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Epicatechin- Nature's Extraordinary Therapeutic Agent: A Review

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Abstract: Plant extracts have been used in folk medicine for centuries to treat a wide array of diseases. Compounds such as alkaloids, polyphenols, glycosides and terpenes are present in these extracts. Epicatechin is a flavonoid that falls under the polyphenol group. It is a major constituent in tea, fruits and chocolate. Epicatechin has been extensively researched for its diverse actions on human health. It's a potent antioxidant, has antiviral, antimalarial and anticarcinogenesis properties among others. Frequent consumption of epicatechins has been proven to be beneficial to individual's health. It exhibits a promising future as a drug formulation that is cost effective, highly biocompatible and has low toxicity.
Keywords: Epicatechin; Flavanoid; Polyphenol; Therapeutic uses; Green tea.

Introduction

Traditional medication from plant extracts have recently been given the limelight and are being used increasingly for the treatment of diseases.[1]These natural medications have been used in many ancient civilizations and their uses recorded. Traditional Chinese medicine, Indian Ayurveda medicine and the Tibetan Amichi medical system are some of the written ancient knowledge that have gained modern popularity and interest. Plants are the natural storage houses for a diverse group of chemicals that have proven to be beneficial to human health. These phytochemicals can be classified as alkaloids, polyphenols, glycosides and terpenes.[2]

Flavonoids are a group of polyphenolic compounds that can be broadly classified into flavones, isoflavonoids and neoflavonoids. Flavonoids are free radicle scavengers acting as electron donating agents.[3]

Natural sources of flavonoids are: [3]

- Fruits –Grapes (*Vitisvinifera*), raspberries (*Rubusidaeus*), cranberries (*Vacciniummacrocarpom*), etc.
- Vegetables – Onions (*Allium cepa*), tomatoes (*Lycopersiconesculentum Mill.)*, etc.
- Tea (*Camellia sinensis)*– Green tea, Black tea, Oolong tea
- Cocoa (*Theobroma cacao*) products – Dark chocolate, hot chocolate
- Red wine

Epicatechin is a type of flavonoid which is mainly found in green tea (*Camellia sinensis*) and dark chocolate. Polyphenols comprise of 30-40% of extractable solids from dried green tea leaves. The main catechins present are epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate.[4](Fig. 1)

Epicatechins have been proven to have diverse benefits to human health. It reduces the risks of diabetes mellitus and cardiovascular diseases. They have pharmalogical effects such as anti-hyperlipidemic, anti-inflammatory, antioxidative effects, anticarcinogenic, and cytoprotective. These flavonoids can be used as therapeutic agents individually or in combination with other synthetic drugs and antibiotics to produce a new generation of phytopharmaceuticals.[5]Furthermore, this natural product is cost effective, highly biocompatible and has low toxicity.

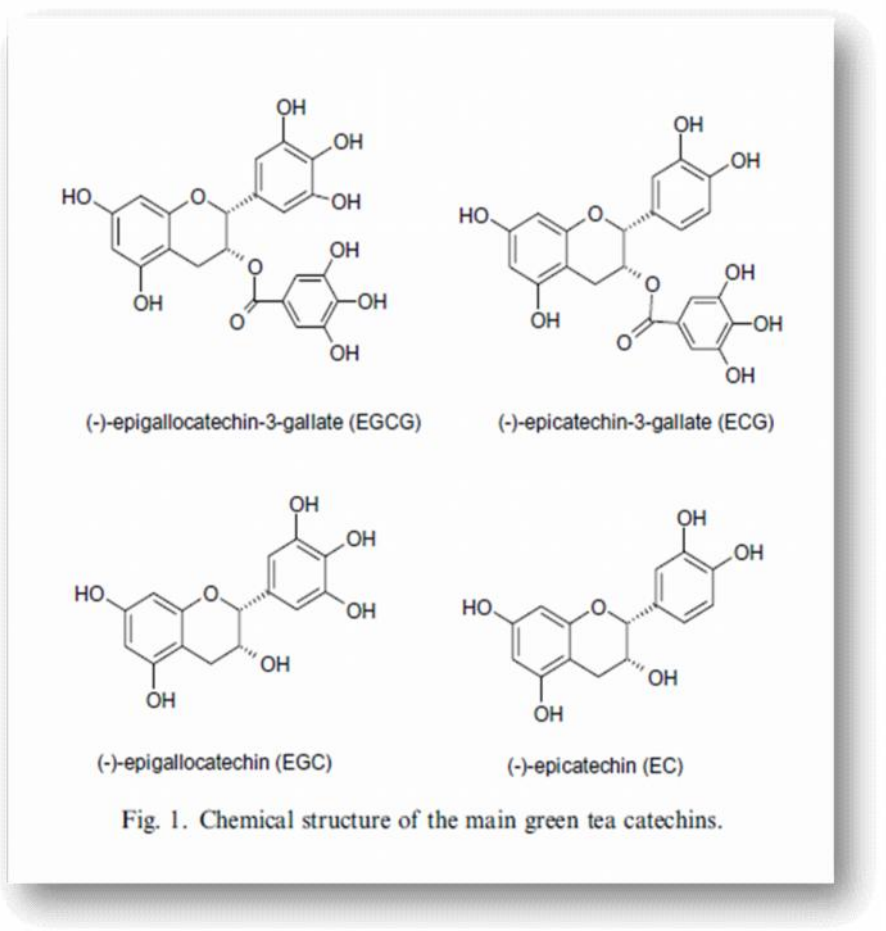

Fig. 1. Chemical structure of the main green tea catechins.

Therapeutic Uses

A. Antimalarial Effect

Green tea catechins were tested for its inhibition effect against two *Plasmodium falciparum* strains, 3D7 drug-sensitive (CQS) and FCR-1/FVO resistant to chloroquine (CQR). Epicatechin-3-gallate (ECG) and epigallocatechin-3-gallate(EGCG)exhibited a higher antiplasmodial effect on the CQR strain. ECG was generally more “active” than EGCG.

Artemisinin is a well-known, potent and clinically established antimalarial drug. A combination between artemisinin with EGCG or ECG showed an essentially additive effect against *P. falciparum*.[6]This essential additive effect of the drug combination suggests that it interferes with *P. falciparum* at two distinct sites. It is also hypothesized that epicatechins possess relevant antifolic effects that inhibits *P. falciparum*, which is a typical mechanism of a few established antimalarial drugs.

C-3 gallic acid esters of catechins, namely ECG, EGCG, (-)-catechingallate and (-)-gallocatechingallate are potent inhibitors of three important enzymes (FabG, FabZ and FabI) involved in the fatty acid biosynthesis of *P. falciparum*.[7] Thus giving it an antimalarial effect.

B. Antiviral Effect

EGCG acts as a strong inhibitor of HIV replication in cultured peripheral blood cells.[8] EGCG and ECG were found more effective than epigallocatechin (EGC) or epicatechin (EC) in the inhibition of HIV-1 reverse transcriptase in vitro.[9]EGCG binds directly to CD4 molecule with consequent inhibition of gp120 binding.[10] EGCG inactivated viruses in vitro by deformation of phospholipids.[11]

ECGC inhibited expression of viral protein[12] and host factors[13] of Epstein-Barr virus.ECGC was shown to agglutinate influenza viruses, thus preventing it from absorbing to Mardin-Darby canine kidney (MDCK) cells.[14]Hence, reduced the infectivity of influenza virus. This was an in vitro study. Green tea extract had an inhibitory effect on the acidification of intracellular compartments such as endosomes and lysosomes, resulting in inhibition of growth in influenza virus.[15]

EGCG and ECG inhibited plaque forming activity of influenza A and B virus whereas ECG exhibited little inhibition. A polyphenol mixture is more efficient than a single compound in plaque inhibition. (-)-Epicatechin had no antiviral effect and only a little inhibition on plaque formation.

Catechins inhibited replication of influenza virus on MDCK cells. The inhibitory effect is in a concentration-dependant manner and throughout the virus infection cycle after initial infection. Antiviral effectis exerted not only on initially infecting viruses but on newly propagated viruses as well.

Down regulation of viral RNA synthesis was evident at high concentrations. EGCG and ECG decreased neuramidase activity significantly.[16]Neuramidase is required for the release of new viral particles from the infected cells by cleaving of its sialic acid moiety. It also prevents the self-aggregation of viral particles.

(+)-Epicatechin and (-)-epicatechin was found to inhibit Hepatitis C virus (HCV) replication by inactivating Cyclooxgenase-2-depandant signalling pathway. Cyclooxygenase-2 (COX-2) produces various prostaglandins (PG) which result in chronic inflammation and fibrosis. PGE_2, thromboxane B2 and prostacylin gives rise to cellular proliferation, cancer invasiveness, angiogenesis and is anti-apoptotic. Therefore, leading to hepatocarcinogenesis.

(+)-Epicatechin and (-)-epicatechin may suppress the gene expressions of pro-inflammatory enzymes and cytokines that are induced by HCV.

Inhibition of HCV replication is at protein and RNA levels. A great advantage is that it does not cause host cell toxicity.[17]

C. Antioxidant Effect

Epicatechins are antioxidants, they are effective scavengers of free radicles such a reactive oxygen species, reactive nitrogen species and superoxide.In a study of the effect of green tea extract in tamoxifen intoxication of the liver, green tea extract scavenged free radicles and protected the liver from oxidative stress that would have brought about hepatic carcinogenesis.[18]Epicatechin and other polyphenols decreases the susceptibility of low density lipoprotein to oxidation which prevents the initiation of artherosclerosis.[19]

HIV proteins Tat and gp120 is known to cause neurotoxicity in humans via mechanisms that activate macrophages and glial cells and finally, oxidative stress. Epicatechins are neuroprotective by blocking the neurotoxic effects of the HIV proteins which causes oxidative stress.[20]

Pre-treatment with epicatechin prior to exposure of gamma (γ) radiation prevents hepatic and testicular damage. Damage would be due to oxidative stresses that is produced by formation of free radicles as a result of radiation. Epicatechin is radioprotective, especially to patients undergoing radiotherapy.[21]

Catechins have the ability to modulated antioxidant enzymes in vivo. It has been shown to increase the activity of superoxide dismutase and catalase, thus enhancing their abilities to scavenge reactive oxygen species and repair oxidized DNA.[22]

D. Anticarcinogenic Effect

Catechins have an antiproliferative effect on tumour cells as well as inhibiting metastasis. It also suppresses lipid peroxidation of tumour cells.[23] EGCG and ECG not only inhibits cell growth but also makes rigid the tumour cell membrane by interacting with the lipid bilayer.[24]Rigidification of cell membrane disrupts proliferative cellular events and depresses lipid peroxidation by inhibiting diffusion of free radicles through lipid bilayer.[25,26]

It also binds to secondary bile acid (taurodeoxycholic acid). Secondary bile has been associated with increased risk of developing colorectal cancer. Hence these polyphenolic compounds may reduce the risk factor for developing colorectal cancer.[27]

E. Cholesterol Lowering Activity

Catechin and epicatechin significantly inhibited cholesterol esterase in a concentration dependant manner.[28] However it is less potent than simvastatin, a pancreatic cholesterol esterase inhibitor. Inhibition of cholesterol esterase may enhance control of the bioavailibilty of dietary cholesterol and limitation of absorption of free cholesterol into blood circulation.

Catechin and epicatechin also bind to bile acids (taurocholic acid and glycodeoxycholic acid) in a concentration dependant manner. Binding to bile acids and increasing their faecal excretion has been hypothesized as a possible mechanism for lowering plasma cholesterol levels.Catechin and epicatechin exhibit a primary bile acid binding capacity.[28]

Catechin and epicatechin significantly reduced the solubility of cholesterol in artificially prepared micelles.[28] Reducing solubility of micellization in intestinal lumen is a new target of intervention for the treatment of hyperlipidemia and obesity.[29] EGCG interferes with the structure of micellar cholesterol, inducing the micelles to be larger and insoluble, thus inhibiting micelle formation.[30]

F. Effect on Endothelium and Vascular Smooth Muscles

Phenylephrine produces contractile responses in endothelium rings. Contraction is greater in endothelium-denuded rings compared to endothelium-intact rings. A pre-treatment of (-)-epicatechin significantly attenuated the response of phenylephrine in endothelium-intact rings. The pre-treatment had no effect in endothelium-denuded rings.

Pretreatment with (-)-epicatechin enhanced acetylcholine-induced relaxation.[31]

Since epicatechin derivatives are found to be strong antioxidants, and oxidation of nitric oxide is one of its major pathways of inactivation, it is possible that epicatechin may enhance the nitric oxide-mediated vasorelaxation.[31]Green tea extract reduces the proliferation of arterial smooth muscle cells,[32] which prevents the formation of artherosclerotic plagues.[33]

G. Effect on Bone Health

EGCG increases formation of bone nodules from human osteoblast-like cells by increasing osteoblastic differentiation.[34] A positive association between regular green tea drinkers and bone mineral density (BMD) of the total body, lumbar spine and hip regions in both men and women.[35]Protective effect of green tea catechins against bone loss has been shown in some animal studies.[36]

Catechin diet aided in normalizing decreased BMD and bone mineral content caused by cadmium intoxication in rats.[36]Catechins may be effective in preventing bone loss due to ovarian hormone deficiency.[37] EGCG has been shown to inhibit bone resorption by inducing apoptotic death of mouse osteoclast-like cells.[38]Therefore, this suggests that green tea catechins may have beneficial effects on bone health.

H. Effect on Skeletal Muscles

(-)-Epicatechin treatment improved treadmill performance, delayed onset of fatigue, increased muscle capillarity, increased levels of proteins comprising the oxidative phosphorylation machinery as well asmitofilin and porin in skeletal and cardiac muscles and increased mitochondrial volume density and cristae abundance in hindlimb and heart muscles in rats. There is also increased in mitochondrial transcription factor A (Tfam) expression.Combination of exercise and epicatechin treatment resulted in greater improvements in all above mentioned. Hence this can lead to a sustained increase in exercise performance.[39]Catechins prevent muscle atrophy by decreasing unloading-mediated expression of atrogenes. These expression of atrogenes are induced by oxidative stress.[40]

Conclusion

Epicatechin has proven itself to be nature's extraordinary therapeutic agent. More time and attention should be spent on developing it as a sustainable drug for prophylaxis and treatment of complications and diseases.

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