# Introduction

Secondary metabolites are extensively distributed in the plant kingdom. They play an essential role in growth, devel- opment and reproduction of plants. Moreover, they are known to impart protection to plants against their competi- tors via allelopathy. Secondary metabolites also protect the plants by herbivores, insects, microorganisms, exposure to UV radiation, drought, and heat stress (Commisso et al. [2016](#_bookmark194); Heleno et al. [2015](#_bookmark204); Mandoulakani, Eyvazpour, and Ghadimzadeh [2017](#_bookmark249); Saibabu et al. [2015](#_bookmark289); Sarkar and Shetty [2014](#_bookmark299)). Phenolics are major group of secondary metabolites, which can be sorted into following subgroups, i.e., the phen- olic acids, flavonoids, coumarins, curcuminoids, stilbenes, quinones, lignans, tannins, phenolic terpenoids and phenolic alkaloids (Gan et al. [2019](#_bookmark218); Taofiq et al. [2017](#_bookmark308)). Further, phen- olic acids are categorized into two main groups: (i). hydrox- ybenzoic acids, comprising of a backbone of seven carbon atoms (C6-C1), includes p-hydroxybenzoic acid, protocate- chuic acid, gallic acid, vanillic acid and syringic acid; (ii). hydroxycinnamic acids (HCiA), containing nine carbon atoms (C6-C3) phenylpropanoid backbone, includes p-cou- maric acid (p-CoA), caffeic acid (CA), ferulic acid (FA) and sinapic acid (SA) (Taofiq et al. [2017](#_bookmark308)). Both plant-based, as well as synthetic phenylpropanoids (PPs) and their deriva- tives have gained attention due to their low toxicity and wide array of bioactive properties, involved in human dis- ease management. These compounds possess various

biological activities, for instance, antioxidant (Jia, He, and Lu [2018](#_bookmark219)), antimicrobial (KeR pa et al. [2018](#_bookmark228)), anti-inflamma- tory (Doss et al. [2016](#_bookmark207)), antidiabetic (Anlar et al. [2018](#_bookmark176); Prabhakar et al. [2013](#_bookmark279)), anticancer (Bouzaiene et al. [2015](#_bookmark199); Kabała-Dzik et al. [2017](#_bookmark222); Rathee et al. [2018](#_bookmark285)), neuroprotective (Deshmukh et al. [2016](#_bookmark201); Liang et al. [2015](#_bookmark236)), reno-protective (Matboli et al. [2017](#_bookmark253); Navaneethan and Rasool [2014](#_bookmark282); Tohamy et al. [2016](#_bookmark319)), hepatoprotective (Cha et al. [2018](#_bookmark178); Fu et al. [2016](#_bookmark216)), cardioprotective (Aswar et al. [2013](#_bookmark184); Chowdhury et al. [2016](#_bookmark192); Silambarasan et al. [2016](#_bookmark294)) as well as prevents aging and other complications associated with photodamage (Oresajo et al. [2008](#_bookmark262)) ([Fig. 1](#_bookmark21)). Phenylpropanoids and its derivatives have significance in food, cosmetics, and pharmaceutical industries (Burns et al. [2013](#_bookmark202); Nadal et al. [2016](#_bookmark272); Ou and Kwok [2004](#_bookmark266)), electrochemical sensors (Keyvanfard, Karimi- Maleh, and Alizad [2013](#_bookmark230)). There are also few reports of its application as an antioxidative additive in biodiesel (Dodos, Tsesmeli, and Zannikos [2017](#_bookmark206)) and as a colorant in textile industries (Shahid et al. [2018](#_bookmark310)).

This review attempts to describe various bioactive proper-

ties of PPs and their derivatives. The article highlights the potential applications of PPs in food, pharmaceutical and cosmetics industries concerning their biological properties, especially their antioxidative, antimicrobial and photoprotec- tive activities. Various commercially available PPs products in the form of health supplements and skincare products have also been discussed.

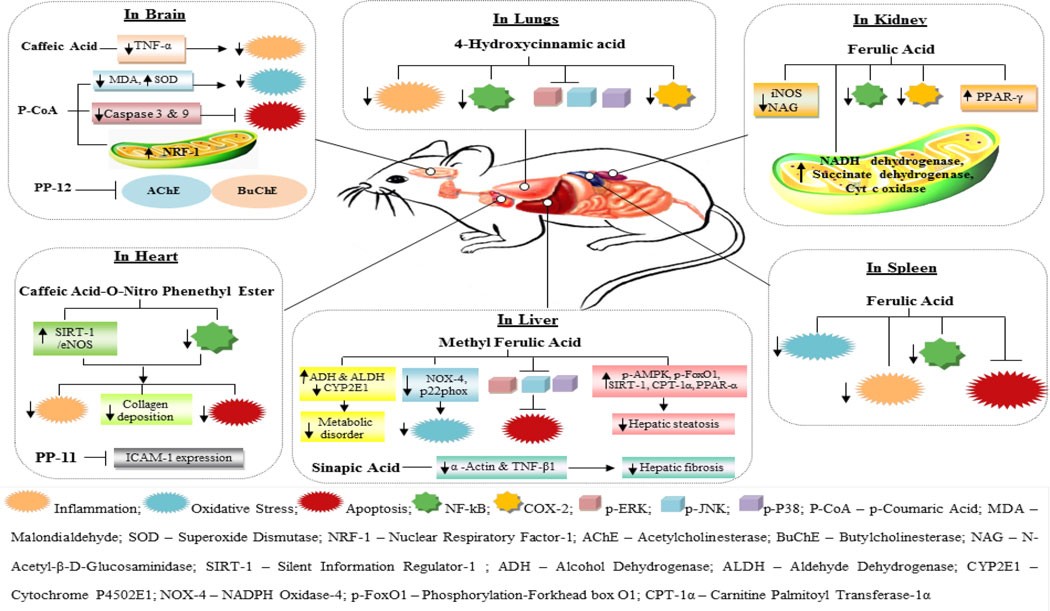


Figure 1. Renoprotective, neuroprotective, cardioprotective and hepatoprotective effects of phenypropanoids and its derivatives.

*Phenylpropanoids: biosynthesis and their occurrence*

Phenylpropanoids, have C6-C3 carbon skeleton as core struc- ture and is one of the main categories of phenolic acids with widespread distribution in plants (Natella et al. [1999](#_bookmark280); Teixeira, Gaspar, et al. [2013](#_bookmark313)). The carbon flow of erythrose-4- phosphate and phosphoenolpyruvate is channeled to the shi- kimate pathway to convert shikimate into chorismate, which acts as a branch point for the synthesis of phenylalanine (Phe), tyrosine (Tyr) and tryptophan (Trp) in plants (Zabalza et al. [2017](#_bookmark330)). The first step in the biosynthesis of PPs is cata- lyzed by the enzyme phenylalanine ammonia lyase (PAL) to convert Phe into trans-cinnamic acid (t-CiA). Hydroxylation of t-CiA yields p-CoA by the action of an enzyme, C4H. P- coumaric acid is also formed from the deamination of Tyr catalyzed by tyrosine ammonia lyase (TAL). Hydroxylation of p-CoA leads to the transformation of 3, 4-dihydroxycinnamic acid (caffeic acid, CA), which in turn forms 4-Hydroxy-3- methoxycinnamic acid (ferulic acid, FA) by methylating action of caffeic acid/5-hydroxyferulic acid 3/5-O-methyl- transferase (COMT). Further, it converts FA into 3,5-dime- thoxy-4-hydroxycinnamic acid (sinapic acid, SA), as shown in [Fig. 2](#_bookmark44) (Sharma [2012](#_bookmark312); Heleno et al. [2015](#_bookmark204)).

Phenylpropanoids are obtained from various plant-based food sources such as cereal grains including, wheat, barley, rye, oats, rice bran (Schmidt et al. [2014](#_bookmark302); Zielinski, Kozlowska, and Lewczuk [2001](#_bookmark340)), fruits, coffee, spices, herbs (Maurya and Devasagayam [2010](#_bookmark256); Teixeira, Silva, et al. [2013](#_bookmark314)), vegetables such as potato (Devi, Das, and Deka [2018](#_bookmark204)), mushrooms (Lee et al. [2018](#_bookmark248); Seong, Hwang, and Chung [2016](#_bookmark309)) and red wine (Filipe-Ribeiro, Cosme, and Nunes [2018](#_bookmark214)).

Cinnamic acid (CiA) is a major active component of *Cinnamomum* spp., commonly named as cinnamon (Tohamy et al. [2016](#_bookmark319)). It is also readily available in coriander, cloves, black pepper, and turmeric (Roller and Seedhar [2002](#_bookmark287)), *Syzygium alternifolium* (Kasetti et al. [2012](#_bookmark224)).

P-Coumaric acid is found in blood orange juice – a nat- ural mutant of orange (Destani et al. [2013](#_bookmark203)), cranberry beans (Chen et al. [2015](#_bookmark185)), chinese cabbage (Lee et al. [2018](#_bookmark248); Seong, Hwang, and Chung [2016](#_bookmark309)), flowers of *Helichrysum arenarium* and *Antennaria dioica* (Babot˘a et al. [2018](#_bookmark188)).

Caffeic acid occurs as an essential constituent in various plants, for instance, in roots of *Cichorium intybus* (Azay- Milhau et al. [2013](#_bookmark186)), *Canarium album* commonly known as chinese olive (Jia et al. [2016](#_bookmark220)), and green coffee (Palmieri et al. [2018](#_bookmark268)). The white rot fungus *Pycnoporus cinnabarinus* is a natural CA producer. This organism is used to develop a production process for the biotransformation of p-couma- ric acid to CA. However, the conversion of p-coumaric acid to CA has been reported using several microbial sources including the bacterium *Streptomyces griseus* and the fila- mentous fungi *Gliocladium deliquescens* (Hern´andez-Ch´avez, Martinez, and Gosset [2019](#_bookmark206)).

Ferulic acid, one of the most studied phenylpropanoid

occurs in *Ferula foetida* (Hing), sugar beet pulp, corn kernel, wheat bran, rice bran oil (Samad and Zainol [2017](#_bookmark295)), chicory (Azay-Milhau et al. [2013](#_bookmark186)), spinach, broccoli (El-Ashmawy et al. [2018](#_bookmark208)), coffee (Gawlik-Dziki et al. [2017](#_bookmark221)), and *Phyllanthus emblica* (Kumnerdkhonkaen et al. [2018](#_bookmark243)). Recently, ferulic acid production from wheat bran has been reported by solid-state fermentation of *Aspergillus niger*

Chorismate

*AS*

*CM*

Tyrosine

Prephenate

Phenylalanine

Anthranilate Tryptophan

Benzoic acid

p -Coumaric acid Caffeic acid

*COMT*

*C3H*

Ferulic acid

*F5H*

5-hydroxy ferulic acid

Quinic acid

Trans- Cinnamic acid

*C4H*

*PAL*

*TAL*

4-Caffeate CoA ligase and quinate O-hydroxyl cinnamoyltransferase

3,4 or 5-*O*-caffeoylquinic acid

Sinapic acid

*COMT*

Figure 2. An overview of the biosynthesis of phenylpropanoids in plants. The shikimate and phenylpropanoids pathway enzymes are: EPSPS – 5- Enolpyruvoylshikimate-3-Phosphate-Synthase; CM – Chorismate Mutase; AS – Anthranilate Synthase; TAL – Tyrosine Ammonia Lyase; PAL – Phenylalanine Ammonia Lyase; C4H – Cinnamic Acid 4-Hydroxylase; C3H – 4 Hydroxycinnamte 3-Hydroxylase; COMT – Caffeic Acid/5-Hydroxyferulic Acid 3/5-O-Methyltransferase; F5H – Ferulate 5-Hydroxylase (Heleno et al. [2015](#_bookmark204); Sharma [2012](#_bookmark312); Zabalza et al. [2017](#_bookmark330)).

strain FA-WB (Yin et al. [2019](#_bookmark322)). Whereas, sinapic acid is widely found in rye (Andreasen et al. [2001](#_bookmark175)), wheat bran (Arranz and Saura Calixto, [2010](#_bookmark182)), rapeseed and canola seeds (Mayengbam, Aachary, and Thiyam-Holl€ander [2014](#_bookmark257)), broc- coli, kale, cabbage (Yilmaz and Bagci [2018](#_bookmark324)), fruit and spices (Ero˘glu et al. [2018](#_bookmark210)).

In plants, PPs are mostly found in its conjugated forms, for instance, chlorogenic acid (an ester of caffeic acid and quinic acid) from *Foeniculum vulgare* (Salami, Rahimmalek, and Ehtemam [2016](#_bookmark292)), *Hypericum laricifolium* Juss (Quispe et al. [2017](#_bookmark281)). Cherry, scientifically named *Prunus avium* contains chlorogenic acid (CGA), 3-p-coumaroylquinic acid and neo- chlorogenic acid (Basanta et al. [2018](#_bookmark195)). Esters of SA, namely sinapoyl glucose and sinapines, are abundantly present in mus- tard and canola seeds (Mayengbam, Aachary, and Thiyam- Holl€ander [2014](#_bookmark257)). Recently, a group of researchers obtained a large number of hydroxycinnamic acid derivatives from the roots of purple carrot and heads of red cabbage, i.e., ten and twenty-one derivatives, respectively (Mizgier et al. [2016](#_bookmark264)).

*Phenylpropanoids: guards against microbes*

Food-borne illness due to the consumption of microbial contaminated food and the emergence of resistance to con- ventional antibiotics in bacteria is considered as one of the most pressing threats to human health (Ni´ciforovi´c and Abramoviˇc [2014](#_bookmark283)). Therefore, there should be a choice for appropriate antibiotic therapy (Kon and Rai [2012](#_bookmark239)). As an alternative to the specific negative impact associated with synthetic antimicrobials; antimicrobial compounds from the natural source have gained acceptance from both consumers and industries (Letsididi et al. [2018](#_bookmark250)).

Phenylpropanoids and their derivatives possessed a broad spectrum of antimicrobial activity. In various studies, PP and its derivatives exhibited inhibitory effect towards bac- teria, fungi and yeast. Phenylpropanoid derivatives such as p-hydroxycinnamic acid methyl ester have been reported as a potent antibacterial compound that was formed from bio- transformation of *L*-tyrosine methyl ester using *Rhodotorula glutinis* phe/TAL. Methyl ester of p-CoA has inhibitory activity against *Proteus vulgaris* and *Bacillus cereus*, compar- able with a standard antibiotic, ampicillin (MacDonald et al. [2016](#_bookmark245)). A group of researchers investigated the effect of CiA, CA and FA on pyocyanin production, swarming motility and biofilm formation of *Pseudomonas aeruginosa*. Pycocyanin is one of the vital quorum sensing molecule that has been reported to regulate extracellular virulence factor involved in the establishment and maintenance of infection by *P. aeruginosa* (Ugurlu et al. [2016](#_bookmark325)). Among the three PPs studied, CA showed maximum swarming motility inhibition followed by CiA and FA. Caffeic acid ester and CiA ester inhibited biofilm formation of *Candida albicans* and was found to be comparatively more active than a reference drug, fluconazole (De Vita et al. [2014](#_bookmark197)). The antibacterial and antifungal potential of PPs and their derivatives are well documented against human pathogens and food spoilage microorganisms, as enlisted in [Table 1](#_bookmark59), highlighting their mechanism of action and structure-activity relationship.

Caffeic acid is reported to inhibit the growth of *C. albicans,* an opportunistic pathogen via targeting its one of the import- ant enzyme, isocitrate lyase. It is one of the key enzymes of the glyoxylate cycle, which facilitates *C. albicans* to survive and grow under glucose-depleted environment (Cheah, Lim, and Sandai [2014](#_bookmark183)). Based on docking studies, Wang et al.

Table 1. Antibacterial and antifungal potential of phenylpropanoids and its derivatives.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Compound | Target microorganism | MIC | Mechanism(s)/ Structure-activity relationship | Reference |
| Cis-cinnamic acid | *Mycobacterium tuberculosis* | 0.5 lg/mL | Disrupted outer layer | (Chen et al. [2011](#_bookmark187)) |
| P-Coumaric acid | *Bacillus subtilis* | 20 lg/mL | Increased OM permeability, potassium ions | (Lou et al. [2012](#_bookmark243)) |
|  | *Staphylococcus aureus* | 20 lg/mL | leakage, Binds to the phosphate anion in |  |
|  | *Streptococcus pneumoniae* | 20 lg/mL | bacterial DNA and halted cellular functions |  |
|  | *Escherichia coli* | 80 lg/mL |  |  |
|  | *Shigella dysenteriae* | 10 lg/mL |  |  |
|  | *Salmonella typhimurium* | 20 lg/mL |  |  |
| Ferulic acid | *Staphylococcus aureus* | 1100 lg/mL | Altered cell surface hydrophobicity and charge, | (Borges et al. [2013](#_bookmark198)) |
|  | *Listeria monocytogenes* | 1250 lg/mL | potassium efflux |  |
|  | *Escherichia coli* | 100 lg/mL |  |  |
|  | *Pseudomonas aeruginosa* | 100 lg/mL |  |  |
| Chlorogenic acid | *Candida albicans* | 80 lg/mL | Dissipated fungal plasma membrane potential | (Sung and Lee [2010](#_bookmark303)) |
|  | *Trichosporon beigelii* | 40 lg/mL |  |  |
|  | *Malassezia furfur* | 40 lg/mL |  |  |
| Chitosan-caffeic | *Propionibacterium acnes* | 256 lg/mL | Altered cell permeability Conjugation increased | (Kim et al. [2017](#_bookmark237)) |
| acid conjugate | *Staphylococcus epidermidis* | 64 lg/mL | antibacterial activity |  |
|  | *Staphylococcus aureus* | 8 lg/mL |  |  |
|  | *Escherichia coli* | 250 lg/mL |  |  |
|  | *Pseudomonas aeruginosa* | 16 lg/mL |  |  |
| Butyl caffeate | *Staphylococcus aureus* | 0.21 lM | Aliphatic substituent on CA side chain enhanced |  |

Propyl caffeate

anti-*S. aureus* activity

*Escherichia coli* 0.22 lM Median linear chain length substituents on CA

Pentyl caffeate

0.20 lM

side chain improved antibacterial activity

Octyl caffeate *Staphylococcus aureus* 0.1 mM Altered cell permeability, charge, and cell surface

*Escherichia coli* 0.1 mM hydrophobicity, potassium leakage

Decyl caffeate *Staphylococcus aureus* 0.1 mM Altered cell permeability, cell surface

*Escherichia coli* 0.1 mM hydrophobicity, charge, and potassium efflux

Dibromo cinnamic acid *Bacillus subtilis* 2.73 lM/ml^ Removal of double bound of CiA side chain via (Narasimhan et al. [2004](#_bookmark277))

*Staphylococcus aureus* 2.73 lM/ml^

*Escherichia coli* 2.73 lM/ml^

*Candida albicans* 3.10 lM/ml^

*Aspergillus niger* 3.10 lM/ml^

bromination enhanced antimicrobial potential

Lauryl ferulate (LF) *Escherichia coli* 1.25 mM Aliphatic chain (Lauryl group) substituted on (Shi et al. [2017](#_bookmark314))

*Listeria Monocytogenes* 2.5 mM

*Staphylococcus aureus* 5 mM

FA side chain may increased the hydrophobicity and lipophilicity, thus enhanced the antibacterial activity

Ferulic-*p*-amino ester *Staphylococcus aureus* 2.01 lM/ml✧ Electron donating group on p-position of phenyl (Khatkar et al. [2015](#_bookmark232))

*Candida albicans* 1.71 lM/ml✧

*Aspergillus niger* 1.71 lM/ml✧

nucleus increased antimicrobial activity

p-Coumaric-8-hydroxy

*Staphylococcus aureus* 1.67 lM/ml✧ Bulky aromatic groups enhanced the

(Khatkar et al. [2017](#_bookmark234))

quinoline ester

*Aspergillus niger* 1.97 lM/ml✧

*Candida albicans* 1.67 lM/ml✧

antimicrobial activity

(Di-(4-

chlorobenzyl)) caffeate

3-p-trans-coumaroyl-2-

*Escherichia coli* 0.23mM Electron withdrawal group such as chloro at the

*p*-position of the aromatic rings improved antibacterial activity

*Bacillus cereus* 2.5 mg/ml Membrane hyperpolarization, induced

(Wu et al. [2016](#_bookmark337))

hydroxyquinic acid

*Clostridium perfringens* 5 mg/ml

*Staphylococcus aureus* 5 mg/ml

*Escherichia coli* 10 mg/ml

*Salmonella enterica* 5 mg/ml

*Vibrio parahaemolyticus* 5 mg/ml

morphological changes in membrane protein, increased membrane fluidity and destructed membrane integrity

*N*-(2 Hydroxyphenyl)

*Bacillus pumilus* 3.38 lg/mL✧ o-hydroxyphenyl group on the amide nitrogen

(Nimse et al. [2015](#_bookmark288))

cinnamamide

*Bacillus subtilis* 3.68 lg/mL✧

*Escherichia coli* 3.68 lg/mL✧

*Salmonella TyphiTY2* 3.68 lg/mL✧

*Shigella dysenteriae 8* 3.68 lg/mL✧

*Shigella bondii* 3.08 lg/mL✧

*Shigella flexneri* 3.08 lg/mL✧

*Vibrio cholera* 3.68 lg/mL✧

increased antibacterial activity

^MIC presented as log(1/MIC); ✧MIC presented as pMIC.

([2015](#_bookmark334)) found that CGA prevented the interaction of the sort- ing signal of a target protein by occupying the active site of Sortase A, a surface adhesion protein from *S. aureus*. Efflux pumps have an important role in bacterial resistance to some drugs such as erythromycin, fluoroquinolones, omeprazole, quinolones and verapamil. A group of researchers has observed the inhibitory effect of CA on MrsA and NorA pumps of *S. aureus* (Santos et al. [2018](#_bookmark297)). Phenylpropanoids and their derivatives along with its structure and IC50 values against their microbial protein targets are enlisted in [Table 2](#_bookmark79).

The antimicrobial potential of PPs are not just limited to food spoilage microorganisms and human pathogens, but they also have growth inhibitory effect against phytopatho- gens such as *Erwinia amylovora*, *Erwinia carotovora*, *Xanthomonas vesicatoria* (Alkan and Yemenicio˘glu [2016](#_bookmark158))), *Fusarium solani, Pyricularia grisea, Valsa mali, Botryosphaeria dothidea* (Zhou et al. [2017](#_bookmark336)), *Botrytis cinerea* (Patzke and Schieber [2018](#_bookmark273)), and *Alternaria alternate* (W. Li et al. [2018](#_bookmark254)). In addition to the aforementioned activities, PPs and their derivatives also possess antiviral activity against

Table 2. Antimicrobial and antiviral targets of phenylpropanoids and their derivatives.

Compound/Structure Antimicrobial Target Microorganism IC50 (mM) Reference

Trans cinnamic acid

OH

O

FtsZ *Escherichia coli* 100 (Rastogi et al. [2008](#_bookmark284))

Caffeic acid

|  |  |  |  |
| --- | --- | --- | --- |
| FtsZ | *Escherichia coli* | 105.96 | (Hemaiswarya et al. [2011](#_bookmark205)) |
| Peptide deformylase | *Helicobacter pylori* | >100 | (Cui et al. [2013](#_bookmark196)) |
| Isocitrate lyase 1 | *Candida albicans* | – | (Cheah, Lim, and Sandai [2014](#_bookmark183)) |
| MrsA pumps, NorA pumps | *Staphylococcus aureus* | – | (Santos et al. [2018](#_bookmark297)) |
| Peptide deformylase | *Helicobacter pylori* | >100 | (Cui et al. [2013](#_bookmark196)) |

O



HO OH

HO

Ferulic acid

HO

O OH

Chlorogenic acid

O

HO

HO HO

O

OH OH O



FtsZ *Escherichia coli* 69.55 (Hemaiswarya et al. [2011](#_bookmark205))

Peptide deformylase *Helicobacter pylori* >100 (Cui et al. [2013](#_bookmark196))

Sortase A *Staphylococcus aureus* 33.86 lg/ml (Wang et al. [2015](#_bookmark334))

OH

Caffeic acid phenethyl ester (CAPE)



O



Peptide deformylase *Helicobacter pylori* 4.02 (Cui et al. [2013](#_bookmark196))

PP-1

HO O

HO



N

N

O2N

*b*-ketoacyl carrier protein synthase III (FabH) *Escherichia coli* 2.5 (Zhang et al. [2011](#_bookmark335))

PP-2

O O

PP-3

O

O

O

O CN

O

H



O N

*b*-ketoacyl-ACP reductase (FabG) *Escherichia coli* 180 (Kristan et al. [2009](#_bookmark240))

HO OH

PP-4

O

OH O

O

|  |  |  |  |
| --- | --- | --- | --- |
| LecB | *Pseudomonas aeruginosa* | – | (Hauck et al. [2013](#_bookmark231)) |
| LecB | *Pseudomonas aeruginosa* | 19.9 | (Sommer et al. [2015](#_bookmark298)) |

H

O OH

HO OH

N O O

(*continued*) 

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Table 2. Continued.

6

O

NH

HN

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|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Compound/Structure | Antimicrobial Target | Microorganism | IC50 (mM) | Reference |
| PP-5 DNA gyrase |  | *Mycobacterium tuberculosis* | – | (Adeniji, Uba, and Uzairu [2018](#_bookmark159)) |

O

PP-6

O

O H

Influenza Neuraminidase H1N1 Influenza A virus, 8.5 (Xie, Huang, Yu, Shi, et al. [2013](#_bookmark317)) H9N2 Influenza A virus 7.2

O OH

HO OH

PP-7

N O O

O

OH

Influenza Neuraminidase H5N1 Influenza A virus 10.7 (Xie et al. [2013](#_bookmark317)) H9N2 Influenza A virus 3.2

HO

PP-8

O

HN

NH

HO

O

HN O

O

O2N

H1N1 Neuraminidase H1N1 Influenza A virus 90 (Hariono et al. [2016](#_bookmark229))

O

O

O

O

N-oleylcaffeamide HIV-1 reverse Transcriptase HIV-1 0.68 (Sonar et al. [2017](#_bookmark300))

O



N OH

H OH

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Table 3. Antidiabetic potential of phenylpropanoids along with underlying mechanism using *in vivo* and *in vitro* approaches (" increased, # decreased). Compound Mechanism Experimental Model Reference

Cinnamic acid DNA damage, GR activity, 8-OH-2’-deoxyguanosine, MDA, LDL, TC, triglycerides level, AST, ALT, ALP and *c*-glutamyl transferase

#

SOD, CAT, GPx, glutathione S-transferase, glutathione and HDL level

"

Blood glucose level

#

Glucose tolerance and insulin secretion

"

Glycogen synthase (GS) and dephosphorylation of GS at Ser641

"

Glycogen synthase kinase (GSK) activity, hepatic nuclear factor-4 and phosphoenolpyruvate carboxykinase (PEPCK) expression

#

P-Coumaric acid #Plasma glucose, G6Pase, FBPase and GLUT-2 expression

"Insulin, GSH, hexokinase and G6PD

Blood glucose, HbA1c, TNF-*a*, HDL, cardiovascular index 1 and 2

#

Insulin, lipid profile, insulin sensitivity, adiponectin, PPAR*c* mRNA levels, antiatherogenic index

"

#Blood glucose, HbA1c, lipid profiles, lipid peroxidation

"Plasma insulin, Hb, HDL, SOD and CAT activity Caffeic acid "Glucose uptake Hepatic glycogenolysis

#Blood glucose, serum TC, LDL and total triglycerides

GS activity and dephosphorylation of GS at Ser641, Suppressed GSK in insulin resistant FL83B cells, inhibited HNF-4 and PEPCK in TNF-*a*-treated insulin induced FL83B hepatocytes

"

Ferulic acid Blood glucose, NO, ROS, lipid peroxidation, protein

#

carbonylation, inflammatory cytokines, apoptosis Insulin level, arginase, SOD and CAT activity

"

Suppressed NF-*j*B activation and normalized hepatic dysfunction associated markers

Glucose uptake, glucose oxidation

"

Interactions of SREBP1c, HNF1*a* and HNF3*b* with GLUT 2 gene promoter and thus, suppressed over-expression of GLUT 2

#

Insulin secretion and decreased hepatic glycogenolysis Sinapic acid Hypergylcemia, protein carbonyls, lipid peroxides and

#

"

hydroperoxides

GPx, GST, SOD, CAT, vit C, vit E, GSH and ceruloplasmin Plasma glucose level, and hyperglycemia via PLC-PKC

#

"

pathway

"Glucose uptake and GLUT-4 expression

STZ-induced diabetic rats

STZ injected non-obese type2 diabetic rat

Insulin resistant mouse FL83B hepatocytes

STZ-induced diabetic rats

NA-STZ-induced type2 diabetes in rat STZ injected diabetic rats

L6 Myocyte cells, rat hepatocytes HFD-STZ-induced diabetic rats

Insulin resistant mouse FL83B hepatocytes

STZ-induced diabetic rats

HFD and fructose-fed type 2 diabetic rats INS-1*b*-cells, rat hepatocytes

HFD-STZ- induced type2 diabetic rat Fructose fed and STZ-diabetic rats

(Anlar et al. [2018](#_bookmark176)) (Hafizur et al. [2015](#_bookmark226))

(Huang and Shen, [2012](#_bookmark212))

(Amalan et al. [2016](#_bookmark160))

(Abdel-Moneim et al. [2018](#_bookmark161))

(Ambika, Saravanan, and Thirumavalavan [2013](#_bookmark173))

(Azay-Milhau et al. [2013](#_bookmark186)) (Matboli et al. [2017](#_bookmark253)) (Huang and Shen [2012](#_bookmark212))

(Ghosh et al. [2018](#_bookmark223))

(A. Narasimhan, Chinnaiyan, and Karundevi [2015](#_bookmark276))

(Azay-Milhau et al. [2013](#_bookmark186))

(Nithya and Subramanian, [2017](#_bookmark259))

Cherng et al. [2013](#_bookmark190)

Isoferulic acid Improved glucose stimulated insulin secretion, glyoxalase 1 activity

ROS formation, caspase-3 and mitochondrial Ucp-2 expression

#

INS-1 832/13 cell line (Meeprom et al. [2018](#_bookmark260))

influenza virus (Xie, Huang, Yu, Shi, et al. [2013](#_bookmark317)), H1N1 virus (Hariono et al. [2016](#_bookmark229)), hepatitis C virus (Amano et al. [2017](#_bookmark172)), and canine distemper virus (Wu et al. [2017](#_bookmark315)). The antiviral potential of *N*-oleylcaffeamide and tetradecyl feru- late has been reported against the HIV-1 virus (Sonar et al. [2017](#_bookmark300)). It has been found that *N*-oleylcaffeamide and tetra- decyl ferulate inhibited HIV-1 reverse transcriptase activity, thus halts the replication of HIV-1 virus ([Table 2](#_bookmark79)). Further, CA and its hybrid with triclosan have been observed for its potent trypanocidal and leishmanicidal activity against *Trypanosoma cruzi* and amastigotes of *Leishmania (V.) pan- amensis*, respectively (Otero et al. [2017](#_bookmark265)).

*Phenylpropanoids: Strong antioxidants*

Phenylpropanoids are of considerable interest owing to its antioxidant capacity, probably by quenching free radicals

against reactive oxygen species (ROS), inhibiting lipid peroxi- dation, chelating metal ions and protein binding (Maurya and Devasagayam [2010](#_bookmark256)). The antioxidant potential of these com- pounds depends on their structural configuration, i.e., the number and arrangement of hydroxyl function(s) in the aro- matic structure. The presence of propenoic side chain could stabilize the phenoxy radicals by resonance (Natella et al. [1999](#_bookmark280); Teixeira, Gaspar, et al. [2013](#_bookmark313)). In recent years, the antioxidant activity of PPs and their derivatives have been evaluated by numerous *in vitro* assays, including reduction potential, 2,2-azobis (2-amidinopropane hydrochloride) (AAPH), 2,20- Azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) rad- ical cation decolorization, ferric reducing/antioxidant power (FRAP), cyclic voltammetry, DNA strand breakage-inhibition and anti-hemolysis activity, hydroxyl, nitric oxide, superoxide anion and 1,1-Diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging assays (Yan Li et al. [2014](#_bookmark233); Mathew, Abraham, and Zakaria [2015](#_bookmark255); Maurya and Devasagayam [2010](#_bookmark256)).

Based on kinetics studies, esters of SA showed higher rates of DPPH radical scavenging, lipid radical scavenging efficiency and lipophilicity than its parent compound. Thus, esterification of SA by the addition of alkyl moieties in *p*- position to an –OH group in its derivatives improved their antioxidant status (Ni´ciforovi´c et al. [2017](#_bookmark286)). Compound PP-9, a CiA derivative, is a strong antioxidant which scavenges hydroxyl radical and inhibits soybean lipoxygenase (LOX) activity more efficiently compared to standard antioxidant, Trolox and nordihydroguaretic acid. However, linoleic acid peroxidation inhibitory effect of PP-9 was found to be simi- lar to that of Trolox (Pontiki et al. [2014](#_bookmark278)) ([Table 4](#_bookmark112)). In a similar study, PP-10 (a hybrid of phenoxyphenyl cinnamic acid and propranolol) proved to be a good LOX and lipid peroxidation inhibitor. Further, it also exhibited antiproteo- lytic activity by inhibiting trypsin (Peperidou et al. [2017](#_bookmark274)) ([Table 4](#_bookmark112)). Hydroxycinnamic acids coupled with triphenyl- phosphonium cation (MitoHCAs), targeted hepatic mito-

chondria, which inhibited lipid peroxidation in the following order Mito-CA > Mito-FA > Mito-*p-*CoA ([Table 4](#_bookmark112)). Besides, these compounds attenuated the endogenous mitochondrial

H2O2 generation by enhancing the activities of glutathione peroxidase (GPx) and catalase (CAT) (Li et al. [2017](#_bookmark251)).

Earlier, a comparative *in vitro* study was conducted to assess the antioxidant potential of FA obtained from *Parthenium hysterophorus* and poly (D, L-lactide-co-glyco- lide)/polyethylene oxide nanofibers encapsulated FA. It was reported that encapsulated FA has higher radical scavenging activity than free FA (Vashisth et al. [2015](#_bookmark331)). Based on the above results, it is suggested that polymeric nanofibrous matrix may maintain its chemical integrity and its antioxi- dant activity after encapsulation.

*Phenylpropanoids: curb inflammation*

Various molecular mechanisms have been proposed to be accountable for the anti-inflammatory potential of PPs. A sinapic acid derivative, PP-11 acts as an excellent anti- inflammatory agent as it down-regulates intercellular adhe- sion molecule-1 (ICAM-1) and vascular cell adhesion mol- ecule-1 (VCAM-1) expression in endothelial cells (ECs). Moreover, oral administration of PP-11 prior to croton oil application resulted in the reduction of ear edema in experi- mental mice (Zeng et al. [2013](#_bookmark332)). Further, PP-11 could inhibit TNF-*a* mediated inflammatory response by suppressing oxi- dative stress and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) activity ([Table 4](#_bookmark112)).

Ferulic acid pretreatment significantly suppressed nitric

oxide (NO) production in lipopolysaccharides (LPS) exposed macrophage cell line RAW 264.7. The mechanism of action was further determined by the ability of the compound to modulate translocation of NF-E2-related factor translocation and NF-KB to the nucleus via suppressing phosphorylation of I-KB Kinase, thus halted the expression of interleukin-6 (IL- 6), a cytokine mediator (Lampiasi and Montana [2016](#_bookmark246)). Further, CA is reported to alter the expression of pro-inflam- matory cytokines and level of brain oxidative stress markers: malondialdehyde (MDA) and reduced glutathione (GSH)

induced by LPS in experimental mice (Mallik et al. [2016](#_bookmark247)). 4- hydroxycinnamic acid (4-HCA) suppressed pulmonary inflammation induced by exposure of cigarette smoke and LPS in laboratory mice. Oral administration of 4-HCA reduced inflammatory cytokines, neutrophils, inflammatory cells and cyclooxygenase-2 (COX-2) expression in lung tissue. Moreover, it also down-regulated the phosphorylation of mitogen-activated protein kinase (MAPK) signaling cascade including, Erk, JNK, p38 and NF-*j*B expression (Park et al. [2017](#_bookmark270)). Resolvin E1 is a metabolite of omega-3 polyunsaturated fatty acids that exerts anti-inflammatory action in several inflammations mediated disease models (Sawada et al. [2018](#_bookmark301)). The concentration of resolvin E1 has been reported to effi- ciently raise in kidney tissue after FA administration in com- parison to gentamicin intoxicated mice (El-Ashmawy et al. [2018](#_bookmark208)). It also reduced advanced glycation end products medi- ated inflammatory activity in human umbilical vein endothe- lial cells (HUVEC) via modulating the activation of NF-*j*B and p38 MAPK signaling pathways (Liu et al. [2018](#_bookmark244)).

*Fighting diabetes with phenylpropanoids*

Diabetes is a metabolic disorder characterized by a malfunc- tion in insulin production due to the degeneration of pan- creatic *b*-cells and insulin resistance associated with hyperglycemia (Deepa et al. [2018](#_bookmark200)). It is also associated with the abnormalities in protein metabolism, hyperlipidemia and oxidative stress (Ambika, Saravanan, and Thirumavalavan [2013](#_bookmark173); Kayama et al. [2015](#_bookmark227)). Various *in vitro* and *in vivo* mod- els have been used to explore the antidiabetic potential and the underlying mechanism of PPs ([Table 3](#_bookmark82)).

In streptozotocin (STZ) induced rats, CiA reduced DNA

damage and improved lipid profile, levels of insulin and liver enzymes. The activities of antioxidant enzymes such as superoxide dismutase (SOD), glutathione S-transferase (GST), CAT, GPx, and glutathione is increased; while plasma 8-OHdG and MDA levels and glutathione reductase (GR) activity is reduced in liver and kidney of diabetic rats upon treatment with CiA (Anlar et al. [2018](#_bookmark176)). In a separate study, P-Coumaric acid improved the glucose metabolism disturbance, through suppression of hepatic gluconeogenesis enzymes [glucose-6-phosphatase (G6Pase) and fructose-1,6- bisphosphatase (FBPase)] and enhanced expression of the glycolytic enzymes [hexokinase and glucose-6-phosphate dehydrogenase (G6PD)]. In addition, pancreatic Glucose Transporter-2 (GLUT-2) mRNA level has been altered by p- CoA; indicating its role in controlling glucose homeostasis in STZ-induced rats (Amalan et al. [2016](#_bookmark160)). Further, in nico- tinamide (NA)/STZ-induced diabetic rats, p-CoA treatment significantly attenuated the elevated levels of glucose, glyco- sylated hemoglobin, TNF-*a*, HDL-cholesterol and increased the serum insulin and body weight. It improves insulin sen- sitivity, antiatherogenic index and decreases cardiovascular index-1 and 2 in type 2 diabetic rat model. Further, it rises in serum adipocytokines secretions and PPAR*c* mRNA level in adipose tissue (Abdel-Moneim et al. [2018](#_bookmark161)).

Ferulic acid acts as the hypoglycemic agent, as it mark-

edly lowered blood glucose level and ameliorates serum

Table 4. Various phenylpropanoids derivatives along with different biological activities and their effects (" increased, # decreased). Compound/Structure Activity Effects Reference

PP-9

O

Br

OH

Antioxidant activity Scavenges hydroxyl radicals,

Inhibited linoleic acid peroxidation and soyabean LOX activity

(Pontiki et al. [2014](#_bookmark278))

PP-10

O

N

OH

O

Antioxidant and

Anti-proteolytic activity

Inhibited lipid peroxidation, LOX and trypsin activity

(Peperidou et al. [2017](#_bookmark274))

O



R1

R2

O



O PPh3Br

Antioxidant activity Inhibited mitochondrial lipid peroxidation,Glutathione peroxidase and Catalase activity

(Li et al. [2017](#_bookmark251))

Mito-p-CoA, R1¼H, R2 ¼OH, Mito-CA, R1¼R2¼OH,

Mito-FA, R1¼OCH3, R2¼OH

PP-11

O O Cl

Antioxidant and Anti- inflammatory activity

Intracellular ROS and ear edemaInhibited TNF- *a*-induced NF-*j*B activation, ICAM-1 and VCAM-1 expression in ECs

(Zeng et al. [2013](#_bookmark332))

HO N

N

O

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N-trans-feruloyldopamine

HO

H

O N OH



O OH

Antioxidant andNeuroprotective activity

Scavenges free radical and chelates ferrous ions Inhibited AChE activity

(Dizdar et al. [2018](#_bookmark205))

PP-12

O

O

O

N

Neuroprotective activity Inhibited BuChE and AChE activityPrevented self- induced A*b*1-42 fibrils aggregation and

N promoted its disaggregation

(Sang et al. [2017](#_bookmark296)

PP-13

Anticancer activity Inhibited tubulin polymerization,Anti-proliferation of A549 and MCF-7 cell lines

(Yang et al. [2012](#_bookmark320))

S H



O



O

N

N N O

9



(*continued*)

Table 4. Continued.

10

Compound/Structure Activity Effects Reference

PP-14

PP-15

F

O N N O

S

O N S O

F3C

O N N

S

O

O N S

O

OH OH

OH OCH3

Anticancer Activity Inhibited COX-1/COX-2 and 5-LOX,Anti- proliferation of A549, Caco-2, PC-3 and B16- F10 cell linesInduced apoptosis and arrests cell cycle at G2 phase in A549 cell line

Anticancer Activity Inhibited COX-1/COX-2 and 5-LOX,Anti- proliferation of A549, PC-3, Caco-2 and B16- F10 cell linesInhibited tumor growth in mice

(Cai et al. [2016](#_bookmark177))

(Cai et al. [2016](#_bookmark177))

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Caffeic acid hexylamide

O



HO N

H

HO

Anticancer Activity Human neutrophils’ oxidative burst, Anti- proliferation of colon cancer cells Triggered mitochondrial dysfunctionApoptosis

(Tavares-da-Silva et al. [2016](#_bookmark311))

Caffeic acid-o-nitro phenethyl ester

O



HO O

HO

4-methoxy cinnamic acid

HO

O

O

NO2

Cardioprotective Activity ROS, cardiac inflammation, collagen deposition and NF-*j*B activationStimulated (SIRT-1)/eNOS expressionReduced necrocytosis and

cell apoptosis

Food Preservative Inhibited polyphenol oxidase activity

Browning, electrolyte leakage, superoxide anion and MDA

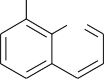
#

(Li et al. [2018](#_bookmark254))

(Hu et al. [2016](#_bookmark211)).

p-Coumaric-8-hydroxy quinoline ester

O



O

HO

N

Pharmaceutical Preservative Antibacterial and Antifungal activity (Khatkar, Nanda, and Narasimhan [2013](#_bookmark235))

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insulin level, spleen weight to body weight ratio, and spleen size in diabetic rat. Moreover, it is reported to decrease oxi- dative stress, inflammatory cytokines, inhibit apoptosis, enhance antioxidant enzymes activity, suppress nuclear translocation of p65 subunit of NF-*j*B, and corrected the activity of markers associated with hepatic dysfunction (Ghosh et al. [2018](#_bookmark223)). Recently, Nithya and Subramanian ([2017](#_bookmark259)) illustrated the antihyperglycemic activity of SA in the high-fat diet (HFD)-STZ-induced diabetic rats. Their results have shown that SA treatment improved enzymatic and non-enzymatic antioxidant status, decreased the elevated lev- els of protein carbonyls, lipid peroxides and hydroperoxides in diabetic rats (Nithya and Subramanian [2017](#_bookmark259)).

Furthermore, FA acid has been found to suppress overex-

pression of GLUT-2 via weakening interaction of SREBP1c, HNF1*a* and HNF3*b* (transcription factors) with a promoter of GLUT 2 gene in the liver of HFD and fructose-induced type 2 diabetic rats (A. Narasimhan, Chinnaiyan, and Karundevi [2015](#_bookmark276)). In fructose-fed and STZ-induced diabetic rats, SA improves GLUT-4 expression and increased glucose utilization via phospholipase C-protein kinase C (PLC-PKC) signals thus exhibits its antihyperglycemic effect in experi- mental rats (Cherng et al. [2013](#_bookmark190)). Cinnamic acid exerts anti- hyperglycemic effect chiefly due to increased glucose tolerance and insulin secretion to glucose stimulation in non-obese type 2 diabetic rats (Hafizur et al. [2015](#_bookmark226)). Caffeic acid did not affect insulin release in INS-1 *b*-cells at 5.6 mm glucose, but in the association with insulin, it promoted glu- cose uptake in L6 myocyte cells (Azay-Milhau et al. [2013](#_bookmark186)). In contrast, FA shows an insulinotropic effect on INS-1 pan- creatic *b*-cells and inhibited glucose uptake. In hepatocytes, CA and FA both show a remarkable reduction in glucagon induced glycogenolysis.

Isoferulic acid also plays a defensive role against methyl- glyoxal induced dysfunction in insulin-secreting-1 (INS-1) rat pancreatic *b*-cell. Its pretreatment increased cell viability, glyoxalase 1 activity and glucose-induced insulin secretion and decreased the ROS, caspase-3 and mitochondrial uncou- pling protein-2 (Ucp-2) levels in rat pancreatic *b*-cells (Meeprom et al. [2018](#_bookmark260)).

# Protective effects of phenylpropanoids on kidney

Kidneys are vital organs that regulate necessary functions of the body; one of the important role is filtration and excre- tion of nitrogenous waste products from the blood (Basile, Anderson, and Sutton [2012](#_bookmark197)). Anti-neoplastic drugs, non- steroidal anti-inflammatory drugs, antibiotics, angiotensin- converting-enzyme inhibitors (Trujillo et al. [2013](#_bookmark323)) and other stimuli (Shelton, Kevin, and Copple [2013](#_bookmark313)) leads to kidney malfunction by inducing oxidative stress, release of inflam- matory cytokines, renal inflammation, and necrosis of renal tubular cells (Ansari et al. [2016](#_bookmark179); Kumar et al. [2017](#_bookmark242)). The deleterious effects of acute renal injury are extended to induce complications to other organs via the circulating fac- tors released by the injured kidney (Ismail et al. [2016](#_bookmark217)).

In sepsis-induced mice, FA attenuated blood urea nitro-

gen (BUN), creatinine (CTN), lipid peroxides, and

inflammatory cytokines levels in kidney of LPS exposed mice. In sepsis-induced renal tissues, levels of the enzymatic and non-enzymatic antioxidant, mitochondrial respiratory enzyme; NADH dehydrogenase, succinate dehydrogenase and Cyt c oxidase and mitochondrial redox activities was significantly restored upon FA treatment ([Fig. 1](#_bookmark21)). Additionally, it reduced expression of iNOS, Cox-2 and toll- like receptor-4 mediated NF-*j*B activation thus resulted in down-regulation of inflammatory events (Mir et al. [2018](#_bookmark263)). PPAR*c* belongs to a nuclear hormone receptor superfamily. It plays an essential role in cell differentiation, proliferation, immune/inflammation responses, lipid metabolism and glu- cose homeostasis (Yun, Han, and Park [2018](#_bookmark328)). Ferulic acid increased PPAR-*c* expression and decreased urinary albumin excretion and urinary N-acetyl-*b*-D-glucosaminidase (NAG) activity, thus reduced gentamicin-induced nephrotoxic effect in experimental rats (El-Ashmawy et al. [2018](#_bookmark208)).

In cadmium intoxicated rats, SA treatment decreased the elevated levels of serum Ca , lactate dehydrogenase (LDH), CTN, uric acid and urea. It also improves the anti- oxidant defense system and modulates the inflammatory response in experimental rats via diminishing both nuclear NF-*j*B (p65) protein expression and DNA-binding activity (Ansari et al. [2017](#_bookmark180)). The same group also demonstrated the curative effect of SA pretreatment in gentamicin-induced nephrotoxicity in rats (Ansari et al. [2016](#_bookmark179)). Whereas, P- Coumaric acid treatment significantly ameliorated the ele- vated levels of kidney function indicators in NA*/*STZ intoxi- cated diabetic rats (Abdel-Moneim et al. [2016](#_bookmark162)). It also shows its renoprotective effect against cisplatin-induced kidney damage in rats (Akdemir et al. [2017](#_bookmark163)).

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*Neuroprotective effects of phenylpropanoids*

Spinocerebellar ataxia type 3 (SCA3), a neurological dis- order, caused by an aberrant expansion of polyglutamine repeats in the ataxin-3 protein. The mutant ataxin-3 protein (MA3P) is prone to misfolding and aggregation, results in neurotoxicity and ultimately neurodegeneration (Li et al. [2015](#_bookmark258)). Even though the specific mechanism is not known, the neurobiological abnormalities of this disease are related to malfunction of transcription, protein degradation, mito- chondrial function, apoptosis, and antioxidant potency. Caffeic acid has been reported to reduce the expression of MA3P and its aggregation; it also reinstates the level of mitochondrial membrane potential, Hsp27, Bcl-2 and sir- tuin1. It also resulted in Nrf2 activation, which in turn raised the antioxidant profile and enhanced the expression of proteins related to autophagy (Wu et al. [2018](#_bookmark338)).

Nuclear respiratory factor-1 (NRF-1) is involved in the

expression of several essential genes such as genes required for regulation of cell growth and development, nuclear genes needed for respiration, heme biosynthesis, and DNA tran- scription and replication in mitochondria ([Fig. 1](#_bookmark21)). In the embolic cerebral ischemic rat, p-CoA elevated NRF-1 level was reported to improve mitochondrial function. Further, it also decreased the oxidative stress in brain tissues by increasing SOD and decreasing MDA levels, as well as

reduced apoptosis by decreasing caspase-3 and caspase-9 activities (Guven et al. [2015](#_bookmark225)).

A group of researcher’s noticed that alkyl amides of CA show neurotrophic action by increasing the PC12 neuronal cells survival and differentiation induced by the nerve growth factor. Further, it exhibit its neurotrophic effect via inducing phosphorylation of ERK1/2 and AKT signaling pathways most probably by activation of phosphoinositide 3-kinase (Moosavi et al. [2017](#_bookmark267)). *N*-trans-feruloyldopamine displayed free radical scavenging activity and ferrous ions chelating ability, as well as exerted inhibitory effects against acetylcholinesterase (AChE) from *Electrophorus electricus* (Dizdar et al. [2018](#_bookmark205)) ([Table 4](#_bookmark112)). A ferulic acid-O-alkylamine derivative, PP-12, promoted significant inhibition of butyryl- cholinesterase (BuChE), AChE, prevented the formation of A*b*1-42 fibrils as well as disassembled self-induced A*b* fibrils. It also possessed mild peroxyl radical absorbance capacities and protected PC12 cells from damage caused due to H2O2 with low toxicity ([Table 4](#_bookmark112)). Further, it can cross the blood- brain barrier, *in vitro*. Moreover, it did not induce any acute toxicity and annulled scopolamine mediated memory loss in mice (Sang et al. [2017](#_bookmark296)).

*Fighting cancer with phenylpropanoids*

Phenylpropanoids could be used as an anticancer agent via suppressing the overexpression of histone deacetylase (HDAC) in cancerous cells. Sinapinic acid, a major phenolic compound from the rhizome of *Hydnophytum formicarum* Jack, exhibited antiproliferative activities in human T-cell leukemia, cervical and colon cancer cell lines. Further, it has been reported to inhibit the expression of HDAC in HeLa cell lines, as well as displayed inhibitory effect on the growth of HeLa cells via inducing apoptosis (Senawong et al. [2013](#_bookmark304)). Zen and coworkers have observed that trans-cinnamic acid significantly inhibits the growth of colon cancer in a mouse xenograft model. It inhibited HDAC activity and modulated the expression of apoptosis-related proteins; down-regulation of PARP and Bcl-2, up-regulation of Bax, caspase 3 and increased annexin V apoptotic cells in a mouse xenograft model (Zhu et al. [2016](#_bookmark339)). Recently, caffeic acid has also been reported to inhibit the induction of colon and cervical cancer cells via inhibition of HDAC activity. Further, it halted the progression of cells at G2/M phase, raised ROS production, up-regulated expression of p21 and caspase-3. Therefore, it can be concluded that CA invoke antiproliferation and induced cell death via apoptosis (Anantharaju et al. [2017](#_bookmark174)).

Recently, FA has been reported to suppress the epidermal

growth factor receptor (EGFR) activation via down-regulat- ing autophosphorylation of Tyr 1068, which ultimately pre- vented the proliferation of human breast cancer cells (Sudhagar et al. [2018](#_bookmark301)). The derivatives of cinnamic acyl 1,3,4-thiadiazole amide; especially, PP-13 significantly inhib- ited tubulin polymerization with an IC50 value of 1.16 mg/ mL. It also prevented the proliferation of human cancer cell lines, i.e., A549 and MCF-7 (Yang et al. [2012](#_bookmark320)) ([Table 4](#_bookmark112)).

A critical aspect of cancer initiation and propagation is recognized to be the involvement of inflammation. For

instance, the over-expression of enzymes such as COX-2 and 5-LOX in inflammatory responses is believed to be asso- ciated with various types of cancer (Cai et al. [2016](#_bookmark177)). By hybridizing diaryl-1, 2, 4-triazoles and CA, dual targeting COX-2 and 5-LOX inhibitors have been developed. Most of these compounds possess an inhibitory effect against COX- 1/COX-2 and 5-LOX. Compound PP-14 was found to inhibit *in vitro* proliferation of different cancer cells, arrest cell cycle at G2 phase and cause apoptosis in A549 cell line; while PP-15 inhibited tumor growth in experimental mice (Cai et al. [2016](#_bookmark177)) ([Table 4](#_bookmark112)). Caffeic acid hexylamide pre- vented the proliferation of colon cancer cells by means of human neutrophils’ oxidative burst suppression and triggers mitochondrial dysfunction that induces apoptosis (Tavares- da-Silva et al. [2016](#_bookmark311)) ([Table 4](#_bookmark112)).

In a work by Ero˘glu and coworkers (2018), it was

observed that SA inhibits proliferation of PC-3 and LNCap human prostate cancer cells. It also increases the expression of apoptotic genes and decreases the expression of metastatic genes (CDH2, MMP-2 and MMP-9) (Ero˘glu et al. [2018](#_bookmark210)). Zinc oxide nanoparticle combined with FA (ZnONPs-FA) inhibited hepatocellular cancer (HCC) cell proliferation, both *in vitro* and *in vivo* by means of apoptosis and repressing diethylnitrosamine (DEN)-induced HCC in the experimental rat. In the liver of DEN-induced HCC rat, ZnONPs-FA reduced nodule formation, nodular regenerative hyperplasia and liver function marker enzymes including aspartate trans- aminase (AST), alkaline phosphatase (ALP), alanine transfer- ase (ALT), *c*-GT and TBARS (Ezhuthupurakkal et al. [2018](#_bookmark213)).

*Phenylpropanoids: protects against cardiotoxicity*

The therapeutic aspect of p-CoA has been investigated against doxorubicin (DOX) associated cardiotoxicity in H9c2 cardiac muscle cells. P-Coumaric acid mitigated DOX mediated deleterious effects on cell morphology, improved cell viability, inhibited apoptosis and decreased ROS levels, while modulated MMP and intracellular Ca2þ concentration in DOX intoxicated H9c2 cell lines (Chacko et al. [2015](#_bookmark181)). The same group of researchers, further elucidated the cardi- oprotective role of p-coumaric acid associated with aug- mented Nrf2 and autophagy to counteract cardiac damage caused due to DOX (Sunitha et al. [2018](#_bookmark305)).

Ferulic acid possesses cardioprotective effect, which is evi-

dent by reduced activity of AST, ALT, ALP, creatine phosphate kinase (CPK), LDH, and total cholesterol (TC). It also lowered the lipid peroxidation in mercuric chloride-induced myocardial infarction in experimental rat studies (Vijayakumar, Jagadeesan, and Bharathi [2014](#_bookmark333)). It also attenuated (I/R) mediated injury via increasing expression of heat shock protein 70 (HSP70) medi- ated through NO-ERK1/2 pathway (Liao et al. [2017](#_bookmark238)). Ferulic acid-4-O-sulfate (a conjugated metabolite of FA) exhibited a concentration-dependent blood pressure lowering effect in mice. In addition, it showed vasorelaxation in femoral and saphenous arteries and aorta, most probably mediated by sol- uble guanylate cyclase and Kþ channels such as voltage-gated Kþ channels in mice (Rymenant et al. [2017](#_bookmark290)). Sinapic acid owing to its antioxidant efficiency exhibits a cardioprotective

effect against I/R induced oxidative stress and cardiac dysfunc- tion (Silambarasan et al. [2015](#_bookmark293)). Owing to low oral absorption of CGA, Yi Li and his team (2018), has designed a new com- pound by conjugated CGA with phospholipid (C-PPL) and studied its role against I/R induced myocardial injury in SAMP8 mice. The results revealed that C-PPL treatment altered oxidative stress induced by oxygen consumption deficits and ROS production in mitochondria, as well as modulated expres- sion of inflammatory cytokines via MAPK phosphatase- 1(MKP-1)/JNK pathway (Li et al. [2018](#_bookmark254)). *In vivo* and *in vitro* studies on myocardial I/R injury model confirmed the curative role of CA-o-nitro phenethyl ester against myocardial I/R induced ROS generation, cardiac inflammation, collagen depos- ition, apoptotic and necrotic cell death via stimulating expres- sion of silent information regulator-1 (SIRT-1)/eNOS and down-regulating expression of NF-*j*B (Li et al. [2018](#_bookmark254)) ([Table 4](#_bookmark112)).

*Phenylpropanoids: protects against chemical induced hepatic damage*

Phenylpropanoids and their derivatives exhibited hepatopro- tective effects against glyoxal or methylglyoxal provoked cyto- toxicity and oxidative damage in the following order; CA > FA > ethyl ferulate > methyl ferulate > p-CoA in differ- ent models of rat hepatocytes. Besides, FA treatment signifi-

cantly attenuated the glyoxal or methylglyoxal-induced protein carbonylation in GSH-depleted rat hepatocytes (Maruf et al. [2015](#_bookmark252)), whereas co-administration of p-CoA sig- nificantly prevented cisplatin-induced oxidative stress- medi- ated liver damage by improving antioxidant and oxidative stress parameters. It also shows the capacity of PPs to reduce MDA levels in the liver of experimental modal (Akdemir et al. [2017](#_bookmark163)). Sinapic acid has the potential to rectify dimethyl- nitrosamine (DMN)-induced alterations in body weight, serum hepatic biomarkers, hepatic MDA, and hydroxyproline levels as reported by Shin et al. ([2013](#_bookmark291)) in a hepatotoxicity rat model. Moreover, SA decreased hepatic fibrosis by reducing the expression of *a*-smooth muscle actin (*a*-Actin) and trans- forming growth factor-*b*1 (TNF-*b*1) ([Fig. 1](#_bookmark21)).

Recently, methyl FA has been reported to possess hepato-

protective effect against alcohol-induced abnormalities in the liver of C57BL/6 mice. Methyl FA treatment altered lipid profile, level of antioxidant enzymes, inflammatory media- tors and serum hepatic biomarkers in alcohol-intoxicated mice. It also improved alcohol and aldehyde dehydrogenase activity and decreased cytochrome P4502E1 expression in methyl FA treated group. Moreover, it suppressed NADPH Oxidase-4 (NOX-4) and p22phox expression, thus inhibited oxidative damage caused due to alcohol intoxication in experimental mice (Li et al. [2017](#_bookmark251)). It also improved hepatic steatosis in ethanol exposed L-02 human hepatocyte cell line and rat through the AMP-activated protein kinase/Forkhead box O1 signaling pathway and SIRT1, PPAR-*a*, and Carnitine palmitoyl transferase-1*a* (CPT-1*a*) genes expres- sion (Cheng et al. [2018](#_bookmark189)).

Earlier, Mu and colleagues has reported the curative role of CA against I/R induced hepatic injury in rats. They observed that CA suppressed microcirculatory disturbance,

hepatocyte apoptosis, hepatic inflammation and oxidative damages caused due to I/R in rat liver. Moreover, CA also prevented downfall in sirtuin 3 expressions (an oxidative stress modulator in mitochondria) and improved mitochon- drial dysfunction (Mu et al. [2015](#_bookmark269)).

*Applications of phenylpropanoids and their derivatives in food industry*

In recent years, PPs owing to its potential biological effects has magnetized food industries. As a consequence, many diet- ary/sports supplements containing PPs, especially FA and CA alone or in combination with other compounds are commer- cially available in the market. Owing to its free radical scav- enging activity, FA is used as a sports supplement which can lessen muscle tenderness and fatigue as mentioned by Tee- ngam in his recent work (Tee-Ngam et al. [2013](#_bookmark312)). According to ‘The Japan Food Chemical Research Foundation’, FA and CiA along with its derivatives, have been approved as food additives/flavoring agents in food products (The Japan Food Chemical Research Foundation [2014](#_bookmark316); The Japan Food Chemical Research Foundation [2016](#_bookmark318)). Cinnamic acid and some of its derivatives have also been recognized as safe (GRAS) in food by the U.S. Food and Drug Administration ([2018a](#_bookmark326)). Moreover, PPs have the potential to decrease the allergenicity of food, such as ovalbumin from an egg. Tong and coworkers also observed that CA-aided tyrosinase cata- lyzed cross-linking lowered the allerginicity of the egg white protein in mouse (Tong et al. [2018](#_bookmark321)).

Ou and Kwok reviewed the role of PPs in food preservation

and they confirmed the antimicrobial and antioxidant potential of PPs, particularly FA (Ou and Kwok [2004](#_bookmark266)). Lipid oxidation is a major concern during the processing and storage of food products because it generates volatile compounds that result in off-flavor and thus rancidity of food products. Hydroxycinnamic acids inhibited lipid oxidation of frozen minced fish, *Trachurus trachurus*, commonly known as Atlantic horse mackerel (Medina et al. [2009](#_bookmark259)). Ferulic acid inhibited the growth of food-borne pathogenic bacteria, *L. monocytogenes* in ready-to-eat foods, such as smoked salmon and cheese. The increase of FA concentration in media leads to a decrease in its pH, possibly one factor that contributes in its antilisterial activ- ity (Takahashi et al. [2013](#_bookmark306)). Postharvest application of 4-methoxy cinnamic acid (4-MCiA) resulted in a significant reduction in weight loss, cap opening, browning, electrolyte leakage, super- oxide anion formation and MDA level of *Agaricus bisporus* (Hu et al. [2016](#_bookmark211)). Moreover, 4-MCiA treated mushrooms signifi- cantly inhibited the polyphenol oxidase activity as compared to the untreated samples, thus extending its shelf-life ([Table 4](#_bookmark112)).

To decontaminate fresh produce, investigated the effect of

FA deposited on the surface of spinach leaves using a fog. They followed the experiment by treating it with UV-A radi- ation. Integration of CA into food packaging films, made from bio-renewable natural materials (N,O-carboxymethyl acid chi- tosan and methyl-cellulose), showed better antioxidant activity. Moreover, it also exhibited inhibitory effects on the growth of

*E. coli* and *S. aureus* as compared to CA nonintegrated films. During storage, the CA-integrated films reduced lipid oxidation

Table 5. List of commercially available health supplements and skin care products containing phenylpropanoids.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Product name | Major components | Manufacturers | Applications | URL |
| Source naturals trans- | Trans-FA, calcium, stearic | Source Naturals, Inc. | Dietary supplement, | [https://www.sourcenaturals.](https://www.sourcenaturals.com/products/GP1298/) |
| ferulic acid | acid etc. |  | antioxidant support | [com/products/GP1298/](https://www.sourcenaturals.com/products/GP1298/) |
| Source naturals muscle mass | Trans-FA, Vit C, Vit B-6, | Source Naturals, Inc. | Dietary supplement, strength | [https://www.sourcenaturals.](https://www.sourcenaturals.com/products/GP1224/) |
|  | pantothenic acid, *L*-lysine, |  | anabolic complex | [com/products/GP1224/](https://www.sourcenaturals.com/products/GP1224/) |
|  | branched chain amino |  |  |  |
|  | acids, etc. |  |  |  |
| Source naturals Triathlete | Trans-FA, vitamin (A-C and E), | Source Naturals, Inc. | Dietary supplement, | [https://www.sourcenaturals.](https://www.sourcenaturals.com/products/GP1300/) |
|  | niacin, pantothenic acid, |  | Nutritional | [com/products/GP1300/](https://www.sourcenaturals.com/products/GP1300/) |
|  | Ca, PABA etc. |  | endurance formula |  |
| BPI vivoprex | White peony flower, turmeric | BPI health | Joint response formula, | [http://www.gnc.com/vitamins-](http://www.gnc.com/vitamins-supplements/477058.html?cgid=vitamins-supplements) |
|  | root/rhizome, ginger root, |  | promotes healthy cartilage | [supplements/477058.](http://www.gnc.com/vitamins-supplements/477058.html?cgid=vitamins-supplements) |
|  | propolis (CAPE) etc. |  | and tissue, supports | [html?cgid=vitamins-](http://www.gnc.com/vitamins-supplements/477058.html?cgid=vitamins-supplements) |
|  |  |  | neurocognitive health | [supplements](http://www.gnc.com/vitamins-supplements/477058.html?cgid=vitamins-supplements) |
| Bee propilis trio | Propilis water extract (CiA, FA, | Natura Nectar LLC | Dietary supplement, Anti- | [https://www.iherb.com/pr/](https://www.iherb.com/pr/NaturaNectar-Bee-Propolis-Trio-60-Vegetable-Capsules/55817) |
|  | CA and CAPE), Brazilian |  | inflammatory response | [NaturaNectar-Bee-Propolis-](https://www.iherb.com/pr/NaturaNectar-Bee-Propolis-Trio-60-Vegetable-Capsules/55817) |
|  | bee propilis blend etc. |  |  | [Trio-60-Vegetable-](https://www.iherb.com/pr/NaturaNectar-Bee-Propolis-Trio-60-Vegetable-Capsules/55817) |
|  |  |  |  | [Capsules/55817](https://www.iherb.com/pr/NaturaNectar-Bee-Propolis-Trio-60-Vegetable-Capsules/55817) |
| Life flo health retinol eye | Retinol, FA, Vit C, D3, E and | Seychelles organics, Inc. | Anti-wrinkle | [https://in.iherb.com/pr/Life-](https://in.iherb.com/pr/Life-Flo-Health-Retinol-Eye-Cream-with-Ferulic-Acid-1-7-fl-oz-50-ml/77734) |
| cream with ferulic acid | green tea extract |  |  | [Flo-Health-Retinol-Eye-](https://in.iherb.com/pr/Life-Flo-Health-Retinol-Eye-Cream-with-Ferulic-Acid-1-7-fl-oz-50-ml/77734) |
|  |  |  |  | [Cream-with-Ferulic-Acid-1-](https://in.iherb.com/pr/Life-Flo-Health-Retinol-Eye-Cream-with-Ferulic-Acid-1-7-fl-oz-50-ml/77734) |
|  |  |  |  | [7-fl-oz-50-ml/77734](https://in.iherb.com/pr/Life-Flo-Health-Retinol-Eye-Cream-with-Ferulic-Acid-1-7-fl-oz-50-ml/77734) |
| Vitamin CE caffeic silk | Vit C, E, CA, grape seed and | Future Derm, Inc. | For brightening and | [https://www.futurederm.com/](https://www.futurederm.com/shop/futurederm-vitamin-ce-caffeic-silk-serum-162-triple-set/) |
| serum 16 þ 2 | avocado oil |  | tightening of skin | [shop/futurederm-vitamin-](https://www.futurederm.com/shop/futurederm-vitamin-ce-caffeic-silk-serum-162-triple-set/)  [ce-caffeic-silk-serum-162-](https://www.futurederm.com/shop/futurederm-vitamin-ce-caffeic-silk-serum-162-triple-set/) |

Sesderma serum ferulac FA, phloretin, jojoba oil, Vit A,

C and E

[triple-set/](https://www.futurederm.com/shop/futurederm-vitamin-ce-caffeic-silk-serum-162-triple-set/)

Sesderma S.L Anti-aging [https://www.sesdermausa.](https://www.sesdermausa.com/us_en/ferulac-serum-30-ml.html) [com/us\_en/ferulac-serum-](https://www.sesdermausa.com/us_en/ferulac-serum-30-ml.html) [30-ml.html](https://www.sesdermausa.com/us_en/ferulac-serum-30-ml.html)

Liposomal ferulac mist FA, phloretin, Vit A, C and E Sesderma S.L. Anti-Photoaging [https://www.sesdermausa.](https://www.sesdermausa.com/us_en/ferulac-mist-20-ml.html)

[com/us\_en/ferulac-mist-20-](https://www.sesdermausa.com/us_en/ferulac-mist-20-ml.html) [ml.html](https://www.sesdermausa.com/us_en/ferulac-mist-20-ml.html)

Ferulic Retinol Fortifying Neck Emulsion

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FA, retinol, ECG complexTM, collagen amino acids etc.

Dr. Dennis Gross Skincare LLC Strengthen and firmness to

jaw line and neck

[https://drdennisgross.com/](https://drdennisgross.com/ferulic-retinol-fortifying-neck-emulsion-1.html) [ferulic-retinol-fortifying-](https://drdennisgross.com/ferulic-retinol-fortifying-neck-emulsion-1.html) [neck-emulsion-1.html](https://drdennisgross.com/ferulic-retinol-fortifying-neck-emulsion-1.html)

Ferulic Retinol Wrinkle Recovery Peel

þ

FA, retinol, butylene glycol, *Aloe barbadensis* leaf juice etc.

Dr. Dennis Gross Skincare LLC Anti-aging and anti-wrinkle [https://drdennisgross.com/](https://drdennisgross.com/ferulic-retinol-peel.html)

[ferulic-retinol-peel.html](https://drdennisgross.com/ferulic-retinol-peel.html)

Lakme Sun Expert UV Lotion SPF 50 PAþþþ

Zinc Oxide, PEG-10 dimethicone, cyclopentasiloxane, dimethicone cross-polymer, ethylhexyl methoxycinnamate etc.

Hindustan Unilever Ltd. Sunscreen, protection from

UV-radiations

[http://beautyandmakeuplove.](http://beautyandmakeuplove.com/lakme-sun-expert-uv-lotion-spf-50-pa-review/) [com/lakme-sun-expert-uv-](http://beautyandmakeuplove.com/lakme-sun-expert-uv-lotion-spf-50-pa-review/) [lotion-spf-50-pa-review/](http://beautyandmakeuplove.com/lakme-sun-expert-uv-lotion-spf-50-pa-review/)

of fish oil emulsions (Yu et al. [2013](#_bookmark327)). As observed by Silveira and others, CiA addition to aqueous solutions or in the form of vapor inactive modified atmosphere packaging results in reduction of microbial spoilage, loss of vitamin C and total phenolic content; without affecting the flavor of freshly cut cantaloupe melon, even after 7 days of storage at 5 ◦C (Silveira et al. [2015](#_bookmark296)). A soy protein-based edible coating containing FA controls weight loss, firmness and browning index of fresh-cut apples, when stored at 10 ◦C and 50% relative humidity (Alves, Gonc¸alves, and Rocha [2017](#_bookmark164)). Thus, it improves the quality and prolongs the shelf life of freshly cut apple.

*Application of phenylpropanoids and their derivatives in pharmaceutical industry*

P-Coumaric 8-hydroxy quinoline ester used as a preservative in the pharmaceutical formulations, such as aluminum hydroxide gel-USP inhibited the growth of microbes more efficiently than standard preservatives, i.e., methyl and pro- pylparaben (Khatkar, Nanda, and Narasimhan [2013](#_bookmark235)) ([Table](#_bookmark112) [4](#_bookmark112)). In order to enhance the stability, bioavailability and bio- logical activity of FA, a novel oral formulation was

developed that is spray-dried micro-particles with FA, formed by EudragitVR L100, methacrylic polymer (Nadal et al. [2016](#_bookmark272)). A wound dressing formed by incorporating chi- tosan-CA conjugate into polycaprolactone (PCL) electrospun fibers inhibited the growth of *S. aureus* and increased the normal human dermal fibroblast neonatal cell proliferation as compared to PCL and PCL-chitosan fibrous membrane (Oh et al. [2016](#_bookmark261)). Recently, a group of researchers fabricated wound dressing material from poly (3-hydroxybutyrate) (PHB) and polyvinylpyrrolidone (PVP) containing CAPE, which inhibited the growth of *E. coli,* whereas exhibited bac- tericidal activity against *S. aureus* (Ignatova et al. [2018](#_bookmark215)). Moreover, *S. aureus* did not stick onto the surface of CAPE incorporated fibrous membranes.

*Phenylpropanids: a secret of healthy skin*

Overexposure to UV radiation has been reported to trigger the generation of ROS, which can cause oxidative damage, ultimately leading to edema, erythema, immunosuppression, sunburn, hyperpigmentation, photoaging and skin cancer (Chaiprasongsuk et al. [2016](#_bookmark180); Hseu et al. [2018](#_bookmark209); Murray et al.

[2008](#_bookmark271)). Photoprotective agents such as PPs are gaining momen- tum in order to prevent deleterious events in UV radiated skin. The U.S. FDA has approved the derivatives of CiA (e.g.,cinoxate and octyl methoxycinnamate) as active ingre- dients in sunscreen (US Food and Drug Administration [2018b](#_bookmark329)). The photoprotective effect of FA is mainly attributed to its antioxidant potential. Ferulic acid (0.5%) in a topical formulation containing Vit C (15%) and Vit E (1%) exhibits the dual effect. Firstly, it enhances the chemical stability of other compounds of topical formulation and secondly, improves the photoprotective response of topical antioxidative formulation against UV-induced skin photodamage (Lin et al. [2005](#_bookmark241)). Topical application of p-CoA cream on human skin resulted in the reduction of UV-induced erythema and hyper- pigmentation in human skin (Seo et al. [2011](#_bookmark307)). Recently, a study was conducted to assess the biosafety and efficacy of FA in alliance with UV filters (ethylhexyl triazone and bis-ethyl- hexyloxyphenol methoxyphenyl triazine) in sunscreens. *In vivo* analysis revealed that FA enhanced photoprotective efficiency of sunscreens formulation, mainly by improving *in vivo* sun protection factor and UVA protection factor (Peres et al. [2018](#_bookmark275)). Balupillai and his team have observed that CA prevents UV-B mediated photocarcinogenesis by regulating the PPAR-c expression in mouse skin (Balupillai et al. [2015](#_bookmark193)) and PTEN activation in human dermal fibroblasts and mouse skin (Balupillai et al. [2018](#_bookmark191)). Caffeic acid regulates the PPAR-*c* expression in mouse skin (Balupillai et al. [2015](#_bookmark193)) and PTEN activation in human dermal fibroblasts and mouse skin thus ultimately prevent UV-B mediated photocarcinogenesis (Balupillai et al. [2018](#_bookmark191)). Trans-cinnamic acid inhibited the dele- terious effects of UV-A exposure, including dermatotoxicity and oxidative damage. Moreover, it modulated the expression of activator protein-1, and Nrf2 in Hs68 fibroblast cells and mouse skin thus imparted its anti-aging effects (Hseu et al. [2018](#_bookmark209)). A study was conducted to elucidate the cytoprotective action of SA against UV-B mediated DNA damage in human keratinocytes (HaCaT). In a dose-dependent manner, SA inhibited the production of ROS and DNA damage indicators including cyclobutane pyrimidine dimers (CPDs), tailed DNA formation and lipid peroxidation in UV-B exposed HaCaT (Kim and Lim [2018](#_bookmark236)). Therefore, PPs are used by cosmetic industries in skincare for products such as facial serums, sunscreens, creams, moisturizers, and peels; which helps in treating wrinkles, fine lines, loss of firmness, hyperpigmenta- tion, and photoaging ([Table 5](#_bookmark151)).

# Conclusion

Phenylpropanoids are plant secondary metabolites which have aroused a keen interest among the scientific community due to its various health benefits. This review article provides the cur- rent knowledge on the diverse bioactive properties of phenyl- propanoids and their plausible molecular mechanisms. Phenylpropanoids are very promising ingredients for the pre- vention of food deterioration due to oxidation and microbial attack. Owing to its antimicrobial and antioxidant activities, PPs are finding applications in pharmaceutical products as a preservative. Currently, in many countries, PPs mainly FA,

CA, CiA and its derivatives have been approved as food addi- tives and active ingredients in skincare products. Therefore, many health supplements and cosmetic products with PPs have been developed commercially by leading companies. Despite their enormous biological potential, their application for the improvement of a wide range of diseases in humans remains unrealized due to the lack of pure PP standards and fewer human clinical trials.

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