed decrease in weight gain, liver weight and also supress the genes of adipogenesis (Choi *et al.*, 2016). Tanakal *et al.* also studied anti-obesity activity of green coffee beans on male Sprague-Dawley rats fed with normal diet which showed that green coffee bean extract decreased the fatty acid synthetic enzyme in liver and fatty acid oxidative enzyme increased in hepatic mitochondrial (Tanakal *et al.*, 2009).

According to a meta-analysis (Table 3) the following results were reported.

Table 3 : Meta-Analysis Results conducted by Onakpoya *et al.* (Onakpoya *et al.*, 2010)

Study	Body Weight at baseline	Dose	Treatment Duration	Results
*Ayton, 2009	76.65 ± 7.25 kg (GCE) 77.44 ± 12.93 kg (PLA)	180 mg	4 weeks	Weight loss was 1.35 ± 0.81 kg and 0.12 ± 0.27 kg for GCE and PLA respectively
Thom, 2007	85.2 ± 4.5 kg (GCE) 84.3 ± 4.3 kg (PLA)	200 mg	12 weeks	Mean weight loss was 5.4 ± 0.6 kg (GCE) and 1.7±0.9 kg (PLA).Mean fat loss was 3.6 ± 0.3% (GCE) and 0.7 ± 0.4% (PLA)
Dellalibera, 2007	Not reported	200 mg	12 weeks	2 Mean weight loss was 4.97 ± 0.32 kg and 2.45 ± 0.37 kg for GCE and PLA, respectively

*Not Published GCE: Green Coffee Extract PLA: Placebo

As per the results of the studies that were included in the meta-analysis, there was an achievable loss in the weight of the enrolled subjects.

Antihydroxyl Radical Activity

Daglia *et al.* studied the antiradical activity of aqueous extract of green coffee against the hydroxyl radicals in vitro by the chemical deoxyribose and ex-vivo in a biological cellular system (IMR32cells). Green coffee extract showed higher antiradical activity than roasted coffee. They investigated that 5-CQA active compound for antiradical activity which could be also used in neuroprotective effects. A large number of phenolic compounds are present in green coffee but when roasted coffee used the polyphenols compounds are destroyed due to Maillard reaction product (Daglia *et al.*, 2004).

Antioxidant Property

Patriche *et al.* studied the antioxidant property of green coffee bean extract by measuring radical scavenging capacity

(RSC) by DPPH method. This method revealed the elimination of free radicals. The antioxidant property found in green coffee extract due to chlorogenic acids and caffeine identified through HPLC (Patriche *et al.*, 2015). In other study Nosari *et al.* revealed the antioxidant property of green coffee oil which is prepared through cold pressing method of unroasted coffee beans. Microencapsulation was done by spray drying method which increase the antioxidant property in green coffee oil and widely used in cosmetic industry (Nosari *et al.*, 2015).

Wound Healing

Affonso *et al.* studied the improvement in skin wound healing by the aqueous extract of the coffee bean residual press cake prepared after oil extraction from green coffee beans. They investigated the effect of aqueous extract of coffee bean press cake on animal model through topical route after format .They investigated the effect of topical application of hydrogels containing the aqueous extract of coffee bean press cake (AE), chlorogenic acid (CGA), allantoin (positive control), and Carbopol (negative control) on wound skin and found that green coffee aqueous extract had the superior result compared to allantoin and roasted coffee extract and the size of wound reduced day by day (Affonso *et al.*, 2016).

Antidiabetic Activity

Song *et al.* studied that antiobesity and antidiabetic activity in Male C57BL/6N mice (N = 48) of green coffee extract by attenuate the obesity and insulin resistance. Mice were divided in six dietary groups each group ingested with chow diet, HFD, HFD-supplemented with 0.1%, 0.3% and 0.9% decaffeinated green coffee bean extract, and 0.15% 5-caffeoylquinic acid. The group which ingested with green coffee bean extract showed the decrease in weight, plasma lipids, glucose levels and insulin resistance with minimum effective dose 0.3%. The mechanism for decrease in plasma glucose level was stimulation of GLUT4 translocation to the plasma membrane in white adipose tissue and decrease in the regulation of genes which involved in adipogenesis were WNT10b, galanin-mediated and TLR4-mediated proinflammatory pathway (Song *et al.*, 2014).

Neuroprotective

Lee *et al.* investigated the antiparkinson's activity in MPTP model. Anti-inflammatory and antioxidant property of coffee showed neuroprotection. Coffee contained many compounds which have antioxidant property one compound eicosanoyl-5hydroxytryptamide (EHT) present in coffee bean decreased the protein aggregation, phosphorylation, neuroinflammatory and preserved the nigral dopaminergic neurones in transgenic mice. The mice which fed with EHT for four weeks showed the better result than others (Lee *et al*., 2013). In other study Islasa *et al.* investigated the benefits of coffee in Alzheimer's disease. The rat fed with dietary supplement with EHT for 6-12 months which reduced the interaneuronal amlyoid -β accumulation and increase PP2A activity through demethylation (Islasa *et al.*, 2014).

Use as Sun Protector

Wagemaker *et al.* investigated that green coffee seeds contained linolenic acid in high concentration which protect the skin from UV-rays which are harmful for our skin and due to this property fatty acids of green coffee beans can be used in cosmetic industries as sun screen agent (Wagemaker *et al.*, 2011).

Use in Improving Skin Properties

In a double blinded placebo controlled study done by Fukagawa *et al.*, the ingestion of coffee polyphenols had good effect in improving skin dryness, decrease in water loss from the skin, decreasing skin surface pH and improving the hydration of the stratum corneum. The ingestion of these polyphenols also improves the skin blood flow (Fukagawa *et al.*, 2017)

Use in Liver Disease

Shahmohammadi *et al.* investigated that on administering 1gm of green coffee bean extract for 8 weeks, individuals with Non Alcoholic Fatty Liver Disease may be benefitted. This may be because of the ability of green coffee extract to improve insulin sensitivity. The anti-inflammatory and antioxidant properties of green coffee extract can also be a cause for the above improvement (Shahmohammadi *et al.*, 2017).

Use in Veterinary

In a double-blind study of placebo-controlled, 10 ml coffee seed extract administered through subcutaneous route showed the 30% antidiarrheal effect in new-born calves (Ponepal *et al.*, 1996).

Conclusion

Green Coffee has various health benefits. The article focuses on the few of those which includes anticancer, antifungal, anti-inflammatory, antihypertensive activities etc. Green Coffee is used world-wide both as stimulant and for medicinal purposes. Although there are various benefits of green coffee, but most of them are unknown to the individuals. Yet there are various trials going on to explore many more benefits from green coffee. Although there are many medicinal activities of green coffee, but before using an advice from the physician is suggested.

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