Review Article

A Review on Therapeutic Potential of Caffeic Acid and its Derivatives

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Received: 22-02-2020; **Revised:** 18-04-2020; **Accepted:** 25-05-2020.

ABSTRACT

Caffeic acid is the hydroxy cinnamic acid belonging to the phenolic acid family, which is a phenyl propanoid structure with a dehydroxylated aromatic ring attached to a carboxylic acid group through an ethylene bridge. It occurs naturally in the wide range of food items such as vegetables, fruits etc. The caffeic acid and its derivatives such as caffeic acid esters and caffeic amide possess various biological activities. This review article aimed to describe the characteristics and therapeutic potential of caffeic acid and its derivatives including anti-oxidant, anti-microbial, anti-cancer, anti-inflammatory activities.

Keywords: Caffeic acid, polyphenol, characteristics, therapeutic potential.

INTRODUCTION

From earlier decades medicinal plants existed on earth. Thus, medicinal plants are of global paramount importance. The world is decorated with medicinal herbs, which is a rich wealth of endurance. The vital and appreciables roles are played by natural drug substances, reported by modern system of medicine. The presence of the bioactive substances in the natural compound plays a therapeutic role. These bioactive compounds which are less toxic and more effective and provide biological and chemical means of modification and extraction of natural products into potent drugs.[1]

In the search for compounds of therapeutic interest, phenolic acids which are widely distributed in the plants and are a part of large and complex group of organic substances.[2] The biochemical properties of polyphenolic secondary metabolites such as flavonoids and chalcones attract much attention in biology and medicine.[3]

Caffeic acid, the major representative of hydroxy cinnamic acid and poly phenol which are widely distributed in plant is usually found as esters, glycosides and sugar esters. Further modifications in the structure of caffeic acid leads to the formation of amides and esters. These new analogs possess a wide variety of interesting pharmacological activities.[4,5] The review mainly focusses on the pharmacological activities of caffeic acid and its derivatives.

Characteristics of Caffeic Acid

Synonyms:

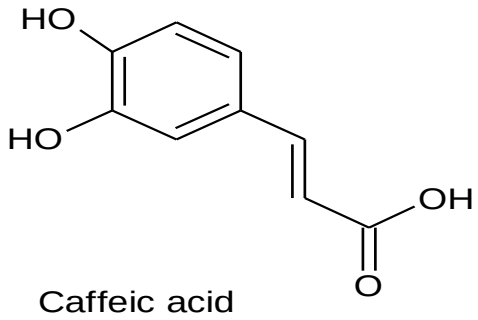
5(4)-(2-carboxyethenyl)-1,2-dihydroxybenzene;

4-(2'-carboxyvinyl)-1,2-dihydroxybenzene; 3, 4-dihydroxybenzeneacrylic acid;

3, 4-dihydroxycinnamic acid;

3-(3,4-dihydroxyhenyl)propenoic acid; 3-(3,4-dihydroxyhenyl)-2-propenoic acid

Molecular structure:



Caffeic acid

Table 1: Chemical and Physical Properties of Caffeic Acid

Mol. formula	$C_9H_8O_4$
Mol. weight	180.15
Description	Yellow prisms or plates from water.[6]
Melting-point	: Decomposes at 225°.C[6]
Solubility	Sparingly soluble in cold water; very soluble in hot water and cold ethanol.[7]
Stability	Caffeic acid exists in cis and trans forms, trans being the predominant naturally occurring form. Solutions of caffeic acid and its derivatives (e.g., chlorogenic and isochlorogenic acids) are unstable in sunlight and ultraviolet light. The trans form of caffeic acid is partially converted to the cis form, which in turn is partially converted to the lactone, aesculetin.[8-9]

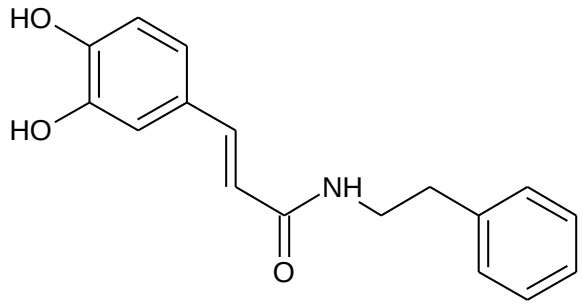
Pharmacological Profile

Anti-oxidant activity

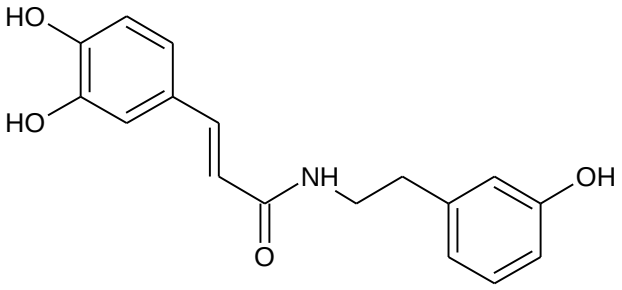
Anti-oxidants are compounds that inhibit or reduce the effects triggered by free radicals and oxidizing compounds. Phenolic antioxidant exhibits radical scavenging activity and metal chelating activity. They act both in the initiation and propagation of the oxidative process.[10]

In the previous studies caffeic acid has been shown to produce protective effect on α-tocopherol in low density lipoprotein.[11] The caffeic acid and its amide have shown anti-oxidant activity against lipid peroxidation in O/W emulsion model. The compounds which have three hydroxyl groups in the structure manifested the highest protection against the induced oxidation.[12]

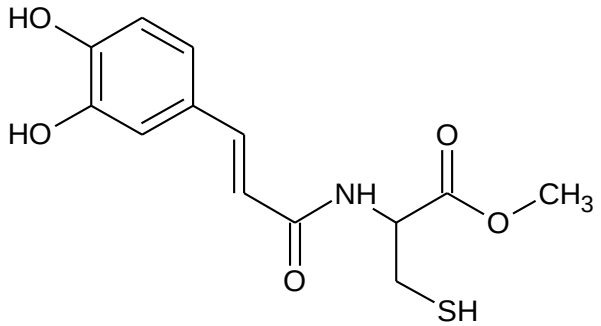
The four amide analogues were synthesized from caffeic acid phenyl ester and they were evaluated for their antioxidant activity. The synthesized compound showed higher activity than the parent compound and also standard Trolox. These compounds possess highest activity due to the presence of hydroxyl and catechol group and number of hydrogen donating groups. The presence of both the groups in the structure provide most active compound.[13]



a) IC_{50}=43.07; (55% of inhibition)



b) IC_{50}=41.62; (59% of inhibition)



c) IC_{50}=2.26; (94% of inhibition)

The radical scavenging activity of caffeic acid and its amide was tested with the DPPH and ABTS assays. The synthetic amides had better inhibitory activity (EC_{50} = 11.1-38.8µM) than caffeic acid. The inhibitory activity of these compounds is due to the presence of halogens and ester groups which were relatively more hydrophobic than the corresponding hydroxyl or methoxy group.[14,15]

A series of caffeic acid amides were synthesized and tested for anti-oxidant activity using lipid peroxidation system. The aromatic amine derivatives showed more potent activity with sub micromolar (IC_{50}=0.29-0.63µM) than the aliphatic amines (IC_{50}=2.2-6.1µM).[16]

Antimicrobial activity

The invitro studies have demonstrated antimicrobial properties of caffeic acid and its derivatives against varies oral pathogens. The thorough search of antimicrobial activity of caffeic acid reveals that it is the promising target for the treatment of dermal diseases such as acne. Some phenyl propanoides, including caffeic acid are able to inhibit the growth of bacteria such as *E. coli*, *Staphylococcus aureus*, *Bacillus cereus* and some fungi such as candida albicans.[17-20]

The mechanism of antimicrobial activity of substance is established considering one of the three following (1) reaction with the cell membrane causing increased permeability and of cellular contituents, (2) inactivation of enzymatic system or essential enzymes including those involved in the production process energy and synthesis of structural components, or (3) destruction or inactivation of functional genetic material.[21,22]

The antimicrobial activity of caffeic acid derivatives has been reported. The antibacterial activity of a series of caffeic acid esters (methyl, ethyl, propyl, and butyl caffeate) against E.coli showed potent antibacterial activity against the test strain. The propyl and butyl caffeate showed good antibacterial activity with the MIC value of 5.00mM when compared to other derivatives.[23,24]

The phenethyl caffeate exhibited antibacterial activity against *S. aureus* and *E. coli*. This compound has structural similarity to ester, which showed strong antibacterial action. The short linear carbon chain ester derivatives of caffeic acid were synthesized and their antibacterial activities were evaluated against E. coli and S. aureus; the esters, methyl and ethyl caffeates, showed activity for both strains, while their by-products were only active for the E. coli strain.[25]

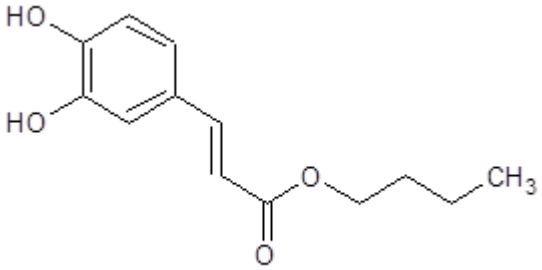
Caffeic acid phenyl ester produced antibacterial activity against Staphylococcus aureus and E.coli, the activity is due to the synthesis of reactive oxygen species that destroy the outer membrane of bacteria. [26]

Caffeic acid phenyl ester inhibits HIV-1 integrase, thus it is believed to be a potential anti -HIV therapy.[27-28]

Caffeic acid and their ester derivatives were tested for anti-fungal activity on candida albicans bio film. The

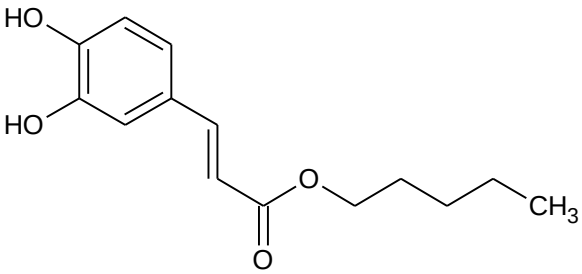
compounds with aromatic ring, conjugation produced a promising anti biofilm activity.[29]

The caffeic acid ester derivatives were synthesized and evaluated against strains of *Staphylocoocus aureus* and *E. coli*. The results showed that five compounds among sixteen showed optimum to strong antibacterial activity against *E.coli*. Propyl caffeate, butyl caffeate and pentyl caffeate were found to exhibit the best antibacterial activity with an MIC value of 0.2.[30]



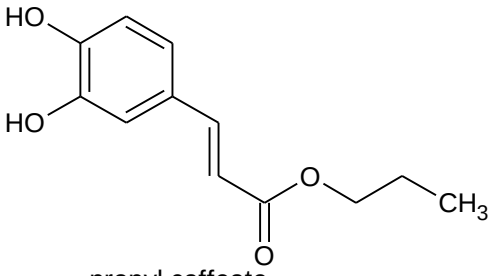
butyl caffeate

MIC = 0.21 µM



pentyl caffeate

MIC = 0.20 µM



propyl caffeate

MIC = 0.22 µM

Anti- cancer activity

Several phenolic compounds have been evaluated for their anticancer activity.[31,32]

The invitro cell viability of caffeic acid derivatives was evaluated using MTT assay. The growth inhibition effect of selected compounds on human breast adenocarcinoma cell line (MCF-7) showed reduced cell viability by roughly at 25µm dose. The seven membered heterocycle ring with an unsubstituted phenyl ring which exhibited best inhibitory activity with 85% growth inhibition and produced enhanced biological activity. [33]

The series of caffeic acid phenethyl amide fluorinated derivatives was investigated for oxidative stress invitro by using hydrogen peroxide as the inducer of oxidative damage. The synthesized compounds exhibited significant cytoprotection against hydrogen peroxide.[34]

The caffeic acid ester on human cervix adenocarcinoma cell line and non-neoplasic cells -fibroblasts from human embryonic lung tissue displayed antitumoral effect. The propyl ester exhibited pronounced antitumoral effect towards both cell lines than octyl and methyl analog.[35]

The series of synthesized caffeic acid esters where assayed against human colan cancer (HCT116) and human epidermoid carcinoma (A431). The methyl caffeate showed significant cytotoxicity against various cancer cell line. The compounds with dihydroxy substituted one seemed to possess most favourable for cytotoxic activity.[36]

Anti-inflammatory Activity

During inflammation, external agents such as pro inflammatory interleukins activate NF-kB.

The caffeic acid and its synthesized derivatives showed their inhibitory activity on NO production. The synthesized compounds also strongly inhibited the production of iNOS and COX -2.[37]

The T-cells are the causative agents for inflammation, and hence the immunosuppressive behavior was evaluated in T-cells.

The series of phenyl alkyl caffeic acid ester derivatives were synthesized and they were assessed for their nitric oxide inhibitors. From the synthesized compounds, compounds having less number of alkyl chain produced enhanced anti -NO activity.[38]

Leukotriene biosynthesis Inhibitor

Caffeic acid phenyl ethyl ester was investigated for its ability to produce significant inhibition of leukotriene biosynthesis in isolated PMN. The CAPE showed similar effect as that of the reference molecule zileuton.[39,40]

CONCLUSION

Caffeic acid is a unique pharmacophore that is associated with the varieties of pharmacological activities. The presence of the hydroxy group in the structure give rise to variety of activities. The activities of the synthesized compound are increased or decreased due to presence of hydroxy group, hydrophobic region, halogens etc. This review article provides some information for further investigation of caffeic acid and its derivatives.

Acknowledgement:

I extend my thanks to The Dean, Mother Theresa Post Graduate and Research Institute of Health Sciences, The Guide, Professor and Head, Department of Pharmaceutical Chemistry.

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Source of Support: Nil, **Conflict of Interest:** None.